FDA Issues Draft Guidance Recommending "Race and Ethnicity Diversity" Plans for Clinical Trial Sponsors

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Key Takeaways:

- The draft guidance represents the first-ever specific expectation by FDA that sponsors develop a diversity plan for trials.
- FDA's recommendations come as part of increasing interest in ensuring clinical trial diversity by FDA, the Biden Administration, and Congress.
- This latest draft guidance complements other guidance from FDA related to how sponsors can increase diversity and report diversity data.

On April 13, the Food and Drug Administration (FDA) published a new draft guidance that, for the first time, recommends that sponsors of clinical trials for submission to FDA develop a proactive "Race and Ethnicity Diversity" plan for addressing diversity in the trial's population, describing the diversity plan as an "important part of the sponsor's development program."

What the Guidance Covers

The Food and Drug Administration Safety Innovation Act (FDASIA) of 2012 required the FDA to assess the degree to which demographic subgroups (such as sex, age, race, and ethnicity) are represented in clinical trials and publish a report on the topic and a subsequent action plan to address any underrepresentation. Since then, the agency has undertaken a number of initiatives to encourage the industry to address underrepresentation of subgroups in clinical trials, including through several existing guidance documents.

The draft guidance notes the importance of enrolling a clinical trial population that reflects the population in which a product will be used and addresses the underrepresentation of racial and ethnic minorities in biomedical research (while these populations often face higher rates of certain diseases). The guidance emphasizes FDA's support for diversity in trial populations across a variety of subgroups (including, e.g., age, sex, or comorbidities) but focuses its recommendations specifically on race and ethnicity.

This draft recommendation is directed at virtually any sponsor of a trial that plans to submit data to the agency to support a marketing authorization submission for a drug, biologic, or medical device, including those submitting:

- An Investigative New Drug application (IND)
- A Biologics License Application (BLA)
- A New Drug Application (NDA)
- An Investigational Device Exemption (IDE)
- A premarket notification (510(k)), premarket approval (PMA) application, a De Novo classification request, or a humanitarian device exemption (HDE) application

What's Expected from Industry under the Guidance

When and How

The agency recommends that sponsors discuss their Race and Ethnicity Diversity Plan with FDA "as soon as practicable during medical product development." For drugs, FDA recommends that this should "occur no later than when a sponsor is seeking feedback regarding the applicable pivotal trial(s) for the drug (often during the End of Phase 2 (EOP2) meeting)."

The guidance provides the following practical recommendations for plan submission:

- IND sponsors can submit plans on their own or as part of a milestone meeting package.
    - Sponsors can request feedback on the plan by including specific questions in the submission.
- Device sponsors should submit plans as part of the investigational plan included in their IDE application.
    - If a sponsor wishes to submit a plan ahead of their IDE or for clinical studies not under an IDE, the plan should be submitted through the Q-submission process.

Sponsors should update the diversity plan to provide the status in meeting enrollment goals.

Content of the Plan

The guidance makes a number of recommendations for elements that must be included in the plan, and provides a template for how the information in the plan can be organized.

The expected elements include:

- Enrollment goals for underrepresented racial and ethnic participants, which should be based in part on the pre-specified protocol objectives of the investigation.
    - The goals should be based in part on any data that may indicate that a product will perform differently across particular populations.
    - Sponsors should leverage a variety of sources in order to develop goals based on epidemiological data on the disease in particular populations, but where there is limited data on this question, it is appropriate to set the goals based on demographics in the overall population with the disease or condition.
- A description of the planned assessment of race and ethnicity and other associated covariates with known potential to affect the performance of the product.
- Where there is data indicating that product performance may be affected by race and ethnicity, an explanation of the study design features that will support analysis to inform the safety and effectiveness of the product in the relevant racial and ethnic populations.
- Efforts to explore the potential for differences in safety and/or effectiveness associated with race and ethnicity throughout the product's development life-cycle, not just during pivotal trials.
- Where applicable, any clinical pediatric studies that are planned.
- A description of metrics that will be used to ensure enrollment goals are achieved and specific actions to be implemented if planned enrollment goals are not met.
- An outline of operational measures to ensure diverse clinical trial participation and the planned use of data to characterize the safety, efficacy, and optimal dosage in these participants, when applicable, including:
    - Specific trial enrollment and retention strategies, including with respect to site location and access.
    - Other recommended measures, such as providing language access to participants with limited English language proficiency and partnering with community-based organizations to provide support to study participants.
    - Notably, as part of efforts to increase diversity, the draft guidance suggests offering financial reimbursement for expenses, such as travel or lodging. A footnote explains that FDA "does not consider reimbursement for reasonable travel expenses to and from the clinical trial site and associated costs such as airfare, parking, and lodging to raise issues regarding undue influence." Other forms of consideration may be appropriate as well, provided that the investigational review board (IRB) reviews and addresses the "difficult questions" raised by such arrangements.

Broader Context for the Guidance

As discussed above, FDA has previously published three final guidance documents for sponsors regarding diversity in clinical trials:

- Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs (November 2020), which recommends practices for improving demographic and non-demographic diversity in clinical trials that drug and biologics sponsors can use, such as broadening trial criteria to encompass participants who might have been excluded due to certain risk factors and using adaptive clinical trial designs.
- Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies (September 2017), which encourages the collection of relevant demographic data in clinical studies on medical devices, recommends certain analyses of such data, and sets forth expectations for reporting such data to FDA.
- Collection of Race and Ethnicity Data in Clinical Trials (October 2016), which lays out recommendations for a standardized approach to collecting and reporting race and ethnicity data from clinical trials for medical products.

These guidance documents were issued alongside other efforts at FDA and across the Department of Health and Human Services (HHS) on clinical trial diversity, and FDA points to the new draft guidance as part of an effort to promote diversity in clinical trials under the broader Cancer Moonshot initiative. The new draft guidance was prepared by the FDA Oncology Center of Excellence in collaboration with FDA's centers for drug, biologics, and devices, and the HHS Office of Minority Health.

Legislative Initiatives to Improve Clinical Trial Diversity

Various legislative initiatives have also been proposed to improve the diversity of enrollment in clinical research. One initiative, the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act would require the FDA to revise its regulations to require sponsors of an IND or IDE to provide demographic prevalence data, develop enrollment targets, and submit a diversity action plan to meet those targets. The bill would allow FDA to mandate post-approval clinical trials or studies if there is insufficient subgroup data in the sponsor's clinical trials and the sponsor does not provide an adequate justification for the lack of diverse data. Another bill, the Clinical Trial Diversity Act, would require any entity seeking public funding through the National Institutes of Health (NIH) and other agencies to provide a clinical trial diversity plan to the agency when submitting the application for funding. A sponsor's failure to meet the clinical trial diversity conditions may result in penalties or the termination of funding.

Other initiatives are aimed at addressing systemic issues that potentially affect diverse clinical trial enrollment, such as by increasing community engagement, education, and outreach to underserved communities. The Diversifying Investigations via Equitable Research Studies for Everyone Trials Act ("DIVERSE Trials Act"), for example, would allow HHS to issue grants or enter into contractual arrangements to support education, outreach, and recruitment for clinical trials for drugs that treat diseases with disproportionate impacts on underrepresented populations. The DIVERSE Trials Act also would require FDA to provide recommendations on conducting decentralized clinical trials to increase demographic diversity and would provide a statutory safe harbor from civil monetary penalties for certain forms of patient support remuneration when offered to facilitate clinical trial diversity.

Given the significant interest in this issue, it is possible that some provisions related to clinical trial diversity will be included in FDA's user fee legislation that Congress is expected to pass by September 30, 2022. Certain clinical trial diversity measures have also been proposed as part of the comprehensive "Cures 2.0 Act" legislative package that has been introduced into Congress.

Next Steps

Comments on FDA's draft guidance are due on June 13, 2022. Prior FDA guidance documents on diversity in clinical trials were finalized relatively quickly, within approximately a year, but the process for finalizing this draft guidance could potentially take longer because it establishes a new expectation for sponsors. The high level of congressional interest in this issue also could affect the timing of FDA's decision-making and may shape the ultimate content of the final guidance document.

Although the guidance may change between its draft and final forms, sponsors should consider preparing diversity plans as recommended by the draft guidance before the policy is finalized.

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