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Diversity Enrichment: US FDA Guidance Suggests Sponsors May Need To Overenroll Key Groups

by Sarah Karlin-Smith

New draft guidance on clinical trial diversity action plans pushes for disproportionately high enrollment of traditionally underrepresented groups, while also asking companies to tailor global programs to US populations and consider diversity aspects that Congress did not outline.

Drug sponsors may need to overenroll key patient populations under the US Food and Drug Administration's new *diversity action plan guidance*, a move that could make the revamped clinical trial diversity push more challenging than anticipated.

The 2022 Food and Drug Omnibus Reform Act (FDORA) implemented a requirement for sponsors to submit "diversity action plans" for Phase III or other pivotal studies that specifies goals for enrollment disaggregated by race, ethnicity, sex, and age group demographic characteristics of the clinically relevant population.

Enrollment goals should generally be informed by the estimated prevalence or incidence of the disease in the US intended use population, per the long overdue draft guidance released 26 June.

But greater than proportional enrollment

Key Takeaways

- Aiming high for diversity, the FDA says greater than proportional enrollment for some subpopulations may be warranted as targets in soon-to-be required diversity action plans, but tells the *Pink Sheet* it would not do statistical testing on population subgroups.
- The diversity action plan draft guidance emphasizes that trial diversity goals will

may be needed in certain populations to elucidate potentially clinically important differences in responses between subsets of the study population, the guidance states.

Sponsors should consider whether a certain demographic group may have a different response to the medical product in terms of safety or effectiveness in determining whether to increase proportional enrollment.

apply to global research programs, but says to set targets using US population data.

- Beyond the law, the FDA also encourages subgroup analyses that divide populations by factors geographic location, gender identity, sexual orientation, socioeconomic status, physical and mental disabilities, pregnancy status, lactation status, and co-morbidity status.

The FDA would "not do statistical testing on population subgroups," a spokesperson for the Oncology Center of Excellence, which led the guidance development, told the *Pink Sheet*. The data "would be for descriptive purposes."

Balancing US and Global Approach

The demographic characteristics of the US population for the disease or condition being studied should be used to inform the enrollment goals. The guidance also provides suggestions or alternative approaches if the data is unknown.

Diversity action plans for a multi-national research program must describe participant enrollment goals for the entire study and should not be limited to US-enrolled participants, the draft guidance says.

The guidance recognizes the importance of global product development when appropriate, but also stresses that the overall study design and selection of study sites should account for the need to enroll a population representative of the US population intended to use the drug.

Global programs need to consider differences in disease characteristics, medical practice and available therapies when selecting foreign sites, the FDA wrote.

The guidance also acknowledges that sponsors may face challenges identifying corresponding populations in other countries, given a lack of uniformity in the use of population descriptions around the world, but does not provide new advice for handling the predicament. Sponsors should engage with the FDA early to discuss how to address the issues, including when the distribution of the disease or condition across the clinically relevant population differs by demographic region.

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Sponsors conducting multiple Phase III or pivotal trials don't necessarily need proportional representation in every individual study, but the total pivotal program should reflect proportionate representation.

Sponsors must justify proposed enrollment goals, including when the goals may deviate from the estimated prevalence or incidence of the disease or condition in the intended use population. *(See sidebar for more information on the submission process.)*

Drug developers are expected to explain their methods for determining the enrollment goals, preferably using publicly available data sources. If using non-public data, sponsors should provide the rationale for the approach, a synopsis of the analysis used, and citations for the data sources, the FDA said.

Diversity Action Plans Should Be Brief And Waiver Requests Filed Early, US FDA Says

By Sue Sutter

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In what could amount to a de facto enforcement mechanism, the new draft guidance also "strongly encourages" sponsors to share details about their diversity action plan and enrollment goals with the public.

Read the full article here

Going Further Than Congress

The guidance encourages drug sponsors to go beyond Congress' focus in FDORA and consider factors beyond age, sex, and racial and ethnic demographic characteristics for subgroup analyses when developing diversity action plan enrollment goals, such as geographic location, gender identity, sexual orientation, socioeconomic status, physical and mental disabilities, pregnancy status, lactation status, and co-morbidity status.

If factors like geographic location or social economic status could impact enrollment and retention of various subgroups, a diversity action plan also is expected to describe if and how the information informed enrollment goals and how the barriers may be mitigated.

FDA Commissioner Robert Califf alluded to the potentially broader focus at the BIO conference earlier this month, saying that "solving for sex, race, ethnicity, age, is just a start." (Also see "*US FDA Commissioner Robert Califf Says No Formulas For Trial Diversity*" - Pink Sheet, 11 Jun, 2024.)