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Clinical Trial Diversity Plans: Early Oncology Experience Shows More Work Needed, US FDA Says

by Sue Sutter

Few plans submitted to FDA's oncology review divisions in the wake of the April 2022 draft guidance were deemed acceptable, with enrollment goals being the most common topic of agency feedback. However, representatives from FDA and industry say the regulatory demand for such plans is pushing sponsors to build diversity into clinical trial programs from the start.

The US Food and Drug Administration's expectation that pharmaceutical sponsors submit clinical trial diversity plans has forced companies to plan early in drug development for adequate representation of historically under-represented populations.

However, the FDA's early experience with such plans suggests there is plenty of room for improvement, with oncology drug sponsors having to do more work when it comes to setting appropriate enrollment goals.

The agency and industry's early experiences with clinical trial diversity plans were discussed during a recent two-day meeting on enhancing clinical study diversity. The meeting, sponsored by the FDA and Clinical Trials Transformation Initiative, fulfills a requirement under the Food and Drug Omnibus Reform Act provisions on clinical trial diversity and modernization.

Under FDORA, sponsors will be required to submit "diversity action plans" for Phase III or other pivotal studies. These plans should include the sponsor's goals for enrollment and supporting rationale, and an explanation of how they intend to meet those goals. (Also see "*Clinical Trial Diversity Action Plans Required Under US Funding Bill*" - Pink Sheet, 21 Dec, 2022.)

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These provisions build upon an April 2022 FDA draft guidance that recommends sponsors submit race and ethnicity diversity plans to enroll representative numbers of participants from historically under-represented populations. (Also see "*US FDA Calls For Clinical Trial Diversity Plan 'As Soon As Practicable' In Product Development*" - Pink Sheet, 18 Apr, 2022.)

However, the FDORA requirements take those plans a step beyond race and ethnicity to also include enrollment by age group, sex and potentially other demographic characteristics.

The agency must issue new draft guidance on diversity action plans, or update its existing draft guidance, by late December. The FDORA submission requirement for diversity action plans applies to clinical trials that begin enrolling 180 days after publication of the final guidance.

Comprehensive Strategy Often Missing

The Oncology Center of Excellence recently published a *summary* of the first year of diversity plans submitted under the draft guidance to the Center for Drug Evaluation and Research's oncology review divisions. (Also see "*Diversity Plans For US FDA: Oncology Experience Will Inform New Policies*" - Pink Sheet, 14 Aug, 2023.)

Although 87% of plans submitted during the initial one-year period contained all five recommended components, only a small proportion of plans on which the agency provided feedback were deemed acceptable. Enrollment goals were the most common topic of feedback, followed by trial enrollment monitoring and strategies to enhance accrual to meet goals. (*See chart at end of story.*)

> ***"A comprehensive strategy to enroll a representative population that includes specific goals and metrics for success is missing most of the time, as evidenced by our one-year experience receiving diversity plans in the oncology review divisions at FDA." - FDA's Lola Fashoyin-Aje***

"From my experience advising sponsors on their oncology clinical development programs and encouraging the development of prospective diversity planning, my general observation is that clinical trials remained largely conducted in trial populations that are not representative of those who have the disease, and that clinical trial selection practices are not optimized to enroll representative populations," OCE Associate Director Lola Fashoyin-Aje said.

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"We remain focused on academic sites while insufficiently leveraging community sites where most patients receive their care from a trusted health care team," she said. "A comprehensive strategy to enroll a representative population that includes specific goals and metrics for success is missing most of the time, as evidenced by our one-year experience receiving diversity plans in the oncology review divisions at FDA."

In addition, "we do not routinely engage patients and communities early enough in defining the research questions or incorporating their input when designing and executing the research plan."

Fashoyin-Aje said the diversity plan data analysis shows there is still a lot of work ahead in terms of effecting the type of widespread culture change needed to make "sure that we're not sort of staying in the same place and maintaining status quo in terms of what we expect ... or even just aligning our thinking about diversity with actual goals when they're discussing with the regulators behind closed doors."

Bolt-On Approach Does Not Work

CDER officials previously have suggested the agency will take a pragmatic approach if clinical trial enrollment falls short of diversity plan goals, and the agency does not want diversity efforts to hinder drug development, especially for rare diseases. (Also see "*Clinical Trial Diversity Plans: Will US FDA Offer A Gentle Enforcement Hand?*" - Pink Sheet, 5 Oct, 2023.) (Also see "*Cavazzoni Appeals For Pragmatic Approach To Clinic Trial Diversity Plans*" - Pink Sheet, 30 Oct, 2023.)

At the FDA/CTTI meeting, Office of New Drugs Director Peter Stein suggested that early, proactive and comprehensive planning is key to enrolling diverse study populations without unduly delaying the development and approval of safe and effective drugs to address serious unmet needs.

> ***"There are so many different aspects of this that unless you take a comprehensive A-to-Z type of approach in thinking about what these barriers are and how each one of them are going to be dealt with ... you aren't going to be successful." – FDA's Peter Stein***

"This doesn't work as a sort of a bolt-on, after-the-fact kind of approach," Stein said. "In the past there were often companies who" tried to tackle diversity "around the edges. I think to really make this work, you really do have to start early. You have to be planning and intentional,

because the ... barriers you're dealing with are numerous here."

He proceeded to list a few of those barriers.

"It's patients' interest in and knowledge about trials. It's health care practitioners who either don't have the time, don't have the interest, or have concerns about having patients in trials. It's issues of placebos in trials. It's the access to and availability of sites in areas that have access to the patients that are diverse," Stein said.

"There are so many different aspects of this that unless you take a comprehensive A-to-Z type of approach in thinking about what these barriers are and how each one of them are going to be dealt with if you are going after a particular community that you want to access for your trials, you aren't going to be successful," he said.

"It really does require starting early, being comprehensive, and having the resources to go through and try to identify all of the barriers and do what you can."

Industry 'Standing At Attention'

Despite the challenges encountered to date, representatives from both the FDA and industry say the regulatory expectation for diversity plans is making sponsors think about building diversity into clinical development programs from the start.

"Companies are standing up teams that have the expertise to really evaluate real-world data, epidemiologic data and figure out ways to define benchmarks for enrollment across the different demographic groups, so race, ethnicity, but also sex and age group as important characteristics to think about, and then sort of setting those goals," Fashoyin-Aje said.

"Some pharmaceutical companies are making great strides to take meaningful steps to embed diversity and inclusion principles within their clinical development practices, increasing access to their clinical trials by establishing partnerships with sites that serve under-represented populations, and generally demonstrating a willingness to try practical solutions to address barriers," she said.

Meghan McKenzie, principal of patient inclusion and health equity in *Genentech, Inc.*'s chief diversity office, said the FDA's demand for diversity planning "is helping every level of leadership in every company, including our partners, our vendors, our sites, stand up and think how are we going to do better at reaching our representative patients?"

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The mandate has "made everybody stand at attention and start early before first-in-human. What are our targets? What is the incidence of the disease? What are we missing?" – Genentech's Meghan McKenzie

"There are areas like multiple myeloma, lupus [where] we've always been focused on how to be better at inclusion, but we need to be better everywhere," she said. "I think that's what the mandate has done is made everybody stand at attention and start early before first-in-human. What are our targets? What is the incidence of the disease? What are we missing? We're really worried about the data gaps."

Genentech's regulatory affairs staff "are training our teams and working with the teams to build what good looks like. And what good looks like in [multiple sclerosis] versus oncology is different, so we're learning."

The requirement "really is helping everyone think differently, like we can't keep doing what we're doing. So starting with these inclusive research plans early and then having them build end to end from Phase I through Phase IV, and our sites are actually helping us do that," McKenzie said. "We have these sites who are interrogating our entry criteria. We're leveraging that entry criteria and using it with real world-data. … We can figure out where the levers are where we can be more inclusive and not artificially exclude different patient populations."

Boehringer Ingelheim GmbH has completed five diversity plans to date, said Dooti Roy, director of global biostatistics and data sciences.

Shortly after the FDA published the 2022 draft guidance, the company set up a cross-functional working group to establish business practices and create diversity plan templates to ensure BI teams were working similarly across therapeutic areas and development programs, she said. This group also held educational sessions to bring more awareness to this topic.

"This was basically more or less an immediate reaction as the agency was publishing the draft guidance to make things more permanent and to provide the internal teams with dedicated support," Roy said. "A new clinical diversity lead and a team of diversity strategists are set to take office soon, where we hope that they can continue this great work."

In addition, the company developed an interactive data visualization dashboard to enable real-time tracking of diversity metrics at the site and trial level once a study is underway. "What this

did was help these teams to stay on target, stay focused, and also it told us important insights on where some other strategies might be needed, where something is not working well," Roy said.

'Not About Checking The Box'

Putting together a diversity plan is "is not about checking the box," said Alison Cuff Shimooka, chief operating officer of TransCelerate Biopharma. "This needs to be central to how we conduct clinical trials and think about clinical trials. Diversity plans need to be active, iterative and living documents."

The plan also "needs to be integrated far upstream in clinical development, and you need to be thinking about it early and often," Shimooka said. "It has to be cross-functional. It can't just be one small team operating in a silo. ... It needs to ideally not be at a single-trial level, but thinking more holistically across a program or a disease area. This will allow you to really get scale and have the biggest impact."

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