Diversity In Clinical Trials Drives Better Patient Outcomes

CROs Play Important Role in Operationalizing Sponsor Plans

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Ensuring diversity in clinical trials is not only supported by regulatory guidance, but is critical to completing trials that deliver optimal outcomes for all potential patients. Inclusion of diverse populations in trials may better clarify the understanding of drug effects across the entire population, an effort that receives significant support from Clinical Research Organizations (CROs) that help sponsors in operationalizing their diversity plans. Diverse representation in trials also helps to define benefits and risks in these subgroups. Underrepresentation of diverse populations similarly restricts trial access, which can influence overall trial results, reduce clinical research participation and lead to suboptimal outcomes for entire populations—making diverse representation in clinical trials not only a matter of biology, but also of health equity, fairness, and public trust.

In this article, we'll explore the latest draft guidance from the U.S. Food and Drug Administration (FDA) on diversity in trials. In addition, we'll review industry best practices, such as thoughtful diversity planning and making the most of decentralized trials and innovative technologies to increase diversity.

The Urgency of Diversity Planning

The FDA recently published its draft document, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry*,[1] making this a perfect time to reexamine this important topic. The key takeaway from this April 2022 publication is that the FDA recommends that sponsors develop and submit a "Race and Ethnicity Diversity Plan" early in clinical development. (A framework for such a plan is also in the document.)

The need to create a diversity plan in line with regulatory expectations will be new to some drug developers, so we will start by defining three key concepts[2] at the foundation of any such plan:

- **Diversity** refers to "the identities we carry." Diversity can be based on race, gender and/or sexual orientation. Age, class, education, ethnicity, country of origin, religion, physical or cognitive abilities, and other characteristics (e.g., social determinants, genetics, comorbidities, pregnancy status, environmental factors, etc.) also are included. When we talk about valuing diversity, we're referring to recognizing differences among people and acknowledging value in these differences.
- **Equity** refers to "fairness and justice," which is not the same thing as equality. Equality means "providing the same to all," while equity recognizes that "we do not all start from the same place" and that "power is unevenly distributed." Striving for diverse representation is a critical step toward equity.

- **Inclusion** refers to "how our defining identities are accepted in the circles that we navigate." Inclusion means being valued, respected and supported, and it ensures that individuals can be their authentic selves without fear or shame.

As the FDA's draft guidance indicates, entire groups and subgroups of people historically have been underrepresented in clinical development (either systematically or unintentionally) and understudied. Where clinical trials are concerned, Black, Latinx, Asian, Native American and other underserved populations—as well as underrepresentation at either end of the age spectrum—are all considered to be underrepresented.

Past and present examples of systemic, institutionalized and structural racism lead some patients today to continue to distrust the medical establishment, further compounding trial participation issues. Left unaddressed, we will continue to be faced with, as the American Medical Association has put it, a climate where "Black, Latinx, Indigenous, and other communities of color; women; LGBTQ+ people; people with disabilities; people with low income; and those living at the intersection of communities historically marginalized by the health care system experience even worse health outcomes below [the United States'] dismal national benchmarks."[3]

Toward More Inclusive Trial Participation

For many patients in underserved populations, inclusion in clinical trials offers access to investigational therapies and advanced medical interventions not otherwise available. Inclusion can therefore mean the difference between sickness and health, between life and death. "Over the past few decades, FDA has promoted enrollment practices that would lead to clinical trials that better reflect the population most likely to use the drug if the drug is approved, primarily through broadening eligibility criteria."[4]

Race and ethnicity are social, not biological, determinants; but social determinants of health have a real impact on biology. The World Health Organization (WHO) defines social determinants of health (SDH) as "the conditions in which people are born, grow, work, live and age, and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms, social policies and political systems."[5]

A recent issue of *Cancer*[6] summarized the problem in oncology when it identified that "overall cancer clinical trial enrollment (CTE) in the United States is 8% … and BIPOC [Black, Indigenous and People of Color] patients represent only approximately 15% of that low overall participation." Another article[7] reported that "4%–6% of trial participants are Black and 3%–6% are Hispanic, despite representing 15% and 13% of people with cancer, respectively." Yet another analysis[8] found that "Blacks or African Americans have a 28% higher cancer-specific mortality compared with whites." This is a persistent problem not only in oncology, but across all therapeutic areas.

As described in the *Cancer* article, there is "a staggering mismatch of racial and ethnic representation in cancer clinical trials." Accordingly, underrepresentation of racially and ethnically diverse patients "compromises the generalizability of trial results, may lead to miscalculations of disease-free survival rates and to erroneous estimates of treatment efficacy, and, as a result, may further exacerbate health disparities."[9]

Diversity is, Well … Diverse

Product development trials for pharmaceutical, medical device, vaccine and diagnostic tests are often and intentionally multinational. Patient representation must be balanced so that regulators around the world can review data from their regional populations. For example, in China and Japan, global clinical developers need to include Chinese and Japanese patients to determine whether the investigational product appears to be safe and effective for those populations.

At the same time, countries such as Germany and France[10] have a very different "color-blind"[11] approach to capturing (or not capturing) data related to race and ethnicity. In such cases, public policies are based on socioeconomic rather than racial factors and collection of much race-identifying personal information is forbidden. As such, developers will need to rely on what data points are available (socioeconomic, geographic, migration background, etc.) to plan for inclusion of a racially and ethnically diverse pool of patients.

Interpreting the FDA Draft Guidance

The FDA draft guidance provides recommendations on how to develop a Race and Ethnicity Diversity Plan that outlines how any given study will enroll "representative numbers of participants from underrepresented racial and ethnic populations in the United States." It's worth noting that this draft guidance expands on the previous documents, *Collection of Race and Ethnicity Data in Clinical Trials* (2016),[12] which outlines how to collect and present race and ethnicity data for FDA submissions; and *Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs* (2020),[13] which provides recommendations for increasing enrollment of underrepresented populations in clinical trials.

While we're focusing primarily on race and ethnicity, note that the agency "advises sponsors to seek diversity in clinical trial enrollment beyond these populations defined by race and ethnicity, including other underrepresented populations defined by demographics such as sex, gender identity, age, socioeconomic status, disability, pregnancy status, lactation status and co-morbidity."[14] In other words, a clinical trial should accurately reflect all the populations that potentially could benefit from approval of the treatment.

The new draft guidance clearly outlines the recommended elements of a diversity plan, including:

- **Overview** of the disease/condition, including available data on the pathophysiology in underrepresented racial and ethnic populations. Also includes evidence supporting any similarities and/or differences in the disease or condition that are associated with underrepresented racial and ethnic populations.

- **Scope** of the development program, including a description of the planned trials or studies, including study design, study population and eligibility criteria, endpoints and the expected geographic locations. This section should also specifically address inclusion of underrepresented racial and ethnic populations.
- **Goals** for enrollment of underrepresented racial and ethnic participants.
- **Specific** plan of action to enroll and retain diverse participants, including operational measures, specific strategies, metrics and actions to be implemented if planned enrollment goals are not met.
- **Status** of meeting enrollment goals (as applicable).

While the guidance says that sponsors can discuss their diversity strategy at any time during development, it recommends that plans be submitted with the investigational new drug (IND) or investigational device exemption (IDE) application.

Ultimately, sponsors should develop a diversity plan as early as possible and discuss it with the FDA as soon as is practical. This should be no later than the end of the Phase II meeting, when sponsors seek feedback on applicable pivotal trials. Ideally, efforts to identify which populations are affected by a disease, and should therefore be targeted for inclusion in trials, would begin at the molecule stage.

At present, the FDA guidance is in draft form, with no indication of when the FDA will address submitted comments and issue final guidance. For now, making every best effort to identify and include populations most affected by the disease or condition that is being studied will go a long way toward satisfying regulators and speeding the approval process. The greatest risk of not receiving study approval comes where there is a lack of effort altogether.

If a sponsor's enrollment goals are not met despite its "best efforts," sponsors are expected to discuss with the FDA a plan for collecting the needed data by conducting post-market studies or surveillance on the approved drug.

Successful Inclusion of Diverse, Underrepresented Populations In Clinical Trials With Patient Recruitment Partners

In the absence of a one-size-fits-all approach for data collection or participant recruitment, clinical developers often find it challenging to populate a new trial with a diverse set of patients. With that in mind, here are some items a sponsor might consider when reaching out to a CRO or other partner to begin a new trial:

- **Availability of a global site network to ensure diversity.** Most CROs have a global presence, but sponsors should still be very clear about wanting to tap into those resources and take advantage of the ability to cast a wide net. Sponsors are advised to ask about the CRO's global footprint, as well as the epidemiological and other real-world data it collects.
- **Partnerships with local communities.** Having a presence within a geography is not the same as being fully present there. Does the CRO actively partner with local organizations in the geographies it represents? Who are those partners (including patient advocacy groups) and what are the communities to which they have access? This should include culturally relevant marketing and recruitment tactics that recognize the uniqueness of local participants and engage those patients on their own terms. Patients tend to trust their own doctors and pharmacists, so partnering with those providers also can have a significant impact on educating and enrolling participants.
- **Solid understanding of related guidance.** What is the CRO's level of expertise in managing regulatory processes? Adhering to regulatory guidance should be standard procedure for an experienced CRO, so it will be important to address any gaps related to their understanding of any such guidelines.
- **Established focus and training on diversity.** A preferred CRO should not only be aware of FDA guidance related to diversity, but also be familiar with guidance related to patient centricity and expanded eligibility. The CRO should be actively taking steps to develop and leverage tools and strategies to operationalize trials that will meet the growing regulatory focus on inclusion of diverse populations. Some will even consult with, or have on staff, a social psychologist who can help define the most productive route to connecting with potential participants from a specific population.
- **Proactive CSR organization.** Corporate Social Responsibility (CSR) initiatives often have diversity, equity and inclusion as an internal, companywide goal. For any organization that works with patients, these CSR goals should reflect both an internal and external focus. That is, they should outline ways diversity is being sought within the ranks of the company, as well with all the patients and communities they serve.

Leveraging Technology and Decentralization

Adopting a more patient-centric approach goes hand-in-hand with the growth of Decentralized Clinical Trials (DCTs). DCTs employ sophisticated remote digital tools to make clinical research a more viable possibility for a larger number—and, typically, a wider range—of participants. In DCT models, geographic location is no longer a limiting factor; instead, trial sponsors bring clinical research to the patient, meeting them where they are and making participation as easy as possible. While not specific to underrepresented participants, it is worth noting that travel to a study clinic (the primary challenge that DCTs address) is consistently reported as the most significant burden of trial participation across all populations and therapeutic indications.[15]

A DCT might include a range of options, from virtual and mobile sites to wearables, telehealth visits, home care visits, eConsent and custom smartphone apps. These and other virtual tools reduce trial

complexity and ease patient participation, and they can broaden access and outreach to all interested participants, wherever they reside. This can be especially true for patients with rare diseases and those in underserved or underrepresented populations.

From the patient's perspective, technology can be very useful indeed. In a recent Center for Information & Study on Clinical Research Participation (CISCRP) report, participants referred to these tools as the most helpful to clinical trial participation: text messaging (49%), video conferences with the study doctor (49%) and smart phone apps (47%). Of note, Hispanic and Black respondents were significantly more likely to show preference for the continuation of virtual clinic visits (61%, 56%) than non-Hispanic (42%) and white (44%) respondents.[16]

Some CROs with expertise in decentralized trials have even developed dynamic protocols to enable the investigator and patient to choose from a menu of solutions. This enables the principal investigator and patient to determine the best approach for that patient. For example, what is the participant's preferred language? Is the patient required to attend onsite visits (and on what schedule)? Or can those visits be performed in the patient's home? If at home, is an in-person visit (by a nurse, principal investigator, etc.) required or can phone or video chat be used?

DCTs also can lead to more inclusive clinical trials. A key component of an inclusive trial is that it goes to where the patients are, and that is precisely what digital tools enable. A DCT makes it possible for a wide range of demographics to participate more easily, such as students, professionals, hourly wage earners, the elderly and those with young children. Mobile sites also present opportunities to staff patient-facing roles (nurses, phlebotomists, etc.) with employees from the community and to otherwise engage with community health departments, church leaders, food pantry managers, manufacturing site managers and patient advocacy groups. Whether physicians and staff come from within the community or not, it is important to note that diversity in the clinical research workforce has been strongly associated with clinical trial patient diversity.[17]

DCTs are not a one-size-fits-all solution to the diversity issue, they simply present a different set of tools that can be utilized to meet the needs of diverse participants. Whether a DCT or traditional trial is deployed, recruitment strategies that leverage channels such as online ads, social media and enhanced engagement with patient advocacy groups can be very effective. Likewise, clinical developers should have the ability to assess the demographics of potential participants and change course to achieve broader diversity. For example, a study could move away from channels dominated by white participants and include channels that target less represented communities.

Conclusion

Diverse patient representation in clinical trials, and improved quality and accuracy of trial outcomes, are more attainable than ever; but to meet these goals, trial sponsors will need to undertake a range of efforts. While it is important to follow the recent draft guidance provided by the FDA, it is just a starting point. Among the other tactics that help ensure inclusion of underrepresented populations are: enlisting the help of a CRO and site administrators skilled in engaging with historically underrepresented patients and physicians, partnering with community leaders and local health care providers, and partaking in decentralized trials that utilize digital tools to reach a diverse pool of patients.

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