

A COLLABORATIVE FRAMEWORK FOR ACHIEVING DIVERSITY, EQUITY, AND INCLUSION IN CLINICAL TRIAL POPULATIONS

Over the past few years, the importance of diverse participation in clinical research has gotten more attention. Have we made progress?

Although the gender balance of clinical trial participants has improved over the years, the demographic proportions remain out of balance in other ways. Studies across therapeutic areas struggle to recruit adequate numbers of racial and ethnic minorities, members of the LGBTQ+ community, adults aged 65 and over, pregnant and lactating individuals, and people with disabilities.¹

The 2021 FDA Drug Trials Snapshots reported both hits and misses when it evaluated therapies approved that year. Lupkynis, a drug approved to treat patients with kidney disease due to lupus nephritis, enrolled a population reflective of the disease: 86% female, 38% White, 37% Asian, 10% Black, and 26% of Hispanic/Latino.²

High-quality science requires clinical trial populations reflective of the disease studied. Without appropriate diversity, the data derived from clinical trials may not generalize to a broader patient population. Under-representation in clinical research also exacerbates the health inequities and poor health outcomes already present in the United States as well as our broader global population and limits the ability to identify differences in drug response among demographic subsets of the population.¹

For over two decades, the FDA has encouraged sponsors to recruit populations reflective of the burden of disease and has issued multiple guidance documents on both data reporting and representation. Its most recent draft guidance recommends sponsors submit a Race and Ethnicity Diversity Plan to enroll representative numbers of participants from underrepresented racial and ethnic populations in the United States.³

To achieve adequate representation in clinical trials—now and in the future—sponsors, CROs, and research sites must work together to develop protocol-specific strategies to recruit, enroll, and retain adequate, diverse study populations. By taking a collaborative approach, sponsors can achieve their enrollment goals, meet diversity-related regulatory requirements, and—most importantly—gain an accurate understanding of the drug's safety and efficacy in populations most likely to be impacted by the disease.

WHY DIVERSITY?

To Fully Understand Safety and Efficacy

People of different age, race, ethnic, gender identity, and sexual orientation often carry different disease burdens. For example, of all ethnic groups, Black Americans have the highest cancer death rate and shortest survival rate.⁴

Differences in disease burdens stem from a variety of factors, from social determinants to genetics. For example, Black Americans who undergo percutaneous coronary intervention (PCI) have higher rates of on-treatment platelet reactivity while taking antiplatelet drugs compared to White patients, which is partly attributable to a genetic variation. Higher on-treatment platelet reactivity is an independent risk factor for 12-month cardiovascular death and non-fatal myocardial infarction.⁵ Hypothetically, by under-enrolling Black Americans, researchers developing antiplatelet drugs may not notice these issues in clinical trials.

“If we’re designing a cardiology or oncology trial and we don’t have enough Black Americans enrolled, we’re doing a disservice to the very patients we’re trying to help,” said Medpace Medical Director Satya Shreenivas, MD.

Another hypothetical: Studies have found that Warfarin is associated with increased risk of intracranial hemorrhage in Black, Hispanic, and Asian Americans with atrial fibrillation compared to White Americans.⁶ If researchers hadn't caught this issue in clinical trials due to under-enrollment, the issue could have led to Black Box warnings according to Hansie Mathelier, MD, FACC, Clinical Assistant Professor of Medicine at Penn Medicine, who discussed the topic in a recent Medpace webinar.

These examples illustrate the many ways patient populations differ. Failure to enroll patient populations reflective of the disease or condition studied limits generalizability of clinical research findings to the U.S. population.

WHY DIVERSITY? To Meet Enrollment Goals Amidst Changing Demographics

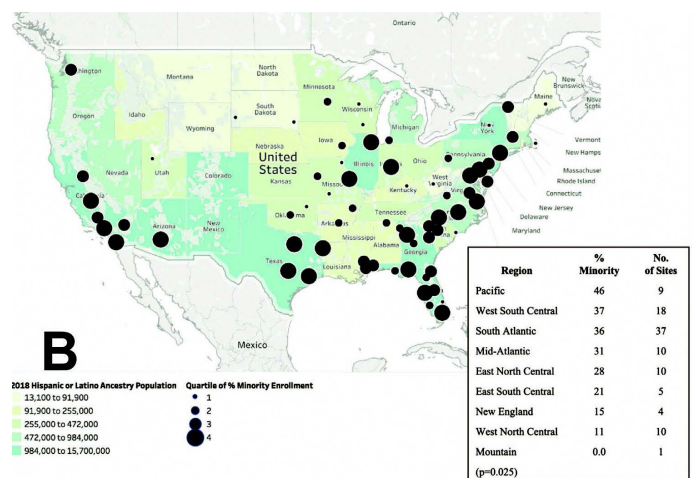
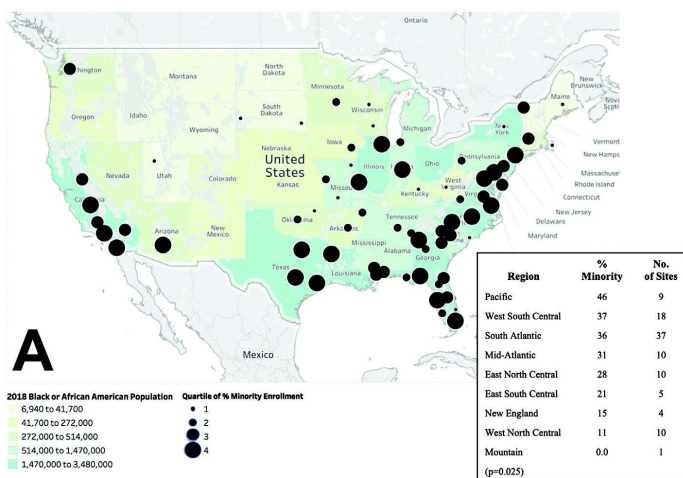
The United States population has diversified significantly over the past 10 years, and that trend is expected to continue in the decades to come. By 2030 one in every five Americans will be over age 65 according to the U.S. Census Bureau. The agency also expects immigration to be the top driver of population growth by 2030.⁷

Not only is the population growing older, we also have a more heterogeneous melting pot. Between now and 2060, the percentage of White Americans will decline while all other groups increase. For example, while the number of Hispanic Americans will grow by about 53 million by 2060, the number of White non-Hispanic Americans is projected to shrink by about 19 million.⁷

Ethnically diverse populations already comprise about 40% of the U.S. population. Adequately representing those minorities raises the odds of meeting enrollment goals by sheer numbers alone. "If you do not have a plan to drive enrollment for 40 percent of the U.S. population who identify as racial or ethnic minorities, you are already starting with the glass half full," said Dr. Shreenivas. "Enrollment will be slower, and efficiency will not be what was expected."

By 2045, the U.S. population will be roughly equally split between White non-Hispanic Americans and minorities. Diversity will continue to vary and shift by region over time. For example, the Pacific and South Atlantic regions are home to higher percentages of Black and Hispanic Americans. To recruit higher ratios of those individuals, work with sites based in these geographic regions.

DIVERSITY DIFFERENCES BY GEOGRAPHY



SITE SPOTLIGHT: MD MEDICAL RESEARCH

MD Medical Research, a clinical research site based in the Washington, DC, area, has participated in clinical trials in multiple therapeutic areas for over 20 years. Stephen Ong, MD, a primary care physician and MD Medical Research principal investigator, not only has decades of experience as a doctor and researcher, but he also has a large, loyal patient population. The site's recruitment database includes over 20,000 active patients: 65% Black American, 20% White, 5% Hispanic, and 10% Asian.

Spencer Ong, director of research and business development for MD Medical Research, estimates the site consistently surpasses its enrollment goals by an average of 300%.

The site performs well not by using aggressive marketing tactics (though they do advertise), but by following simple values:

- Treat people well
- Establish a win-win relationship for patients and study staff
- Mutual appreciation and respect

"Typically, clinical trial participants are patients of Dr. Ong's," said Spencer Ong. "Everyone knows Dr. Ong and he has patients that have trusted him for the past 30 years. The trust aspect is there, and patients are excited to participate. Many are high-risk patients. They understand that they'll get assessments and bloodwork they wouldn't get otherwise. And they appreciate the work they're doing."

WHY DIVERSITY? The FDA Encourages it

The FDA has made efforts toward more equitable representation since the 1980s. While its early work focused on age and gender representation, inclusion of other groups remains a challenge. In addition to guidance on demographic reporting, the agency began publishing Drug Trials Snapshots to bring attention to the demographic characteristics of clinical trials that resulted in drug approvals.

Due in part to the health disparities brought to light by the COVID-19 pandemic, the FDA issued guidance to enhance clinical trial diversity through eligibility and enrollment criteria and trial design. As part of its guidance, the agency encouraged sponsors to implement strategies to make it easier for patients to participate, no matter where they live, work, or seek medical care.⁸

Two years later, the agency built on that guidance by proposing the use of clinical trial Race and Ethnicity Diversity Plans. Sponsors must set diversity targets before they run their pivotal trials, plan operational strategies to hit their targets, and submit this plan early in clinical development and base the plan on a framework outlined in the guidance document.⁹

While diversity has long been considered in the analysis of clinical trial results, developing a proactive plan prior to conducting pivotal trials will be new for most sponsors and CROs. However, it could become standard practice. The Diverse and Equitable Participation in Clinical Trials (DEPICT) Act, if passed, makes diversity plans a requirement. The Act also requires sponsors to report clinical trial enrollment targets by demographic subgroup and gives the FDA authority to mandate post-market studies when sponsors fail to meet those targets.¹⁰

Racial categories are socially constructed and do not have a biological basis. However, some genetic factors that result in heterogeneity in drug response may be more common in certain ancestral populations, which may be associated with self-identified race and ethnicity.¹ Studies with participants diverse by self-identified race may allow for the identification of specific genotypes important for understanding heterogeneity in drug response.

Self-identified race and ethnicity may also be associated with socioeconomic factors that result in specific biological manifestations that are not genetic in origin. These factors also impact the health of LGBTQ+ and older populations.¹

Journal of American Medical Association (JAMA) has similar demographic reporting guidelines.¹² After a recent study found disparities among lead or senior authors, both publications have taken steps to diversify their editorial teams and accept more papers on health equity.¹³

For sponsors, this means it's important to recruit a diverse roster of principal investigators, which may require a closer look at site selection.

A COLLABORATIVE APPROACH FOR IMPROVING CLINICAL TRIAL DIVERSITY

As the global population evolves and multiple organizations take steps to improve diversity, it's time to rethink clinical trial models. Recruiting appropriately diverse patient populations moving forward requires thoughtful advance planning and a focus on patient-centric, culturally sensitive approaches. To improve trust, awareness, and—ultimately—participation, sponsors must lower the hurdles to patient recruitment, enrollment, and retention.

Successful execution of diverse clinical trials requires close collaboration between the sponsor, sites, and the CRO. “We all share responsibility,” said Miaesha Campbell, senior director of patient recruitment for Medpace. “Sponsors are making diversity an organizational strategy rather than a study-by-study strategy. Sites and CROs must support that strategy to drive successful execution.”

WHY DIVERSITY?

Some Medical Journals Require it

Publication is a key component of product launch. Medical journals have historically published research papers that may or may not include statistics and commentary on race, ethnicity, gender, age, and other demographic data within a study sample.

Now, prominent journals have tightened their criteria. The New England Journal of Medicine (NEJM), for example, requires authors to submit a supplementary table with background information on the disease, problem, or condition and the representativeness of the study group.¹¹

BARRIERS TO CLINICAL TRIAL ENROLLMENT

Influencing Factors for Lack of Diverse Representation



Mistrust



Lack of comfort with the clinical trial process



Lack of information about clinical trials



Time and resource constraints associated with clinical trial participation



Lack of clinical trial awareness

THE MEDPACE WAY: RIGOROUS SELECTION, GENEROUS SUPPORT

Medpace takes a holistic approach to clinical trial execution in partnership with sponsors. “We have physicians on staff who are fully engaged in the studies,” said Campbell. “Combined with a full-service recruitment and retention team, that allows us to partner with sponsors and adapt as the study requires.”

5 Components of a Winning Diversity Strategy:

1. Recruit a diverse population based on study-specific epidemiology. As science dictates, study populations must reflect the population diagnosed with the disease. And like the Warfarin complications mentioned previously made clear, they must also take into account genetic factors that may affect drug metabolism.

2. Evaluate each protocol with patients in mind. Recruit a team committed to diversity to develop a protocol that meets diversity objectives. To ensure a well-prepared team, sponsors and/or sites may also want to consider training for investigators and study teams to address unconscious bias.

When planning a trial, review everything—clinical operations, feasibility, patient recruitment strategies, regulatory affairs—through a lens of inclusivity. To help ensure the study design meets patients’ needs, recruit input from patients and patient advocates early in the process.

When developing the protocol, review inclusion and exclusion criteria: can it be loosened without impacting safety and efficacy? Can the study use fewer site visits without impacting quality?

To further broaden the pool of potential participants, implement elements of decentralized clinical trials (DCTs) and remote technology that allow patients to participate from home: eCOA, eConsent, telehealth, and direct-to-patient shipping for study drugs are a few options gaining popularity. Other options such as home health aides, paid transportation, multi-lingual study support, and more flexible appointment times make it easier for people from myriad backgrounds and life circumstances to participate.

3. Identify and engage the right sites. Site selection is critical to study success. Not only must sponsors and/or CROs evaluate sites based on their resources, staff experience, and number of eligible patients, among other criteria, they must also consider the demographic makeup of the staff and patients. When a study requires specific patient demographic ratios, identify and engage with sites located in regions with higher percentages of the populations needed.

Diversity within the study teams and the investigators are additional factors to consider. When recruiting people of color, for example, engaging with physicians and clinicians who look like them helps them feel more comfortable. Clinical staff who can communicate with patients in their native language and who understand cultural differences also helps remove barriers to participation.

4. Develop proactive, targeted messaging and outreach. Words and images in brochures, advertisements, and other study materials must reflect the population sponsors want to attract. An Alzheimer’s disease study that’s recruiting patients aged 55 and over should have photos of people in that age range. Similarly, studies recruiting an ethnically diverse population should feature an equally representative mix of images.

Study materials must also be customized for varying languages and cultural groups. For example, using gender-neutral pronouns in protocols, informed consent, and data collection forms shows respect for those who do not identify as traditionally male or female. Providing documents in patients’ native language ensures patients understand the benefits and risks of the study.

Other best practices include:

- Education and training programs
- Cultural competency training
- Community health fair participation to increase awareness
- Patient concierge services
- Translation services
- Monetary incentives for patient participation
- Use of technology (eCOA, wearables, etc.)

5. Develop diversity plans in alignment with industry demands and regulatory guidelines. During protocol development and before Investigative New Drug (IND) submission, sponsors should develop their study's Race and Ethnicity Diversity Plan per FDA draft guidance. FDA asks sponsors to submit plans "as soon as possible during drug development but no later than the time when the sponsor is seeking feedback regarding the applicable pivotal trials for the drug. The Diversity Plan may be submitted as part of a milestone meeting package or a freestanding document."⁵

Developing diversity plans is new to most sponsors, and the FDA has yet to clarify specifics on the types of data that should be used and how the guidance applies to global studies.¹⁴ To ensure plans align with the underlying disease or condition and meet all of FDA's criteria, seek assistance from your CRO.

Our regulatory and medical experts work with sponsors to develop the overview of the disease, gather epidemiologic data, and set goals for enrollment of underrepresented racial and ethnic participants. The core study team, feasibility group, and patient retention and recruitment experts then develop a specific plan of action to enroll and retain diverse participants in the trial. Finally, our regulatory affairs team can also support submitting the diversity plan to the FDA and assist with responding to any feedback from the review team.

ABOUT MEDPACE

Medpace is a scientifically driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.

CONCLUSION

Enrolling a sufficient number of patients for a clinical trial is a challenge alone, much less tailoring study populations to specific demographic proportions. However, just as clinical trial sponsors adapted to include an equal number of men and women, today's clinical trial models will shift to include the right mix of different races, ethnicities, ages, sexual orientations, and gender identities.

Adequate representation results not only in higher quality results, but also lower risk of a delayed or denied approval. And as minority groups comprise a larger share of the U.S. population, enrollment goals of any sort will depend on inclusivity.

Medpace brings together experienced, cross-functional teams to develop diversity plans in partnership with sponsors. Some large pharmaceutical companies have already pledged ambitious diversity goals.¹⁵ These and other organizations can set and meet diversity targets by viewing protocol development, recruitment strategies, site selection, and other factors through the lens of a diverse patient population.

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