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VIEWPOINT

Advocating for a Path to Increase Diversity in Enrollment in Cardiovascular Clinical Trials

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The current U.S. Black population represents 41.1 million people or 12.4% of the total U.S. population (2020 U.S. Census Data), yet health care disparities persist and have become more evident as Blacks continue to experience disproportionately increased risk of morbidity and mortality in cardiovascular diseases. The all-cause mortality rate among Black populations is an alarming 24% higher than that among White populations nationally.[1] Specific to hypertrophic cardiomyopathy (HCM), the most common inherited cardiovascular condition, Black patients have a higher rate of heart failure and HCM-related sudden cardiac death and lower survival rates after hospital discharge for cardiac arrest.[2,3]

Race-based differences in outcomes are thought to be multifactorial, including less access to specialty care centers and clinical trials than Whites, inaccurate or delayed diagnosis, and late therapeutic interventions, in addition to socioeconomic and traditional risk factors.[2,4] Genetic predisposition, social determinants of health, and implicit bias have also played a significant role. Overall, projected cardiovascular risk factors and cardiovascular disease prevalence are expected to increase, disproportionately affecting racial and ethnic minorities, emphasizing the urgent need to address major gaps in health care.[5]

Clinical trial research is fundamental in informing practice management changes and a clear understanding of treatment efficacy. However, therapies incubated in cloistered clinical trials have often underperformed in the real world because of their Achilles heel: participant representativeness. Despite nearly 30 years of the National Institutes of Health Revitalization Act that called for diversity, inclusion, and equity in clinical trials, we as a health care community have consistently fallen short of including representative trial participants among diverse patient cohorts. From 2006 to 2020, the Food and Drug Administration (FDA) approved 24 new molecular entity drugs for 7 cardiovascular conditions.[6] Black US residents were underrepresented as evidenced by 2.9% Black participants in clinical trials supporting FDA approval of cardiovascular drugs, whereas White US residents were equally represented and even overrepresented.[6] For instance, more recently, advances in our understanding of the molecular mechanisms of HCM have led to the development of mavacamten and aficamten - novel myosin inhibitors and the first disease-modifying therapy that directly targets the underlying pathophysiology of HCM. EXPLORER-HCM is a pivotal, first-in-class randomized, double-blind, placebo-controlled phase 3 trial that demonstrated the efficacy of mavacamten in improving symptoms and functional capacity in obstructive HCM with a positive effect on left ventricular remodeling.[7] Treatment with mavacamten improved exercise capacity, left ventricular outflow obstruction, New York Heart Association functional class, and health status in HCM patients.[7] Among the 123 trial participants who received mavacamten, only 1 patient was Black despite known differences in clinical phenotypes and higher risk adverse outcomes

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TABLE 1 FDA Recommendations for the Establishment of Diversity, Equity, and Inclusion in Clinical Trial Management

Sponsors	Trial Managers	Sites
• Revisit site selection and designation criteria	• Eligibility requirements	• Expand community outreach
• Create new incentives and grant opportunities aimed at increasing enrollment capacity and infrastructure at the federal level	• Eliminate unnecessary exclusion criteria	• Educate participants through their preferred channels
• Establish targets for racial composition	• Re-evaluate the applicability of protocols	• Engage caregivers
• Provide financial incentives for achieving recruitment targets (ie, tax credit)	• Collaborate with patient advocates	• Leverage digital technologies
• Expand reimbursement programs	• Form community planning groups	
• Ensure well-representative population enrollment in post-approval studies	• Leverage digital health technologies	

in Blacks with a potential for the greatest benefit. Additional study of the use of novel therapies such as mavacamten in a well-represented population is needed to understand the interplay of biological (including cytochrome P450 genotypes), behavioral, cultural, and social determinants of health to ensure drug administration is safe and effective for all.

CURRENT BARRIERS

There are several major barriers to underrepresentation. Black patients are commonly evaluated in the community setting with less access to referral to specialty care centers leading to underdiagnoses, late diagnosis, and misdiagnosis and, as a result, can affect their participation in screenings into clinical trials where they could have access to novel disease-modifying therapies.[2] Eligibility criteria are often strict, and participation costs may be prohibitive.[8] There may be innate distrust in the research process coupled with structural racism and implicit bias in our processes along with lack of diversified clinical investigators with whom patients may feel more comfortable. Cultural, language, health literacy, technologic, geographical, and economic differences can pose as barriers that need to be considered to address cardiovascular disparities in minority populations.

BRIDGING THE GAP

As we increase our knowledge on the multitude of factors leading up to health care disparities and adverse outcomes, we must now focus our efforts on not only identification but also implementation of key solutions and determine whether these solutions are effective.

In June 2022, the U.S. House of Representatives passed legislation in efforts to increase the representation of diverse populations in clinical trial enrollment for new drugs. The FDA announced their commitment toward increasing enrollment of diverse populations in medical product and drug development and has provided guidance on enrolling participants who are ethnically and racially diverse in the "Diversity in Clinical Trials Initiative."[2,3] Simple measures that have been outlined in the FDA guidance for the industry on improving diversity in clinical trials are summarized in Table 1.[8] These recommendations highlight the opportunity for the entire clinical trial administration committee (sponsor, trial managers, and sites) to play an active role in transforming clinical trial management with the potential for new federal incentives and regulations to build a more inclusive infrastructure.

COMMUNITY OUTREACH

Beyond education, training, and diversifying the workforce, the first step is reaching out to the community where most of these patients are evaluated and building on partnerships with referral and specialty care centers. Early, accurate diagnosis in the community can lead to timely referrals that can help close gaps in access to health care in marginalized communities and low-resource settings. We can also invest in educating participants on not only the benefits and risks associated with the trial but also reimbursement programs and support services to improve trial participation.

SITE SELECTION CRITERIA

Re-examine the criteria established for determining which facilities are considered preferred or top choice facilities. A site may not have the notoriety or pre-existing relationship with the sponsor; however, they may have access to targeted populations. Such sites should be recognized for their merits and distinguishable contributions. For example, historically Black colleges and universities are commonly denied research funding and overlooked during site selection. These practices by sponsors and trial managers are perpetuating the problem of imparity and disproportionately low representation of minorities.

RACIAL COMPOSITION TARGETS

Sponsors are recommended to set targets for the racial and ethnic makeup of their participants. The composition should minimally reflect the demographics of the populations for which drug therapy is intended. Subsequently, sponsors are encouraged to re-examine their incentive models. Those sites who meet and exceed the targets should be rewarded.

DIGITAL HEALTH TECHNOLOGIES

Providing community access to digital platforms for convenient enrollment, monitoring, and education can further the reach of recruitment efforts. While the recommendation is noteworthy, it is imperative to acknowledge the digital divide. When integrating such approaches into the orchestration of a trial, consider the readiness of the population to participate in these new ways. For example, although 85% of the U.S. population has a smart phone, device compatibility, tech literacy, and access to reliable data network services need to be taken into consideration. The adoption rate of smart devices also infers that 20% of the population do not have access to such technologies. This group tends to be the historically marginalized (minorities, older adults, and low-income communities) for whom barriers to health care exist. Trial managers need to be prepared to provision all the components of tech-based solutions similar to the way in which transportation services and specialty equipment are accommodated.

INNOVATIVE TECHNOLOGY AND INVESTMENT IN FUTURE RESEARCH

Innovative technological solutions such as machine learning and deep learning artificial intelligence algorithms have the potential to be used as decision-support tools to help improve diagnostic accuracy and consistency, which lead to timely diagnoses,[9] appropriate referrals to specialty care and trial sites, and therapeutic interventions, transforming clinical practice. Furthermore, identification of specific high-risk patient phenotypes who may be at increased risk of heart failure, for instance, can help target and personalize treatment by focusing on disease prevention. Machine learning clustering is a method that can identify homogeneous groups among populations with heterogeneous clinical features. Machine learning clustering can be an effective tool that can help accurately diagnose and phenotype various cardiac conditions including asymptomatic individuals who have underlying cardiomyopathy.[9] Current deep learning models under investigation provide precise, reproducible measurements in left ventricular wall geometric measurements and can help differentiate cardiac pathologies and improve disease recognition.[10]

Overall, minority populations have not been well represented in ongoing studies evaluating machine and deep learning algorithms. Integrating diverse data sources and comprehensive clinical data including race, ethnicity, and social determinants of health has not been performed. To make this a reality, regulators such as the US FDA and scientific journals must require future trialists to report attrition by key measures of representativeness.

SUMMARY AND CONCLUSIONS

Despite the significant advances in the field of cardiovascular medicine including drug discovery and overall decrease in age-adjusted mortality, Black women and men continue to be underrepresented in clinical trials and experience disproportionately higher cardiovascular mortality. A complex interplay of medical and social factors along with poor access to specialty care centers and clinical trials have contributed to health care disparities. The value of inclusion and ultimate improvement in care is worth the "extra" efforts by trial managers and investigator sites, even when conducting decentralized, remotely monitored, clinical trials. Presenting opportunities for collaboration, education, shared decision-making, and incentives will prove mutually beneficial. Capitalizing on the establishment of new frameworks and networks will also generate gains in addressing the novel therapies, as well as for future drug therapy discoveries. By emphasizing cultural relevance and community partnership in trial recruitment and implementation, the participation of racial and ethnic minorities should increase. Education and collaboration cannot be overemphasized. Current research efforts are evaluating the effectiveness of various strategies including the use of compensation methods and artificial intelligence strategies and building academic-community partnerships to identify eligible patients. Health care providers in the communities are also receiving training and resources on how to increase participation in clinical trial research. The creation of networks of pharmaceutical technologic and health care institutions can enhance inclusivity in clinical trials. The use of digital devices to improve recruitment, enrollment, retention, and patient

engagement of diverse patients in clinical trials is under investigation. There are ample opportunities to intervene and improve trial management, and *now* is the time to take action to implement change. Diverse representation in trial enrollment must closely be followed by equity in trial completion. Current efforts of diversity, equity, and inclusion have the potential to translate to overall improved participation of underrepresented minorities in clinical research programs, and ensuring randomized trials can effectively advance equitable cardiovascular care.

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