REGULAR ARTICLE

Racial and Ethnic Equity in Pulmonary Arterial Hypertension Clinical Trials

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Over the last several decades, many new therapies have been developed for patients with pulmonary arterial hypertension (PAH). These therapies have led to meaningful improvements in patient outcomes. Despite these advances, little is known about disparities in PAH care and even less is known about equity in clinical trial inclusion. Lack of equitable representation in PAH clinical trials may impact our understanding of risks and benefits in specific populations and may limit uptake of new therapies in minoritized populations. In this review, we begin to explore the racial and ethnic breakdown of patients receiving care for PAH and among participants who take part in clinic trials. We suggest that we have not yet achieved our goal of equitable representation in clinical trials and finish with a discussion of potential barriers and pathways forward. It is likely that progress will depend on addressing a complex interplay of patient-facing and system-derived barriers to participation.

The focus of this review is to examine the Venn diagram of racial and ethnic equity, clinical trials, and pulmonary arterial hypertension (PAH). By way of brief background, PAH is a rare and severe clinical condition caused by progressive remodeling of the pulmonary vasculature, which leads to elevated pulmonary vascular resistance, worse right heart failure, decreasing functional status, and poor prognosis. Over the last several decades, a proliferation of therapies for patients with PAH and meaningful improvements in outcomes have developed; however, little is known about inequity in the care of patients with PAH, and even less is known about racial and ethnic equitable inclusion of participants with PAH in clinical trials.

The relevance of this issue is underscored by the fact that clinical trials are central to evaluating the efficacy of new therapies, identifying adverse effects, and expanding understanding of disease processes. Racial and ethnic minoritized individuals continue to experience worse health outcomes and have more limited access to advancing treatments. Unfortunately, clinical trials that are not representative of the population being treated may widen these existing disparities. Beyond ethical concerns of excluding minoritized populations, poorly representative sampling in clinical trial populations may compromise the external validity of studies and potentially diminish the ability to identify heterogeneity of treatment effects.[1]

Health equity is the assurance that "everyone has a fair and just opportunity to be as healthy as possible" which involves "recognizing and rectifying historical injustices, and providing resources according to need."[2,3] Based on this definition, several important foci need to be considered when ensuring fair access to health. The current review is focused on minoritized populations as defined by racial and ethnic identity, with a particular focus on the United States. Participation in US clinical trials is influenced by a legacy of profound injustices against Black and African Americans as well as Hispanic or Latinx communities.[4] Given this understanding of health equity and the focus on acknowledging and addressing past injustices, it is important to specifically concentrate on the experiences of ethnically and racially minoritized groups when pursuing health equity in clinical trials.

Thirty years after the National Institutes of Health Revitalization Act was passed, which intended to improve enrollment of minoritized populations into clinical trials, imbalanced representation in clinical trials and equitable recruitment remain significant public health issues.[5] Emblematically, among 20,692 US-based clinical trials, only 43% reported race and ethnicity data.[6] Equitable inclusion into clinical trials has become a major goal of National Institutes of Health initiatives, and this focus was included in the 2022

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Consolidated Appropriations Act. The Consolidated Appropriations Act requires studies of drugs or medical devices to include broad populations of participations based on age, gender, race, and ethnicity.

One key barrier to understanding equitable inclusion of participants in US-based PAH clinical trials is a lack of understanding of the racial and ethnic breakdown of patients living with PAH more broadly. Due to the rare nature of this disease, much of what we know about the demographics of patients living with PAH has come from observational studies conducted in economically developed countries organized into national and/or international disease registries. Even these data sources often have sparse descriptions of race and ethnicity and, in the US, have uniformly relied on voluntary enrollment. The reliance on voluntary observational registries to inform the appropriateness of clinical trial populations contributes substantial uncertainty as to whether we are achieving our stated goal of equity. Systematic features that limit minoritized patient participation in trials may similarly limit their participation in voluntary registries. This may give the impression of parity without achieving the goal of equity relative to the true patient population.

Efforts to understand the broader PAH disease population in the US began in the 1980s with the National Institute of Health Patient Registry for the Characterization of Primary Pulmonary Hypertension.[7] This was the first large PAH registry in the US and was comprised predominately of young White women. This racial and ethnic impression was also reflected in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry),[8] which categorized 3,515 patients from 55 centers within the United States. REVEAL suggested that 80% of participants were White, 14% were Black, 9% were Hispanic, and 6% of participants reported another race. This general trend has been reinforced by other US-based registries including the Pulmonary Hypertension Association Registry (PHAR, https://phassociation.org/phar/recent-research-and-the-pha-registry/), the Sphere registry, and the PAH Biobank. These US-based registries have reported a range of White participants from 72.3% to 79%, Black participants from 11% to 15.4%, Hispanic participants from 5.9% to 10%, and participants of another race between 10% and 12%. Only the PHAR specifically identifies participants who report Asian race (3.4% of the registry). One possible exception to a reliance on voluntary participation to characterize demographics is the Centers for Disease Control and Prevention (CDC) WONDER cohort.[9] CDC WONDER includes an attributable death database, and while this carries concern for conflating racial disparities in outcomes and prevalence, it does offer a nonvoluntary picture of the breakdown of death among patients identified as having PAH in the US. CDC WONDER would seem to reinforce the overall impression seen in voluntary registries with deaths among White patients with PAH comprising 83.7%, Black patients responsible for 13.1%, American Indian and Alaska Native patients at 0.8%, and Asian and Pacific Islanders at 2.4%.[10]

Taken together, the available data would seem to suggest that the population of patients with PAH in the US appears to include 20%–30% of patients identified as a minority and 70%–80% identified as White. The validity of these estimates may be cautiously supported by their similarity to the US census in 2020, which found that 71% of people in the US identified as White (61.6% identified as White alone). As such, while likely imperfect, this breakdown may be a reasonable benchmark to begin understanding equity in clinical trials at the national level. Relevantly, PHAR analyses suggest the racial distribution among people living with PAH varies widely by US census region.[11] It is important to recognize that, for any individual trial, the local region may have a different source population of individuals living with PAH, and it may not be appropriate to apply a national standard to assess equity.

Beginning with early therapies for PAH, the initial landmark trial of epoprostenol in 1996 did not include information on race, but subsequent large trials of bosentan (79.8% White participants) and sildenafil (86% White participants) suggested that White participants were likely overrepresented.[12–14] The proportion of non-White participants in international PAH clinical trials has increased over time, but this was primarily through expanding recruitment in Asia and Latin America, not through an increased recruitment in racially diverse populations within North America and Europe.[12] This is an important distinction because race and ethnicity may be associated with a range of social determinants of health that may be quite distinct between countries. In fact, we devote significant time in this review to focusing on issues from the vantage of the US. This is not because other countries and regions lack important barriers to health equity but because these barriers are likely specific and tied to the unique history, policies, and social context of each country. Thoughtfully unpacking each of these country-specific social constructs is beyond the scope of this review. As such, the focus on the US is grounded in practicality and a region with a wealth of PAH-focused research.

Importantly, non-Hispanic Black participants appear to be consistently underrepresented in clinical trial populations. In the recent analysis by Min et al, these participants only constituted about 4% of the overall clinical trial population when accounting for all geographic sites (although this increased to 9.8% when only considering US participants, which does begin to approach the percentage of Black individuals in the most recent US census). Nevertheless, this suggests Black participants were likely underrepresented in clinical trials relative to the US population and certainly underrepresented relative to the global population.[15] In a direct review of some of the largest randomized clinical trials for PAH therapies from the last decade, the pattern of underrepresentation by Black participants is similar. For example, in 2013, the PATENT-1[16] trial evaluated riociguat in 443 participants from 123 centers in 30 different countries. In PATENT-1, only 1% of participants were classified as Black (61% of participants were White, 31% as Asian, less than 1% as mixed race, and 5% categorized as other

Table 1. Potential Barriers and Solutions to Inclusive Clinic Trials[a]

Patient-facing barriers	Possible individual-level solutions
Perceived risk	Clear and culturally informed study materials
Trust in the medical community	Patient- or community-engaged research
Relationship with provider	Providers introducing studies initially or community providers trained in research
Health literacy and awareness of trials	
Time commitment	Monetary support for time of work
Study distance to center	Reimbursement for travel
	Remote study visits
Study-team and institution derived	**Possible study- or institution-level solutions**
Diversity of the study team	Inclusive hiring practices
Awareness of unconscious bias	Bias and cultural competency training
Cultural competency of the study team	
Availability of study resources in multiple languages	Early translation of study materials
	Inclusion of budget for translation services
Inclusion criteria that favor imbalanced race or ethnicity	Unbiased registries to monitor inclusive enrollment
Lack of community outreach	Partner with community advocacy groups
A one-size-fits-all approach to increasing diversity	Qualitative approaches to engage minoritized communities

[a]Included themes from existing literature.[20,27–33]

or not reported). Subsequently, the SERAPHIN trial[17] evaluated macitentan in 250 participants from 151 centers across 39 countries. SERAPHIN's participants only included 2.6% Black participants (54.5% of the study population was White, 27.7% was Asian, 14.7% was Hispanic, and 0.4% were determined to be other). Even in the most contemporary trials, Black participants continue to be underrepresented. The PULSAR trial[18] of sotatercept included 4% participants who self-identified as Black (92% identified as White and 4% as other), and the subsequent STELLAR trial[19] of sotatercept only included 2.2% of participants who self-identified as Black (89.2% as White, 2.2% as Asian, 13% as other, and 8% as missing).

The mechanisms for lack of equitable inclusion in trials are not well understood, likely vary by region, and have not been studied in PAH. Evidence from cardiology and oncology studies suggests logistical barriers to participation include time commitment involved with participation, transportation, long distance to study centers, and financial burden.[20] Poor quality of communication from the research team regarding placebo versus interventional therapy arms may be an additional barrier in experimental studies. Certain language and cultural differences, especially within the context of informed consent, contribute to the decision to enroll in clinical studies.[21] Importantly, clinical trial enrollment also occurs within the broader context of race relations in the United States. The mechanisms for racial inequities in health care in general are numerous, operating on multiple levels and dimensions.[22,23] For Black individuals in the US, medical system distrust, especially in the context of clinical trial research, is rooted in a history of exploitation and mistreatment of Black individuals by the medical and research community.[4,24] The decision to participate in medical trials may be influenced by medical mistrust that is a result of current and historical systemic racism.[25,26]

In addition to these mechanisms in medicine and society more broadly, specific barriers may exist for rare diseases such as PAH. Fewer centers specializing in PAH means less access to centers for care, potentially less involvement in clinical studies, and delays in diagnosis and initiation of therapy. This may be exacerbated by insurance status and other social determinants of health that disproportionately affect minoritized populations. For example, patients with PAH in the lowest tercile of socioeconomic status had a higher risk of mortality in one study (hazard ratio of mortality was 2.98 after adjusting for age, sex, hemodynamics, World Health Organization group, and therapy).[27] Based on data from the REVEAL Registry and PHAR, Black and Hispanic patients were overrepresented among PAH participants in the lower income categories (15.98% and 10.20% of Black and Hispanic patients, respectively, in the lower 2 income groups compared with 6.49% and 4.57% in upper two income groups).[28] For minoritized individuals with PAH, systemic inequities that result in differential access to education, employment, and insurance may result in poorer health outcomes and affect access to clinical care including clinical trial participation.

In summary, these inequities in PAH clinical trials are important. Clinical trial recruitment that is not representative of the PAH population more broadly may impair understanding of drug effects, heterogeneity of treatment, and adverse effects of therapies. Unequal participation in trials also has the potential to limit trust in new drugs for which minoritized participants were not fully represented. While we have

used percentages by race and ethnicity of patients living with PAH to try and understand the scope of the problem, we do not believe that a system of quotas for clinical trial participation is an appropriate solution. A target-based system in isolation has the potential to create a series of unintended effects including pressure on study teams to enroll minoritized population and an incentive that may inadvertently lead to coercion of participation which may exacerbate rather than ameliorate racially and ethnically motivated distrust in medical research.

The Food and Drug Administration published initial guidance in 2020 emphasizing the need to incorporate the following solutions: (1) broaden inclusion and exclusion criteria when able with careful attention to eligibility criteria in rare diseases; (2) trial design that is more accessible and less burdensome, for example, optimizing remote study visits; (3) culture competency training and a focus on patient-engaged research; (4) trial sites in locations with higher concentrations of ethnically and racially minoritized communities; and (5) use of electronic study materials whenever possible, including electronic consent forms (see Table 1).[29] Updated guidance in 2024 went on to highlight the importance of keeping unbiased, accurate disease registries to create an effective diversity action plan. Several key knowledge gaps need to be filled to improve the conduct of equitable PAH trials in the US. These gaps include but are not limited to a better understanding of the racial and ethnic representation among PAH patients more broadly, improved characterization of the overlap of race and ethnicity with other social determinants of health, and a much more nuanced understanding of the barriers that minoritized patients face to participation in registries and trials. Successful strategies for enhancing the representation of ethnically and racially minoritized individuals in clinical trials will need to account for the specific context of the disease—particularly for rare conditions like PAH—as well as the geographical and social contexts of the affected communities (solutions are summarized in Table 1). Community-engaged research which partners with minoritized populations to understand the research needs and priorities of these communities has shown significant promise in improving diversity of clinical studies.[30,31] Other patient-centered strategies may include providing monetary support for time and travel associated with participation, flexible study hours to accommodate those in the workforce, and recruiting diverse study teams and cultural congruency of teams.[32]

Traditional, deficit-based approaches to health disparities focus on characteristics within individuals or communities and often fail to account for a complex, multilevel system of inequity. In contrast, critical approaches incorporate race consciousness, intersectionality, and move away from deficit-based approaches that place the burden of fixing inequities on personal attributes of patients and their families. It is a combination of these approaches paired with the careful reform of clinical trial protocol, design, and organization that will move PAH clinical research toward representativeness and equity.[33,34] The careful study of patient-facing and system-derived barriers is vital to developing a fair and equitable system where minoritized populations want to be included in PAH clinical trials and such opportunities are afforded to them.

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