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Representation matters: a call for inclusivity and equity in heart failure clinical trials

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The burden of heart failure remains substantial worldwide, and heart failure with reduced ejection fraction (HFrEF) affects approximately half of this population. Despite this global prevalence of HFrEF, the majority of contemporary clinical trials in HFrEF have underenrolled individuals from minoritized sex, gender, race, ethnicity, and socioeconomic groups. Moreover, significant disparities in access to HFrEF treatment and outcomes exist across these same strata. We provide a call to action for the inclusion of diverse populations in HFrEF clinical trials; catalogue several barriers to adequate representation in HFrEF clinical trials; and propose strategies to broaden inclusivity in future HFrEF trials.

Over 64 million people worldwide are affected by heart failure (HF), and individuals with HF with reduced ejection fraction (HFrEF) comprise half of this population.[1] Advancements in HFrEF diagnostics and therapeutics have been predicated on the successful execution of clinical trials. Despite the availability of rigorously tested therapies that reduce morbidity and mortality in HFrEF, significant disparities in prevalence, access to treatment, and outcomes exist across sex, gender, race, ethnicity, and income strata.[2–4] The history of HFrEF clinical trials is replete with examples of under-enrolment of clinical trial participants from minoritized groups. These poorly representative trials delay learned experience in diverse groups and may further contribute to therapeutic inertia and healthcare disparities.[2] Herein, we review the importance of the inclusion of diverse populations in HFrEF clinical trials; catalogue several barriers to adequate representation across the HFrEF clinical trial lifespan; and propose multi-level strategies to broaden inclusivity in such trials.

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Importance of representation of diverse populations in heart failure reduced ejection fraction clinical trials

Equitable representation of individuals affected by HF in clinical research is essential to investigate the benefit and harm across diverse populations. However, fewer than half of recognized landmark clinical HFrEF trials report outcome data by race/ethnicity.[3] The majority of contemporary HFrEF trials have primarily enrolled non-Hispanic White men with an inequitable representation of racial/ethnic groups and women across geographic regions. Real-world populations of patients with HF in the USA have demonstrated disproportionately high disease prevalence in Hispanic and non-Hispanic Black individuals compared with those from other racial/ethnic groups.[5] Furthermore, non-Hispanic Black individuals with HF have the highest per capita death rate.[6] In spite of this, enrolment of non-Hispanic Black patients in HF therapy trials remains low. Moreover, although ~40% of patients with HFrEF are women, they comprise just 21% of clinical trial enrolees in the modern era.[2,7] The conclusions drawn from sex-stratified sub-studies of early HFrEF clinical trials have exemplified the hazards of grounding

therapeutic dogma on underpowered and *post hoc* analyses.[2] Safeguarding against extending these practices to other demographic groups should be emphasized.

Globally, indigenous communities are poorly represented in HFrEF clinical trials despite enduring high disease burdens.[8] Sub-Saharan African and Afro-Caribbean participants are nearly absent across the HFrEF clinical trial landscape. Though HF is broadly considered a disease of aging in North America and Europe, the age of HF onset is considerably younger across Latin America, Sub-Saharan Africa, and Asia.[8] Additionally, the primary drivers of HFrEF vary broadly across these global regions, raising doubts regarding the information derived from these HFrEF clinical studies outside of limited demographic scope. HF prevalence and hospitalizations are expected to increase by 50% in the next 25 years as the global population grows and ages and deaths attributable to HF are steadily rising.[6,7] Systematic under-representation of Black and Indigenous People of Color and Women in HFrEF clinical trials does a disservice to the communities most affected by HF. This lack of inclusivity threatens generalizability of therapeutic innovation beyond majority populations, contributes to therapeutic inertia in the cardiovascular community, and ultimately minimizes imperative survival gains.

Barriers to enrolment of diverse populations in heart failure reduced ejection fraction clinical trials

Various obstacles to the enrolment of diverse populations in HFrEF clinical trials exist at the individual, community, institutional, and sponsor levels. Unfortunately, many of these populations are typically under-treated with guideline-directed medical therapies (GDMT) which may prevent them from meeting eligibility criteria for trials of novel agents that seek to determine benefits in addition to contemporary GDMT. Women as well as those from certain racial and ethnic groups are less likely to have access to subspecialty care where opportunities for trial participation are often concentrated. These barriers and others are inextricably linked to social determinants of health which impact access to care and resources need to facilitate clinical trial participation, such as access to transportation and compensation for time away from work.[2,9]

Studies have shown that women are less likely to be enrolled in HF clinical trials when recruitment is performed in ambulatory settings, trials are testing devices or surgical interventions, and when sex-specific eligibility criteria are in place.[10] As women frequently have caregiver responsibilities, they may be less likely to attend in-person research visits and complete supplemental testing. Additionally, the use of sex-specific eligibility criteria related to childbearing or lactation may exclude many women, even when the exclusion criteria are not relevant to the therapy being studied.[10] In one analysis of 317 HFrEF randomized clinical trials, 26% used such eligibility criteria, and none of them provided a rationale.[10]

Mistrust of the research enterprise and lack of diversity among patient-facing trial staff can impede recruitment of racial and ethnically minoritized populations.[9] Screening and enrolment may be challenging if trial documents are not culturally appropriate or translated into a patient's native language. In some cases, non-English speaking patients are specifically excluded. Conversely, patients may be more engaged when interacting with providers and staff who share their cultural and ethnic backgrounds.

Globalization of HF clinical trials, ironically, has served to limit the diversity of clinical trials as many of the increasingly represented countries in Europe, for example, have more homogeneous populations, limiting enrolment of Black and Hispanic adults.[9] Furthermore, many of the countries with a high HFrEF burden do not have the infrastructure to conduct clinical trials.

Strategies to broaden inclusivity and equity in heart failure reduced ejection fraction clinical trials

We offer an actionable, multi-tiered approach toward the goal of improving the participation of historically excluded populations in HFrEF clinical trials (*Figure 1*).

Early-stage clinical trials

Phase I and Phase II studies of drug and device safety and efficacy should be performed in a diverse group of participants, since drug pharmacokinetics, pharmacodynamics, and device–patient interactions vary by age, sex, and race/ethnicity. For example, compared with men, women may achieve up to 2.5-fold higher peak plasma concentrations of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers at similar drug doses. This potential for differential efficacy or harm with equivalent GDMT drug dosing highlights the importance of sub-group-specific investigation.[11] Active participant feedback should be sought with regard to drug/device labelling and ease of correct use in multiple languages.

Trial leadership

Designating an officer responsible for ensuring that targets in diverse patient enrolment are embedded into clinical trial design and are met at periodic intervals may improve representation in clinical trials. Principal investigators, site staff, and steering committees should reflect the diversity of the population being studied.[5,12] The impact of diverse trial leadership on participant enrolment has been recognized; for example, the number of women authors on clinical trial publications has been shown to be positively associated with the proportion of women enrolled in HF trials.[13]

Trial infrastructure

A decentralized hub-and-spoke organization, with major academic centres serving as 'hubs' and trial sites in community-based centres and federally qualified health centres serving as 'spokes', may improve enrolment of minoritized and socioeconomically disadvantaged populations by enhancing access to clinical trials. Harnessing innovative remote monitoring and patient engagement technologies could promote enrolment of individuals who are hindered from participation because of competing caregiving and work responsibilities.[14] The availability of consent and patient-facing educational materials in

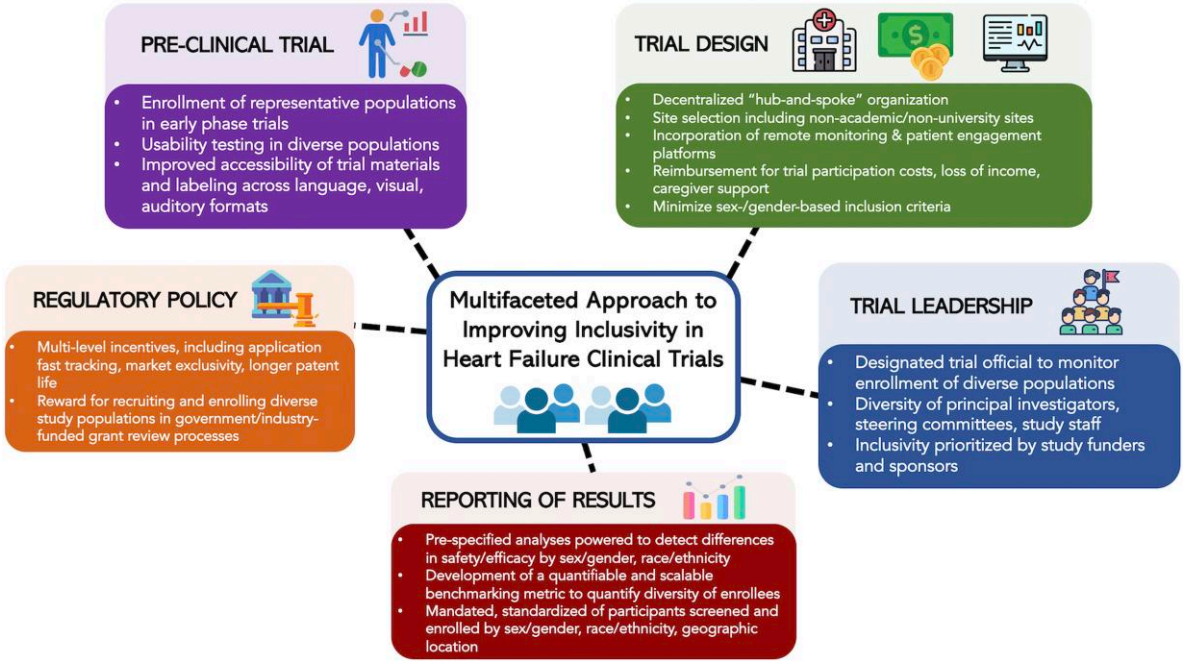

Figure 1 Multifaceted approach to improving inclusivity in heart failure clinical trials.

multiple visual and auditory formats may encourage enrolment of those who would be otherwise excluded.

Reporting of results

Currently, reporting of race and ethnicity data in clinical trials is inconsistent, and standardizing the acquisition and reporting of these data are critical benchmarking steps. A unified and portable measure of diversity and inclusivity, such as the ratio of under-represented participants enrolled in a clinical trial to the under-represented participants in the target disease population, could be used to translate enrolment data across clinical trials. Similarly, a quantifiable metric representative of the diversity of the steering committee and investigators could be developed and reported.

Regulatory policies

Government agencies around the world are uniquely positioned to improve inclusivity in trials. For example, country-specific regulatory and reimbursement agencies could fast-track applications and approval processes, extend patent lives, or provide market exclusivity for those therapeutics tested in a truly representative trial population.[9] Where applicable, research agencies could explore including grant scoring criteria focused on the diversity of the study population and reward those applications that specifically outline plans to promote diverse enrolment.[15] Programmes like the US National Institutes of Health's Faculty Institutional Recruitment for Sustainable Transformation Initiative seek to enhance diversity among faculty and could be replicated in other settings.[16] Standardization and cost-lowering of multi-regional clinical trials designed to be agnostic to country-specific regulatory and reimbursement standards are important to generalize the progress made in HFrEF management across geographical boundaries.

Conclusion

Generating high-quality, generalizable evidence to advance HFrEF practice will require that we prioritize socioeconomic and demographic inclusivity across clinical trial participants, investigators, and funders. All involved in the HFrEF clinical trial enterprise must commit to collaboratively innovating sustainable and scalable strategies to eliminate historical disparities and secure an equitable future for HFrEF clinical research.

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