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## **Incorporating cultural competence and cultural humility in cardiovascular clinical trials to increase diversity among participants**

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## *Introduction*

Despite the recognized importance of representativeness in clinical trials populations, the racial, ethnic, and geographic composition of cardiovascular randomized controlled trial (RCT) participants remains homogeneous, with over-representation of male, White North American and European participants relative to disease distribution.<sup>1-3</sup> Race and ethnicity are primarily sociocultural constructs that may influence treatment outcomes due to differences in socioeconomic factors, lifestyle, comorbidities, quality of care, and to a small extent, genetic polymorphisms that may affect the metabolism of select drugs.<sup>3</sup> While representativeness is important, structural racism and colonial mindsets have impeded the engagement and trust of Black, Indigenous, and People of Color (BIPOC) in the research enterprise.

Cultural competence is a set of congruent behaviours, attitudes, and policies that facilitate effective communication, engagement, and work in cross-cultural settings.<sup>4</sup> Culture is influenced not only by to race or ethnicity, but also factors such as age, gender, sexual preference, ideology, religion, socioeconomic status, education, marital or parental status, geographic region, and country. Cultural competence is a path to cultural humility, an approach that involves self-awareness, self-reflection, and empathy for the lived experience of cultural groups. Cultural humility can enhance the quality of care and rebuild trust in the research enterprise among historically marginalized groups; it entails not only an understanding of culture and beliefs, but also an ongoing reflection on one's own personal values, recognizing and seeking to address biases that arise from life experiences.<sup>5</sup>

In this viewpoint, we argue that cultural competence and humility must be incorporated into trial leadership, study teams, trial design, and execution to better engage under-represented racial and ethnic groups and geographic regions worldwide in cardiovascular research. Without an all-in commitment to cultural competence and humility, we are unlikely to achieve clinical trial diversity.

*The problem of homogeneity among clinical trial participants*

Despite recommendations for the inclusion of diverse racial and ethnic groups by federal grant and regulatory agencies, cardiovascular clinical trial populations remain predominantly male, White, and from North America and Europe.<sup>1</sup> BIPOC across the world bear the greatest burden of cardiovascular disease, but comprise a small proportion of trial participants.<sup>1</sup> In a systematic review of heart failure (HF) RCTs published between 2000 and 2020 in high-impact journals, less than 38% of RCTs reported the racial and ethnic composition of participants; in these trials BIPOC were under-represented relative to disease distribution, accounting for only 19% of 158,200 participants.<sup>2</sup> The representation of BIPOC individuals in RCTs did not increase over time.<sup>2</sup> Another review of 100 cardiovascular RCTs found that nearly half had <25% Black participants.<sup>3</sup> The limited trial recruitment in most low- and middle-income countries (LMIC) – with less than 3% of participants recruited from Africa – contributes to the under-representation of BIPOC.<sup>1</sup>

A well-designed trial with representative enrollment – defined as a trial participant to disease prevalence ratio of 0.8 to 1.2 among demographic groups – facilitates reliable estimates of treatment effect, adverse events, and subgroup differences in people living with disease.<sup>2,3</sup> The

variation in ancestry, comorbidities, nutrition, lifestyle, economic resources, healthcare access, and healthcare quality between racial and ethnic groups can influence treatment effect.<sup>2,3,6</sup> While 95% of the enrolled study participants in the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial were White, nearly 75% of Pacific Islanders are unable to convert the clopidogrel into its active form and are at higher risk for adverse outcomes.<sup>7</sup> Angiotensin Converting Enzyme inhibitors appear to be less effective in blood pressure reduction in Black versus White adults, and up to 86% of Asian adults carry a genetic variant associated with increased warfarin-related bleeding than White and Black individuals.<sup>2</sup> Homogenous trial populations, therefore, may generate data with suboptimal generalizability. Furthermore, marked imbalance in subgroups limits the statistical power required to demonstrate subgroup-treatment effect modification.

In addition to limited generalizability, the under-enrollment of BIPOC participants in clinical trials deprives them of the benefits of trial participation. These benefits include the careful care and close follow-up that trials offer, and the access to potentially beneficial therapies before they become widely available. Under-representation also limits engagement in clinical research – important in implementation at the community level at the end of the trial. Furthermore, regional exclusion from trial participation deprives LMICs and rural areas in high income countries from the research investment and expansion of clinical trial infrastructure.<sup>1</sup> Industry often views African, middle Eastern, and Asian countries as emerging markets, and invest in marketing but no research and development staff or infrastructure.<sup>1</sup>

*A history of racial, ethnic, regional and cultural inequity in research*

The reasons for under-representation of BIPOC in clinical trials are multifactorial and include historical deception, marginalization, and mistreatment of these groups in clinical research. The Tuskegee study of the natural history of syphilis among Black men long after penicillin was available as a treatment, and the acquisition and utilization of tissue from Henrietta Lacks without permission serve as examples of the exploitation of Black people by researchers.<sup>8</sup> Indigenous people were similarly subjected to unethical research, including physician-led experiments that deprived life-saving nutrition to malnourished children in Canadian residential schools; and collection of research data and biobank samples without consent.<sup>8</sup> Recent examples such as the Edmonston-Zagreb measles vaccine study - that enrolled a disproportionate number of Black and Latino infants without informing parents that the vaccine was associated with increased death in Africa - illustrate the inadequate safeguards against medical racism and exploitation.<sup>9</sup> These ethical breaches have fuelled a deep-rooted mistrust of marginalized groups in a research enterprise that, at best, has had little investment in their well-being.

The cultural insensitivity with which research is conducted parallels colonial mindsets in the healthcare system and likely exacerbates the aversion that marginalized communities feel towards research entities. Across the world, Black and Indigenous people face barriers in access to high-quality and research-active healthcare institutions.<sup>1</sup> When in contact with these institutions, they are frequently subjected to implicit biases and systemic barriers that reinforce stereotypes and further marginalize them.<sup>1</sup> The health care system itself is a culture that upholds hypotheses, ideation, protocols, and treatments driven by biomedical training and the scientific process.<sup>10</sup> Yet, many healthcare delivery and research systems are only microcosms of the larger

cultural set points in society. There may be dissonance from or prejudice against cultures which place a stronger emphasis on psychosocial and spiritual influences and on the community. Communication styles, ways of knowing, and the role of family in decision-making vary widely across ethnic and cultural groups, but trial processes do not account for this; thus, cultural competency of the research infrastructure is lacking.<sup>6</sup>

The biases in research are not isolated to participants but extend also to investigators in the form of mentorship, funding, and career advancements.<sup>9</sup> Trial executive teams, steering committees, and authorship teams are primarily male North Americans and Europeans, and often do not include stakeholders from diverse communities or LMICs.<sup>1-3,10</sup> Frontline research personnel often lack training in cultural competence and community engagement. The lack of diversity in health care governance structures, leadership teams, and among trial principal investigators limits the cultural transformation that is necessary to engage diverse participants in clinical trials.<sup>2,9</sup> Given the ethical and health implications of homogenous trial populations, there is an urgent need to apply the critical lens of cultural competence and humility to research settings.

#### *How cultural competence and cultural humility can diversify research engagement*

Greater cultural competence and humility among researchers may enhance the engagement of diverse groups in the research enterprise. Researchers with cultural competence understand the socioeconomic determinants of health and consider the values, beliefs, ways of knowing, lifestyle, and social relationships that shape the decision-making and healthcare journey of participants. These skills and attributes can guide research teams in addressing biases

that adversely impact the participant's experience in the research enterprise, communication barriers that perpetuate mistrust in research personnel, and socioeconomic barriers that challenge research participation. Cultural humility has the potential to encourage authenticity instead of conformity, offer cultural safety, and shift the focus from enrolling diverse participants to meaningfully and authentically engaging them in the research process – from trial codesign to engagement in knowledge dissemination and implementation of research findings.

*Strategies to increase cultural competence and humility in the clinical trial enterprise*

Cultural competence and humility can be enhanced through multi-level interventions (Figure 1). Funding agencies can assess research teams for cultural diversity and require trial funding applications to outline methodological approaches to engage and enrol diverse study participants. At the institutional level, implicit bias training and cultural competence workshops can help principal investigators and frontline staff improve their awareness, knowledge, and skills in culturally competent communication.<sup>10</sup> Investigators and research staff may cultivate cultural humility via institutional self-reflection workshops that include “other-oriented” approaches that reduce power differentials, build partnerships, and actively understand the lived experiences of groups with whom they will be working.

Diverse, culturally competent trial leaders can transform research conduct and processes. Trials led by diverse leaders recruit a greater proportion of diverse participants and include a greater proportion of diverse co-authors on the publication.<sup>1,2,3,10</sup> Research teams led by diverse investigators may be better equipped to ask research questions relevant to the health of diverse populations, design eligibility criteria that facilitate diverse enrolment, recruit patient using



preferred communication strategies, and develop processes that increase transparency and facilitate trust. Thus, efforts must be made to support the career advancement of culturally and geographically diverse trial leaders. Strategies must include equal opportunity, mentorship, and sponsorship, as well as funding investments to build research capacity in diverse communities and LMICs. Similarly, clinical trial executive committees could benefit from the broad perspective of diverse members, including community representatives; open calls for committee members should use inclusive, unbiased, non-gendered language.

Within every trial, efforts should be directed towards engaging culturally diverse stakeholders and implementing culturally sensitive research processes. Public and community-based engagement in research – from conception, design, and execution to dissemination of study findings – may be an effective strategy to build trust among historically marginalized groups. Communication and consent tools for patients should be designed around language, literacy, cognitive or cultural barriers. Purposeful inclusiveness that respects the values, cultural beliefs, and authentic partnership with diverse patients, community members, and organizations could help close the diversity gap that we observe in cardiovascular clinical trial participants.

### *Conclusion*

There is an urgent need to address the under-enrolment of BIPOC individuals, including those from LMICs, within cardiovascular clinical trials to ensure applicable trial findings to the diverse patient populations affected by cardiovascular disease. Implementing practices that reflect cultural competence and cultural humility is a step in promoting trust and engagement in research among under-represented groups. Multifaceted solutions are necessary to promote

cultural competence and humility and foster an inclusive research culture that prioritizes equitable research and generalizable evidence. Ultimately, cultural humility can serve as the foundation for transformative clinical trial policies including shared data governance and access, distributive justice, and reciprocity with historically marginalized populations.



**Figure legend**

**Figure 1. Strategies to overcome barriers to cultural diversity in cardiovascular research.**

Historic barriers in engaging diverse individuals in the research enterprise can be mitigated by incorporating cultural competence and humility in the leadership, design, and execution of clinical trials.

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