JACC: CARDIOONCOLOGY VOL. 6, NO. 3, 2024

HOW TO

Diversity in Cardio-Oncology Clinical Trials

JACC: CardioOncology How To

Yehoda M. Martei, MD, MSCE,[a,b] Henrietta A. Afari, MD,[c] Carmen E. Guerra, MD, MSCE[b,d]

UNDER-REPRESENTATION IN CARDIO-ONCOLOGY CLINICAL TRIALS

New cancer treatments have improved cancer survival in the last 4 decades. However, this progress has been coupled with an increase in therapy-related cardiovascular morbidity and mortality among cancer survivors. The field of cardio-oncology is positioned at the intersection of 2 disease areas that have well-established racial and ethnic disparities in outcomes as well as overlapping social and clinical risk factors. Consequently, without engagement and inclusion of diverse populations and proactive interventions to mitigate these inequities, cardio-oncology clinical trials will likely mirror or amplify long-standing racial and ethnic disparities.

A review of clinical trials that led to the approval of 24 new cardiometabolic drugs between 2006 and 2020 enrolled 187,294 participants but only included 2.9% Black participants.[1] Additionally, cancer trials of potentially cardiotoxic cancer medicines, eg, the APHINITY trial that led to the approval of pertuzumab in 2017 for use in combination with trastuzumab and chemotherapy as adjuvant therapy for human epidermal growth factor receptor 2-positive early-stage breast cancer, included only ~2% Black and ~2% Hispanic participants out of 4,804 total participants enrolled.[2] More recently, the largest U.S.-based cardio-oncology trial that assessed the efficacy of angiotensin-converting enzyme inhibitor or beta-blockers in reducing the rate of trastuzumab-induced cardiotoxicity enrolled 468 patients, ~7% of whom identified as Black and ~9% as Hispanic/Latinx.[3] Although the latter trial demonstrates more diverse enrollment of Black and Hispanic participants, there is a critical lack of reporting on race and ethnicity in cardio-oncology trials in general, especially for relatively smaller racial groups such as American Indian and Alaska Native.[3]

The Consolidated Appropriations Act signed by the Biden administration in 2022 includes the Food and Drug Omnibus Reform Act that requires clinical trial sponsors to include diversity action plans as part of study protocol submissions. This mandate emphasizes the importance and timeliness of evaluating evidence-based approaches to increasing diversity in cardio-oncology trials.

LESSONS FROM CANCER AND CARDIOVASCULAR DISEASE TRIALS. We conducted a comprehensive search of PubMed, Scopus, and Embase and did not identify interventional studies that tested clinical trial access initiatives or strategies specifically in cardio-oncology. Therefore, we sought to identify evidence-based strategies from oncology and cardiovascular disease (CVD) clinical trials that have increased participant diversity and that can be adapted to cardio-oncology trials. We modified a

From the [a]Division of Hematology Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [b]Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [c]Division of Cardiology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; and the [d]Division of General Internal Medicine, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

Eric Chow, MD, MPH, served as Guest Editor for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received October 20, 2023; revised manuscript received March 11, 2024, accepted March 15, 2024.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.03.012

HIGHLIGHTS

- Intersectionality of health inequities in CVD and cancer may compound inequities in cardio-oncology.
- Equitable access to clinical trials is 1 of many key strategies to mitigate these health disparities.
- Cardio-oncology trials should collect and report the race and ethnicity of participants, including disaggregate data on smaller minority groups.
- Successful interventions consist of multilevel strategies targeting structural-, clinical-, provider-, and patient-level barriers.

cancer clinical trial participation framework[4] and present evidence-based strategies along structural-, clinical-, provider-, patient-, and community-level barriers.

Targeting structural barriers. The majority of patients do not enroll in clinical trials because of the lack of availability of trials, including a lack of access to centers that offer clinical trials. Fundamentally, this can be addressed by increasing research funding to and building capacity at institutions that serve predominantly minority populations, leveraging minority research networks and community practice networks (eg, the National Cancer Institute Community Oncology Research Program), and decentralizing trials to community sites and incentivizing research collaborations with minority institutions (eg, American Heart Association's Strategically Focused Research Networks). The lack of access to clinical trials can also be addressed through site requirement of effective and inclusive community outreach and engagement (eg, National Institutes of Health Centers for Translational Science Awards and the National Cancer Institute's Community Outreach and Engagement).

Although the Food and Drug Administration (FDA) has called for collecting and reporting participant age, sex, race, and ethnicity for almost a decade, progress has been slow. Under the Food and Drug Omnibus Reform Act, for the first time, the FDA will have the legal authority to require sponsors of phase 3 or other pivotal drug studies to outline enrollment goals by age, sex, race, and ethnicity. The mandate includes the rationale for these goals, informed by disease prevalence or incidence among various demographic groups, and an action plan for meeting these goals including demographic-specific outreach, education and engagement, and inclusive enrollment strategies and criteria.

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

FDA = Food and Drug Administration

Addressing clinical trial eligibility. The intersection of CVD risk factors in largely older adult populations with cancer necessitates limiting the use of un-necessarily strict exclusion criteria, especially those based on comorbidities. The FDA has issued recommendations for clinical trial sponsors that broaden clinical trial eligibility criteria to consider patients with comorbid illnesses such as chronic kidney, heart, and liver disease; prior or concurrent malignancy; and extremes of weight as well as guidance for adaptive designs that allow the expansion of trial eligibility to a broader population based on interim safety data.[5] This guidance has important implications for the inclusion of patients in cardio-oncology trials because these trials recruit a population with multiple overlapping comorbidities (eg, chronic kidney disease).[5]

Moreover, the ability to speak English may disproportionately exclude minority populations. The FDA recently issued new guidelines for patients with limited English proficiency that may achieve language equity. These still allow for short-form consent for patients with limited English proficiency but require the provision of a translated long consent form in the patient's primary language as soon as it is available and approved by the Institutional Review Board.[6]

Addressing provider bias and site barriers. The proportion of eligible patients offered participation in a clinical trial varies widely (19%-76%)[7] and may reflect bias and reliance on stereotypes by researchers. These barriers may be mitigated by unconscious bias training, enhancing provider resources, and diversity in the clinical trial leadership and workforce.[8] In addition, site self-assessment tools, such as the National Cancer Institute's Clinical Trials Assessment of Infrastructure Matrix and the American Society of Clinical Oncology and Association of Community Cancer Centers' Site Self-Assessment, may help sites develop customized approaches to address barriers; develop infrastructure plans; and adopt procedures that enhance diversity, equity, and inclusion in clinical trials.[7] Long-term

JACC: CARDIOONCOLOGY, VOL. 6, NO. 3, 2024
JUNE 2024:386–389

solutions include programs to diversify the clinical trial physician workforce. Additionally, ensuring financial and adequate staff support for providers is critical to offset the effort involved in patient recruitment and enrollment.[5]

Patient- and community-facing interventions. On average, 45% of patients with cancer who are offered clinical trials decline enrollment.[9] The most common reasons patients decline trial participation are related to the treatment protocol, including side effects. This further underscores the need for community-based research approaches that involve community members with diverse cultural backgrounds in the design phase to ensure all aspects of education, engagement, recruitment, and retention are inclusive. Decentralizing trials that are conducive to implementation in partnership with community organizations offers another strategy for prevention trials and may be critical for improving the accessibility of cardio-oncology trials to underrepresented populations, including rural populations. A pivotal cluster randomized multilevel trial of 52 barbershops that enrolled a total of 319 patients reported a 95% retention rate in each arm by using multiple blood pressure screenings, ID cards, follow-up calls at 3 months, culturally specific health sessions, and payments to offset the costs of generic drugs and transportation to pharmacies.[10] The Jackson Heart study of CVD in African Americans is a 20-year prospective community-based cohort that successfully enrolled 5,306 African Americans by mobilizing community support and engagement through partnerships with 100 churches, schools, and other community-based organizations coupled with an aggressive media campaign channeled through trusted community leaders (eg, churches). These efforts began at least 1 year before trial inception.[11] This large community-based cohort now serves as a biospecimen and data repository and registry for the recruitment of Black participants into randomized CVD ancillary clinical trials. Furthermore, such resources could potentially be adapted to building cancer survivorship cohorts for the management of long-term CVD outcomes. The important elements of community engagement will vary based on cultural beliefs, preferences, community organization structures, and historical contexts and should be tailored accordingly in partnership with the respective community members.

Reactive and active recruitment methods have been shown to be more effective than indirect or passive contact. For instance, studies that only used letters of invitation without follow-up calls reported up to 44% acceptance rates among cancer patients compared to 74% in studies that used up to 15 follow-up calls to eligible participants.[8]

Additionally, the use of a nurse navigator to address patient-level unmet needs, such as transportation barriers, resulted in an acceptance rate of 86% among Black participants.[8] Clinical trial sponsors should also consider reimbursement for other out-of-pockets costs in their budgets to reduce the financial burden of trial participation, which disproportionately impacts low-income participants. Recent FDA guidance does not consider reimbursement for reasonable travel expenses to and from the clinical trial site, including airfare and lodging, as undue influence.[5]

CONCLUSIONS

There is a critical research gap of evidence-based strategies to increase diversity in cardio-oncology clinical trials. Long-standing health inequities that persist in cancer and CVD in Black and Hispanic populations experiencing a disproportionate burden of disease outcomes make it imperative to address the intersectionality of these inequities within cardio-oncology in order to avoid compounding the existing inequities.

Most of the current cancer and CVD literature focuses on increasing the enrollment of Black and Hispanic participants. Other smaller minority populations are frequently grouped as “other,” which presents a barrier to understanding the magnitude of disease burden and potential inequities in these populations. Cardio-oncology trials should collect disaggregated race and ethnicity data on smaller minority groups such as American Indian and Alaska Native to build formative research that informs risk and outcomes in these populations.

Successful interventions that improve representation in cancer and CVD trials consist of multilevel and multicomponent strategies that target the structural-, clinical-, provider-, and/or patient-level barriers.[8] Lessons from cancer and CVD trials provide evidence-based strategies that may be incorporated into multilevel interventions to increase the diversity of patients enrolled in cardio-oncology trials. Importantly, different community-based approaches along the entire continuum of clinical trial design to implementation have demonstrated the highest rates of recruitment and retention and can be systematically adapted for different minority populations.

ACKNOWLEDGMENT The authors acknowledge Maylene Qiu for her valuable help and guidance for the scientific literature search.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Guerra has received grant support from the National Cancer Institute, Genentech, the Breast Cancer Research Foundation, the American Heart Association, and the Lazarex Cancer Foundation; serves as a member of the Advisory Board of Guardant Health; and has received honoraria from the National Comprehensive Cancer Network. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Carmen E. Guerra, Perelman School of Medicine, University of Pennsylvania, 3400 Civic Center Blvd, 12 SPE, Philadelphia, Pennsylvania 19104, USA. E-mail: Carmen.Guerra@pennmedicine.upenn.edu. @GuerraViswanath, @AfariHenrietta, @ymartei.

REFERENCES

1. Chen S, Li J. Participation of Black US residents in clinical trials of 24 cardiovascular drugs granted FDA approval, 2006-2020. *JAMA Netw Open*. 2021;4(3). https://doi.org/10.1001/JAMANETWORKOPEN.2021.2640

2. Howie LJ, Scher NS, Amiri-Kordestani L, et al. FDA approval summary: pertuzumab for adjuvant treatment of HER2-positive early breast cancer. *Clin Cancer Res*. 2019;25(10):2949–2955. https://doi.org/10.1158/1078-0432.CCR-18-3003

3. Omland T, Heck SL, Gulati G. The role of cardioprotection in cancer therapy cardiotoxicity: *JACC: CardioOncology* state-of-the-art review. *J Am Coll Cardiol CardioOnc*. 2022;4(1):19–37. https://doi.org/10.1016/J.JACCAO.2022.01.101

4. Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. *J Natl Cancer Inst*. 2019;111(3):245. https://doi.org/10.1093/JNCI/DJY221

5. Enhancing the diversity of clinical trial populations-eligibility criteria, enrollment practices, and trial designs guidance for industry. 2020. Accessed October 8, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial

6. Food and Drug Administration. Informed consent. Accessed January 23, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent

7. Guerra CE, Fleury ME, Byatt LP, Lian T, Pierce L. Strategies to advance equity in cancer clinical trials. *Am Soc Clin Oncol Educ Book*. 2022;42(42):127–137. https://doi.org/10.1200/EDBK_350565

8. Arring NM, Aduse-Poku L, Jiagge E, et al. A scoping review of strategies to increase Black enrollment and retention in cancer clinical trials. *JCO Oncol Pract*. 2022;18(9):614–632. https://doi.org/10.1200/op.21.00863

9. Unger JM, Hershman DL, Till C, et al. "When offered to participate": a systematic review and meta-analysis of patient agreement to participate in cancer clinical trials. *J Natl Cancer Inst*. 2021;113(3):244–257. https://doi.org/10.1093/JNCI/DJAA155

10. Victor RG, Lynch K, Li N, et al. A cluster-randomized trial of blood-pressure reduction in Black barbershops. *N Engl J Med*. 2018;378(14):1291–1301. https://doi.org/10.1056/NEJMOA1717250

11. Addison C, Campbell Jenkins BW, et al. Twenty years of leading the way among cohort studies in community-driven outreach and engagement: Jackson State University/Jackson Heart Study. *Int J Environ Res Public Health*. 2021;18(2):696. https://doi.org/10.3390/IJERPH18020696

KEY WORDS disparities, health policy, outcomes, provider education