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## Improving representativeness in trials: a call to action from the Global Cardiovascular Clinical Trialists Forum

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1 **Improving representativeness in trials: A Position Statement from the Cardiovascular**  
 2 **Clinical Trialists Forum**

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41 **Introduction**

1  
2           Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality  
3 worldwide, affecting both sexes equally and with a disproportionate burden on older individuals  
4 and those living in low- and middle-income countries (LMICs). Trials with relatively  
5 homogenous participants who are at risk of the outcome but have no complex comorbidities can  
6 be efficient, provide precise estimates of treatment effect, and maximize the estimated safety of  
7 an intervention. Adequate and timely enrollment are important to ensure that trials are completed  
8 in time and under budget; this remains a major focus of clinical trialists. However, trials should  
9 enroll participants who are representative of those living with disease to ensure that estimates of  
10 treatment effect and safety are generalizable; subgroup analyses to assess for treatment  
11 interactions with relevant variables can be undertaken;<sup>1-3</sup> and that communities can benefit from  
12 the research infrastructure and quality healthcare facilitated by trials<sup>4,5</sup> There are also ethical and  
13 moral arguments for representativeness among research participants.<sup>1-5</sup> Finally, enrolling more  
14 representative populations would support the broad and rapid adoption of trial results into  
15 communities and lead to more equitable improvement in health (Figure 1).

16           Despite increasing awareness of the importance of representativeness, participants  
17 enrolled in CVD randomized controlled trials (RCTs) remain largely homogenous, leaving  
18 certain groups consistently under-represented relative to disease distribution (Figure 2).<sup>1,4-10</sup>  
19 While timely, efficient enrollment is often seen as a trade-off in achieving a representative trial  
20 population, it does not have to be. This narrative review summarizes evidence regarding trends in  
21 CVD trial enrollment and strategies that may increase representativeness in clinical trial  
22 populations.

### 23 **Under-represented groups in CVD trials**

24 *Older adults and children*

1 Older adults (> 65 years of age) are underrepresented in CVD trials despite having the  
2 greatest burden of CVD and a growing need for evidence-based cardiovascular care.<sup>3</sup> While the  
3 incidence of many CVDs increase with age, older adults are commonly excluded from clinical  
4 trials due to concerns about comorbidities, drug-drug interactions, and decline in physical and  
5 cognitive ability.<sup>3</sup> As a result, clinical decisions are often informed by evidence from trials  
6 involving younger, less comorbid patients in whom estimated treatment and safety effects may  
7 be different. In recent years, there has been no significant increase in enrollment of older adults,  
8 with only two large CVD trials specifically targeting older adults with heart failure (HF).<sup>12</sup>  
9 Furthermore, in a review on pharmacological management of ischemic heart disease, 53% of 839  
10 clinical trials excluded older adults, most commonly over age 75 or 80.<sup>13</sup> Given the later age of  
11 onset of CVD and HF in women, exclusion of older individuals may exacerbate the under-  
12 enrollment of women in RCTs.<sup>14</sup>

13 While pediatric cardiac conditions including congenital heart disease and  
14 cardiomyopathies have a growing global burden with downstream sequelae, children are  
15 underrepresented in cardiovascular trials. Rigorous studies examining the efficacy of  
16 medications used in children with heart disease are lacking and most cardiovascular medications  
17 are currently not labelled for pediatric use. Less than 25% of Food and Drug Administration  
18 (FDA) approved drugs have sufficient pediatric data to support their dosing, safety, and efficacy  
19 in children.<sup>15</sup> A recent study in over 30,000 children hospitalized with cardiovascular conditions  
20 revealed that 78% received more than one off-label cardiovascular medication.<sup>16</sup> Treatment  
21 decisions in children tend to be based on clinical experience, smaller observational studies, or  
22 extrapolation from adult data rather than primary evidence. RCTs are important in pediatric  
23 health to establish dosing and to generate evidence on the benefits and toxicities of

1 cardiovascular drugs in children. The reliance on anecdotal evidence and observational data to  
2 establish the safety and effectiveness of therapies – and the withholding of possibly effective  
3 therapies – puts children at greater risk than does the closely monitored setting of a clinical trial.

4       People of all ages living with physical and cognitive limitations are also underrepresented  
5 in clinical trials.<sup>17</sup> This extends to trials of healthcare services, which may be particularly  
6 relevant in people with varying ability.<sup>17</sup> Further research specific to the gaps in the  
7 representation of people with disabilities in CVD research is needed.

#### 8 *Women*

9       Despite widespread acknowledgement of the historical under-representation of women in  
10 CVD clinical trials relative to disease prevalence, and the implications on trial generalizability,  
11 little progress has been made.<sup>2,4,6,9,18</sup> Between 2000 and 2019, there were no significant changes  
12 in the representation of women in heart failure trials, with women constituting only 25% of total  
13 participants, despite accounting for approximately 40% of the disease population.<sup>6</sup> Under-  
14 representation of women relative to disease burden also occurred in trials for lipid-lowering  
15 therapies in the context of coronary heart disease.<sup>19</sup> The evidence utilized to inform decisions  
16 around drug dosing, treatment efficacy, and potential adverse effects is often extrapolated from  
17 studies in middle-aged White men, and therefore does not consider sex differences in  
18 pathophysiology, risk factors, coronary artery and cardiac chamber size, drug metabolism, and  
19 treatment effect.<sup>4</sup> These sex differences are relevant across drug and invasive interventions,  
20 including cardiac or vascular device implantations, coronary revascularization, valve  
21 replacement, and arrhythmia ablation.

22       Pregnancy and / or lactation – conditions that change physiology, volume of distribution,  
23 and drug metabolism – often serve as unjustifiable exclusion criteria due to an outdated

1 protection-by-exclusion ideology.<sup>1</sup> This leaves pregnant and lactating women vulnerable, with  
2 little safety or efficacy data to inform treatment decisions in clinical settings, and over-utilization  
3 of historical treatments recommended on the basis of small studies, observational data, or  
4 consensus of experts.<sup>20</sup> Indeed, the guideline recommendations for most cardiovascular  
5 conditions in pregnancy or lactation are informed by level C evidence.<sup>20</sup> To date, pregnant and  
6 lactating women remain susceptible to the dual risk of having potentially effective treatments  
7 withheld or receiving treatments that may have a different efficacy and safety profile than  
8 estimated in the clinical trials that excluded them.

9         Trial reporting around sex or gender does not include transgender individuals,<sup>21</sup> who are  
10 marginalized in clinical care and at higher risk of poor cardiovascular outcomes due to social  
11 factors and gender-affirming hormone therapy.<sup>22</sup> Gender differences are particularly relevant in  
12 health service and behavioural interventions, but rarely considered. With little representation and  
13 reporting around gender diverse populations, there are significant gaps in the evidence to be  
14 bridged.

### 15 *Black, Indigenous, and People of Colour*

16         Although CVD disproportionately affects Black, Indigenous, People of Colour (BIPOC),  
17 race and ethnicity data is under-reported and BIPOC participants remain underrepresented in  
18 CVD RCTs.<sup>8-9,19,23</sup> Race and ethnicity are primarily social constructs that may influence  
19 treatment effect and adverse events due to key differences in ancestry, comorbidities,  
20 socioeconomic status, healthcare access, and quality of care received. There are biological  
21 differences in drug metabolism given the unique genetic polymorphisms identified across ethnic  
22 groups, and these influence can treatment response, both safety and efficacy.<sup>23</sup> For example,  
23 Chinese Americans have a higher incidence of ACE inhibitor-induced cough than others in the

1 population.<sup>24</sup> Differences in clotting factors and enzyme mutations impact response to  
2 anticoagulants, with evidence suggesting that Asian individuals may require lower doses and  
3 Black and Hispanic individuals may require higher doses.<sup>25</sup> These differences highlight the  
4 importance of representative enrollment and reporting of race or ethnicity data in clinical trials.  
5 However, systematic reviews reveal that only a minority of heart failure and atrial fibrillation  
6 trials reported race or ethnicity data.<sup>8,26</sup> Among trials that did report race/ethnicity data, BIPOC  
7 individuals were consistently under-represented.<sup>8,19,23</sup> A review of acute coronary syndrome  
8 RCTs demonstrated that BIPOC individuals accounted for less than 25% of all enrolled  
9 participants.<sup>23</sup> The under-enrollment of BIPOC in cardiovascular drug trials is more pronounced  
10 in Europe than North America; between 2015 and 2016, Black participants accounted for 14.5%  
11 of United States-based cardiovascular drug trials and 1.3% of non-United States participants  
12 (primarily European).<sup>27</sup> These findings are consistent with an analysis of multi-national diabetes  
13 trials, which found a ten-fold greater proportion of BIPOC individuals recruited in trials led in  
14 North America versus Europe.<sup>28</sup>

### 15 *People in low- and middle-income countries*

16 While treatments could translate to the greatest reduction in mortality and morbidity in  
17 LMICs, where CVD cases and deaths are the greatest, individuals from these countries are the  
18 least represented in CVD clinical trials.<sup>7,29</sup> Benefits of engaging centers in LMICs in  
19 multinational clinical trials include the opportunity to collaborate with investigators who offer a  
20 unique perspective, test interventions in lower resource settings, obtain services at lower relative  
21 costs, enroll larger volumes of patients per center, and improve care by virtue of trial enrolment.<sup>7</sup>  
22 However, a review examining 414 heart failure (HF) RCTs found that less than 25% of trials  
23 recruited participants from outside Europe and North America, and that North America and

1 Europe were overrepresented in trials relative to global burden of disease.<sup>7</sup> Only 3% of trials  
2 recruited participants from Africa, which had the lowest participant-to-prevalence ratio of 0.1.<sup>7</sup>  
3 Without regional evidence, care that accounts for important differences in risk factors, etiologies,  
4 and access to health services is not provided, and health decisions are made based on studies that  
5 are not generalizable.<sup>29-30</sup>

6 Because of limitations in trial reporting, the representation of individuals with  
7 intersectional identities that are under-represented in trials, for example, BIPOC women in  
8 LMICs, is unknown.

### 9 **Barriers to representative trial enrollment**

10 There are numerous barriers that may limit the enrollment of certain demographic groups  
11 in CVD clinical trials.

#### 12 *Historic marginalization of BIPOC*

13 Ongoing mistrust of scientific research discourages some underrepresented communities  
14 from participating in trials and engaging with healthcare systems, although this may vary across  
15 countries. The Tuskegee study of the natural history of untreated syphilis in Black men and the  
16 propagation of tissue from Henrietta Lacks without consent are just two examples of the harm  
17 inflicted on Black people in research.<sup>31</sup> Indigenous people have been similarly harmed by  
18 unethical research, including malnutrition experiments in starving children in Canadian  
19 residential schools.<sup>31</sup> There is awareness of structural racism in healthcare and research settings,  
20 particularly in the USA, but discrimination persists. This perpetuates distrust of research among  
21 some BIPOC, likely posing a barrier to clinical trial participation.<sup>31,32</sup>

#### 22 *Recruitment and consent*



1 Recruitment in ambulatory settings is independently associated with the under-enrollment  
2 of women in CVD trials,<sup>6</sup> and may be related to the under-referral to or lack of access for women  
3 with CVD to specialized ambulatory care clinics.<sup>4,8</sup> A lack of cultural competence in trial  
4 recruitment strategies can also serve as a barrier.<sup>29</sup> For example, participants must often be fluent  
5 in English to consent to or enroll in clinical trials.<sup>1</sup>

6 Fears regarding trial participation among both potential participants and researchers may  
7 limit enrollment or consent of some groups of patients.<sup>15,20</sup> Ethical issues around informed  
8 consent in the setting of possible harm may affect children.<sup>15</sup> Parents are frequently hesitant to  
9 enroll their children in studies due to fears around lack of intervention from assignment to a  
10 placebo group and concerns regarding exposing children to potential risks without clear benefit.  
11 Similar fears pertain to pregnant or lactating women, who may hesitate to consent regardless of  
12 whether the intervention can plausibly harm a fetus or a breastfeeding child.<sup>20</sup> Drug and device  
13 interventions are independently associated with the under-enrollment of women;<sup>6</sup> the role of  
14 differential rates of consent for these interventions, potentially due to safety concerns that are  
15 inadequately unaddressed, is unclear.

#### 16 *Eligibility criteria*

17 Restrictive eligibility criteria can limit the participation of equity-deserving groups  
18 including older adults, children, and women.<sup>1,6,10,15,19,20</sup> Eligibility criteria are used in trials to  
19 select patients who are most likely to respond to intervention and least likely to experience  
20 adverse effects, whilst accruing the events required to demonstrate treatment effect to promote  
21 trial efficiency. Certain groups of patients must be excluded from trial participation based on  
22 scientifically plausible risk of harm. However, when trial exclusion criteria are too broad and  
23 without adequate justification, results may not be generalizable to large portions of the

1 population living with disease. In RCTs published in major medical journals over a 12-year span,  
2 age was the basis of exclusion in 72% of all trials with adults over 65 excluded from 38.5% of  
3 trials and children under 16 excluded from 60.1% of trials; age-related exclusion criteria were  
4 poorly justified in 78.4% of these trials.<sup>1</sup> Patients were also commonly rendered trial-ineligible  
5 due to comorbid conditions like physical disabilities, cognitive impairment, polypharmacy, and  
6 visual/hearing deficits that are common in older adults.<sup>1</sup> Additionally, a review of 283 trials  
7 published in major medical journals showed that 39% of studies excluded patients on the basis of  
8 sex-specific criteria, 10.6% on the basis of communication or language barriers and 2.1% on the  
9 basis of ethnicity.<sup>1</sup> The widespread use of sex-specific exclusion criteria – not only pregnancy  
10 and lactation, but also the presence of a functioning uterus or the lack of birth control – renders a  
11 large subset of women ineligible for clinical trial participation and is independently associated  
12 with the under-enrollment of women after adjusting for other trial design factors.<sup>6,20</sup> A review of  
13 317 heart failure RCTs showed that sex-specific exclusion criteria were present in 81 (26%)  
14 trials, none of which provided justification for their use of sex-specific exclusion criteria.<sup>6</sup> These  
15 sex-specific exclusions are common even in exercise trials among healthy participants.<sup>33</sup> The  
16 widespread conflation of pregnancy with lactation in exclusion criteria is another concern as  
17 drugs that may be teratogenic may not be secreted in breast milk, and vice versa. The research  
18 paternalism that commonly excludes women in childbearing years from trial participation,  
19 regardless of the intervention and regardless of the feasibility of pregnancy, has been accepted  
20 without question.<sup>20</sup>

### 21 *Follow-up processes*

22 Participant burden poses financial and social barriers to trial participation. The time and  
23 cost of attending frequent in-person follow-up visits may be more difficult for individuals who

1 face social and financial barriers to participation.<sup>2-3</sup> Importantly, there is intersectionality  
2 between lower socioeconomic and under-represented sex and racial or ethnic groups. Lost wages  
3 and travel expenses may disproportionately affect these groups. For individuals who rely on  
4 caregivers for transportation, like some older adults, or who have caregiver responsibilities, like  
5 many women, frequent follow-up visits may be inaccessible.<sup>2-3</sup> These effects may be exacerbated  
6 for individuals from rural regions.

### 7 *Homogenous trial leadership*

8         Diversity in the gender and geography of trial leaders is associated with greater trial  
9 representativeness. In a bibliometric analysis of trials published over two decades, men-only trial  
10 leadership was independently associated with the under-enrollment of women participants  
11 relative to trials with at least one woman leader (OR 1.32, 95% CI 1.12-3.54;P=0.047).<sup>6</sup> Another  
12 bibliometric review adjusted analysis demonstrated that trial leadership by at least one woman  
13 was independently associated with 8.4% (95% CI, 1.9%-15%;P=0.013) increase in BIPOC  
14 enrollment and twice the odds of reporting race and ethnicity data (OR 2, 95% CI 1.1-  
15 3.8;P=0.028) than trial leadership by men.<sup>6,8</sup> Reasons for this are unclear, and may include  
16 purposeful attention to cultural competency, inclusion of under-represented groups, and designs  
17 that minimize participant research burden in trials led by women, although these need further  
18 exploration.<sup>6-8</sup> In another systematic review, trial leadership outside Europe and North America  
19 was independently associated with ten-fold odds of recruitment in regions outside Europe and  
20 North America, possibly due to greater local access to recruitment pools.<sup>7</sup> Benefits of diverse  
21 trial leadership may extend beyond trial representativeness; diverse trialists are more likely to  
22 have diverse authorship teams and steering committees,<sup>34</sup> may ask research questions and design

1 trial protocols that address the needs of under-represented populations, and may work to increase  
2 research capacity, infrastructure, and human capital in diverse communities.<sup>8,31</sup>

### 3 *Limited research infrastructure*

4 Inadequate research infrastructure in LMICs and in some rural regions in higher income  
5 countries limit trial participation of individuals living in these regions. The World Health  
6 Organization found that while 7% of African countries have moderately developed research  
7 capacity, greater than 90% have minimal or no research capacity.<sup>30</sup> With limited research  
8 capacity due to a combination of factors such as insufficient access to funding, lack of  
9 institutional resources including electronic medical records, and public uncertainty in research,  
10 there are fewer locally-led trials to recruit participants from these regions.<sup>30</sup> Still, even in the  
11 LMICs where significant progress has been made in capacity building and regulatory framework,  
12 industry sponsors do not venture much in enrolling patients in these countries. While  
13 international research collaboration has become more common, some of these partnerships have  
14 been criticized for employing a paternalistic approach that promotes “hit-and-run” research  
15 which is conducted by high-income researchers in low-income countries without promoting  
16 sustainable capacity development, meaningfully involving local investigators, or addressing  
17 questions relevant to local populations.<sup>30</sup>

18 Despite efforts from regulatory and funding agencies to promote representative  
19 enrollment in clinical trials beginning in the 1990s, progress has been slow. The United States  
20 Food and Drug Administration (FDA) has published guidance for sponsors to promote  
21 representative enrollment, while the National Institutes of Health (NIH) ties funding to the  
22 inclusion women and diverse racial and ethnic groups in trials.<sup>35-37</sup> Similar guidance documents  
23 for representativeness and for sex and gender based analysis have been published in the United

1 Kingdom by the National Institute for Health and Care Research and in Canada by the Canadian  
2 Institutes of Health Research.<sup>38-40</sup> Despite these recommendations, trials continue to have  
3 inadequate representativeness. Among 142 NIH-funded RCTs published in 2015, only 13% of  
4 trials analyzing or reported outcomes by race or ethnicity, and 15% of trials enrolled less than  
5 30% women.<sup>41</sup> Temporal trends in the enrollment of women in heart failure trials published in  
6 high impact journals have not changed over 20 years, although enrollment of BIPOC and  
7 reporting of results according to sex or gender and race or ethnicity has increased.<sup>6,8,21</sup>

## 8 **Strategies to Increase Representativeness of CVD Clinical Trial Participants**

9         Several multi-level strategies could increase representative enrollment of participants in  
10 CVD RCTs. Importantly, the knowledge gaps in any under-represented group are likely  
11 amplified in individuals with overlapping marginalized identities, such as female patients who  
12 are BIPOC.<sup>31</sup> As such, trial teams should pay particular attention to including individuals with  
13 intersectional identities in clinical trials.

### 14 *Trial Level Strategies*

15         Clinical trials can be designed to increase representativeness in CVD trials, with  
16 purposeful strategies applied at each trial step. Community-based participatory research and  
17 engagement of people with lived experience as research partners and steering committee  
18 members can be useful in improving trial design and enhancing trust in the research enterprise.  
19 Collaboration with community advisory boards and patient advocacy groups can inform research  
20 questions, enhance trial recruitment, and improve knowledge dissemination and implementation  
21 in the community.<sup>42</sup>

22         Recruitment strategies can be designed to promote diversity. Meaningful research  
23 partnerships between trial teams, patients, and community organizations can effectively engage

1 under-represented communities, build trust, and address the socioeconomic and cultural factors  
2 that influence patient willingness to participate in trials. Recruitment strategies that include  
3 digital platforms and community-based settings can aid in diversifying participants. The use of  
4 digital communication tools provides opportunities to increase the scale of clinical trials and  
5 eliminate barriers created by in-person recruitment. Mobile-application-based recruitment  
6 approaches can be effective in increasing gender, race and ethnicity representativeness.<sup>43</sup> Trial  
7 sites can be selected strategically to increase the enrollment of historically marginalized groups.  
8 Machine learning algorithms can be used to connect eligible patients to trials through the use of  
9 natural language processing which could be used to analyze clinical trial databases and electronic  
10 medical records, identify eligible patients based on demographics, and connect them to the right  
11 trials.<sup>44</sup> Adaptive enrichment strategies based on interim analysis of who is enrolled could help  
12 shift recruitment efforts towards groups that are under-represented.

13         Input from patient partners could be used to create recruitment materials that are tailored  
14 to the cognition, literacy, language, and culture of individuals living with disease in the region of  
15 recruitment; the costs associated with translation can be a deterrent but should be considered an  
16 ethical and scientific obligation and accounted for in grant funding requests. Finally, adaptive  
17 recruitment strategies, which provide the opportunity to continuously modify recruitment  
18 strategies to meet participant diversity targets, could be considered.<sup>2</sup> Prioritizing inclusivity and  
19 cultural competence in all study processes and materials may not only enhance diverse  
20 enrollment, but also translate to better adherence to the intervention and better trial retention.

21         Pragmatic and well-justified eligibility criteria can facilitate more representative  
22 enrollment.<sup>1</sup> Sex-specific eligibility criteria that broadly render women of childbearing age  
23 ineligible should be eliminated; categorical exclusions of pregnancy and lactation should be

1 justified by biological probability or pre-trial evidence of harm.<sup>1,6</sup> Similarly, exclusion criteria  
2 based on age and comorbidities should be adequately justified (Table 1) and those based on  
3 language, race or ethnicity, education level, socioeconomic status, cognitive ability, physical  
4 ability, written or spoken language ability, or chronic health conditions should be avoided.<sup>1</sup>  
5 When there is uncertainty regarding the safety of intervention in certain populations, experts (e.g.  
6 obstetrical specialists for trials involving pregnant women) could be consulted and included in  
7 the trial committees.

8         Consent processes that are carefully designed to match the needs of the participants,  
9 accounting for health literacy, language, culture, and level of education, can promote the  
10 engagement of diverse individuals. Positive patient- or family-facing interactions in the consent  
11 process may help potential participants make better informed decisions regarding trial  
12 participation.<sup>15,45</sup> This may be especially important in BIPOC patients, women, and other  
13 marginalized individuals who exhibit mistrust in medical research due to systemic  
14 discrimination. Digital consent tools can make the research consent process more accessible to  
15 some and can be offered based on patient preference.

16         Efforts can be made to reduce the unique barriers to follow-up that individuals of diverse  
17 identities face when participating in clinical trials. Women, BIPOC, older adults, and people  
18 living in LMICs experience a variety of social challenges, including lower socioeconomic  
19 status.<sup>29-30</sup> Consulting with patients, community organizations, and local healthcare workers may  
20 provide trial teams with a better understanding of the unique barriers to trial participation and  
21 follow-up that some groups face. Solutions for these barriers may include reimbursing  
22 participants for costs associated with transportation and childcare, offering flexible clinic hours,  
23 utilizing remote follow up when possible, and accommodating individuals with physical and

1 cognitive disabilities. Site-less trials are becoming more popular and rely exclusively on virtual  
2 encounters.<sup>46</sup> Trials can be embedded in registries or administrative datasets for clinical  
3 outcomes such as death or hospitalization to be determined without research burden on patients.  
4 <sup>47-48</sup>

5 Trial analysis and reporting could present evidence that better informs the care of patients  
6 living with disease. Subgroup analysis and tests for effect modification can provide evidence on  
7 whether treatment effect varies by subgroups in the trial population. Demographic characteristics  
8 that may affect prognosis or treatment effect should be thoroughly investigated. Tools like the  
9 Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) can aid this  
10 analysis.<sup>49</sup> Trial reporting should include baseline characteristics disaggregated by demographic  
11 variables like sex and race/ethnicity. Furthermore, reporting consent rates by demographic  
12 variables, and reflecting on potential barriers to consent for different groups may be fruitful in  
13 promoting inclusion in future trials.<sup>6,21</sup> Adequate analysis and reporting, along with pooled  
14 analyses of conceptually similar trials, may generate more robust and generalizable forms of  
15 evidence.

#### 16 *Institutional Level Strategies*

17 Equal opportunity in academic settings can promote better representation of diverse  
18 populations in clinical trial leadership. Diversity amongst trial leadership facilitates gender,  
19 racial, and ethnic representation in CVD clinical trials. To harness the strength of women and  
20 BIPOC as clinical trial leaders, academic settings should create an inclusive and equitable  
21 institutional culture, including research salary support, advancement, and mentorship  
22 opportunities to build and maintain capacity for women and diverse researchers (Figure 3). By  
23 conducting rigorous longitudinal monitoring of inequities within their organizations, institutions



1 can better identify and address gaps that disadvantage women and BIPOC researchers. A culture  
2 of respect and accountability not only helps current women and BIPOC in the field but also  
3 encourages more diverse learners to pursue cardiovascular research.

4 Cultural competency training can create trial teams that are well-equipped to understand  
5 the unique needs of diverse trial populations.<sup>31</sup> Staff on a culturally competent trial team will  
6 understand historical and current health inequities and the ways that research can alleviate  
7 them.<sup>31</sup> Cultural humility – reflecting on one’s own cultural identity and aiming to unlearn  
8 cultural beliefs deeply rooted in global power imbalances – can provide researchers with a  
9 perspective that cracks the ethnocentric lens through which Western research is conducted.<sup>31</sup> For  
10 example, the trial team for a trial testing a digital health intervention spent time cultivating  
11 relationships and understanding the values of African American women at risk of CVD.<sup>50</sup> This  
12 involved creating a community advisory board with members from faith-based and community  
13 organizations to help with trial design and execution, consulting with community members on  
14 appropriate cultural messaging for the intervention, and recruiting participants through churches  
15 and community centers.<sup>50</sup>

16 Training a diverse group of clinical trialists may promote more equitable trials in the  
17 future. The CardioVascular Clinical Trialists (CVCT) Future trialists fellowship program and the  
18 US National Heart, Lung, and Blood Institute (NHLBI) supports the development of early career  
19 researchers from underrepresented backgrounds, providing awardees the opportunity to serve on  
20 trial steering committees.<sup>51</sup> Societies such as the American College of Cardiology and American  
21 Heart Association as well as catalyst organizations provide diverse investigators with short  
22 training courses and networking opportunities. The European Society of Cardiology offers a  
23 master’s degree in clinical trials, with a focus on applicants from under-represented regions of

1 the world.<sup>10</sup> Individual scientists can make a difference by funding individuals from under-  
2 represented regions of the world to train as clinical trialists; the senior author of this manuscript  
3 has started such a fellowship program.

#### 4 *Global Level Strategies*

5         Increasing the representativeness of CVD trials worldwide involves action at the global  
6 level to improve infrastructure in regions with low research capacity. Strategies to increase  
7 research capacity involve international research collaboration, citizen engagement, and  
8 promoting research readiness in the healthcare system.<sup>30</sup> International collaboration that builds  
9 sustainable and equitable partnerships can provide better access to funding and technology,  
10 improve representative trial enrollment, increase internationally recognized scientific output, and  
11 investigate research priorities that are pertinent to the local population.<sup>7,29-30</sup> Global organizations  
12 like the CVCT Middle East, Mediterranean and Africa (CVCT-MEMA) aim to connect  
13 stakeholders, promote collaboration, and enhance research capacity in the area. The necessary  
14 human capital and expertise to lead CVD trials can be fostered by increasing opportunities for  
15 remote research training and fellowships, exchange programs, and visiting professorships. Grants  
16 and travelling fellowships from high-income countries, pharmaceutical and device companies, or  
17 professional societies could provide a promising solution to improving local LMIC research  
18 capacity.<sup>7,29-30</sup>

19         Action at the global level should involve funding policy that incentivizes representative  
20 trial enrollment and encourages accountability. Industry and grant funding agencies such as the  
21 US NHLBI and Global Alliance for Chronic Disease (GACD) can ensure more equitable policies  
22 by explicitly requiring inclusion of locally situated investigators for multicenter trials to ensure  
23 adequate representation.<sup>51</sup> Although industry sponsors have started to recognize the importance

1 of adequate representation by instating a Chief Diversity Officer, further transparency with  
2 clearly outlined goals and responsibilities are required in order to ensure accountability and  
3 monitoring of progress.<sup>30</sup>

#### 4 **A call to action: enrollment and reporting**

5 We call on the global scientific community to prioritize representative inclusion in CVD  
6 clinical trials. By implementing strategies throughout the research enterprise, the CVD clinical  
7 trial landscape can become one that serves the entire population equitably. We encourage trialists  
8 and institutions to hold themselves accountable to this goal and suggest a five-year timeframe for  
9 clinical trials to achieve representative enrollment with a participant-to-prevalence ratio of 0.8-  
10 1.2 for age, sex, and ethnicity in a given region. A participant-to-prevalence ratio in this range  
11 ensures that trial participants reflect those living with the disease. Over this time, we advocate  
12 for an approach that improves trial design, analysis, and results. Meaningful improvements in  
13 trial design first require the identification of key demographic variables pertaining to a research  
14 question and evaluation of their potential effect on prognosis and treatment. Trial teams should  
15 adopt inclusive recruitment strategies, eliminate unjustified exclusion criteria, and reduce  
16 barriers to trial participation. Trials should report results that inform care for populations living  
17 with disease by reporting baseline characteristics that include sex or gender, race or ethnicity,  
18 regional of enrollment. Consent rates and trial flow should be disaggregated by sex to assess the  
19 reasons and extent of under-representation in treatment effect estimates.<sup>21</sup> Within trial analysis,  
20 trialists should plan subgroup analysis of the primary outcome that include key demographic  
21 variables that could modify treatment effect; and use evidence-based tools for analysis like the  
22 ICEMAN instrument for robust subgroup analysis.<sup>49</sup> Adverse events should also be  
23 disaggregated by sex.<sup>21</sup> Subgroup analysis should be incorporated into the abstract, methods,

1 results, and discussion of a paper. Finally, we call upon trialists and institutional leaders  
2 worldwide to increase recruitment of trial participants from under-represented regions by  
3 collaborating to promote sustainable research development in LMICs. In absence of trial  
4 representativeness and biological plausibility of variation in treatment or safety effect in an  
5 under-represented group, results should be applied to all demographic groups so that we do not  
6 doubly jeopardize underrepresented groups and deprive them of care.

## 7 **Conclusion**

8         The continued under-enrollment of older adults, children, women, BIPOC, and those  
9 from LMIC reduces the generalizability of high-quality RCTs, ultimately exacerbating existing  
10 health inequities that negatively impact these populations. Strategies at several levels – global,  
11 institutional, and trial design – could facilitate more diverse participant enrollment.

12 Representativeness in CVD trials could ensure that estimates of treatment efficacy and safety are  
13 generalizable, that subgroups are balanced and powered for meaningful analysis, and that there is  
14 equitable evidence available to guide decisions at the point-of-care, ultimately creating a culture  
15 of health justice within cardiology.

## 16 **Credit statement**

17         HGCV conceived the manuscript and supervised the work. LF, JWZ, FD and HGCV  
18 drafted and edited the manuscript. All authors edited the manuscript and approved the final  
19 version.

## 20 **Data availability**

21         No new data were generated or analysed in support of this research.

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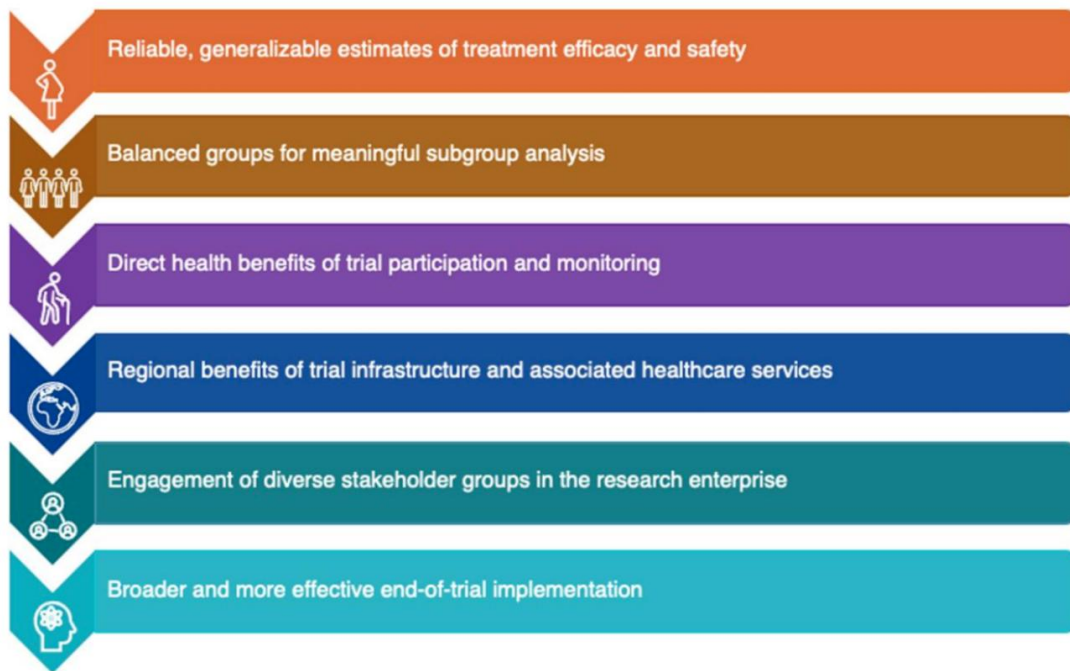
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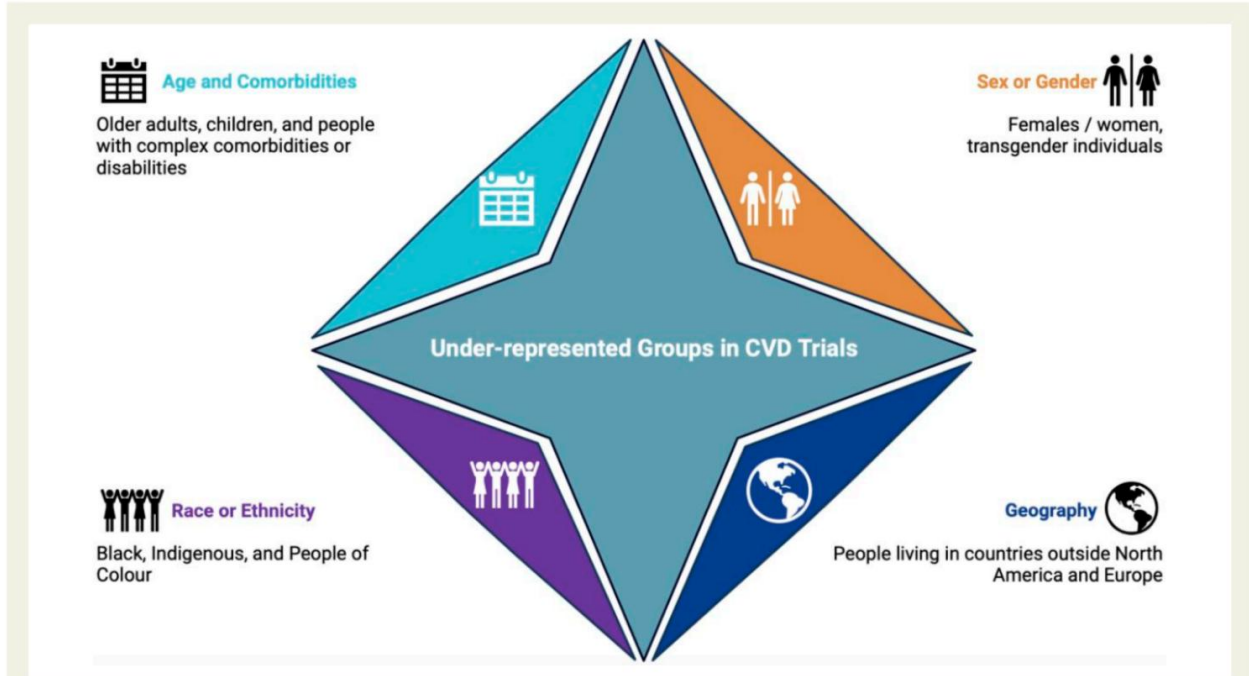
**Graphical Abstract**



1 Barriers to enrollment of diverse populations and strategies to achieve representative enrollment in cardiovascular clinical trials.

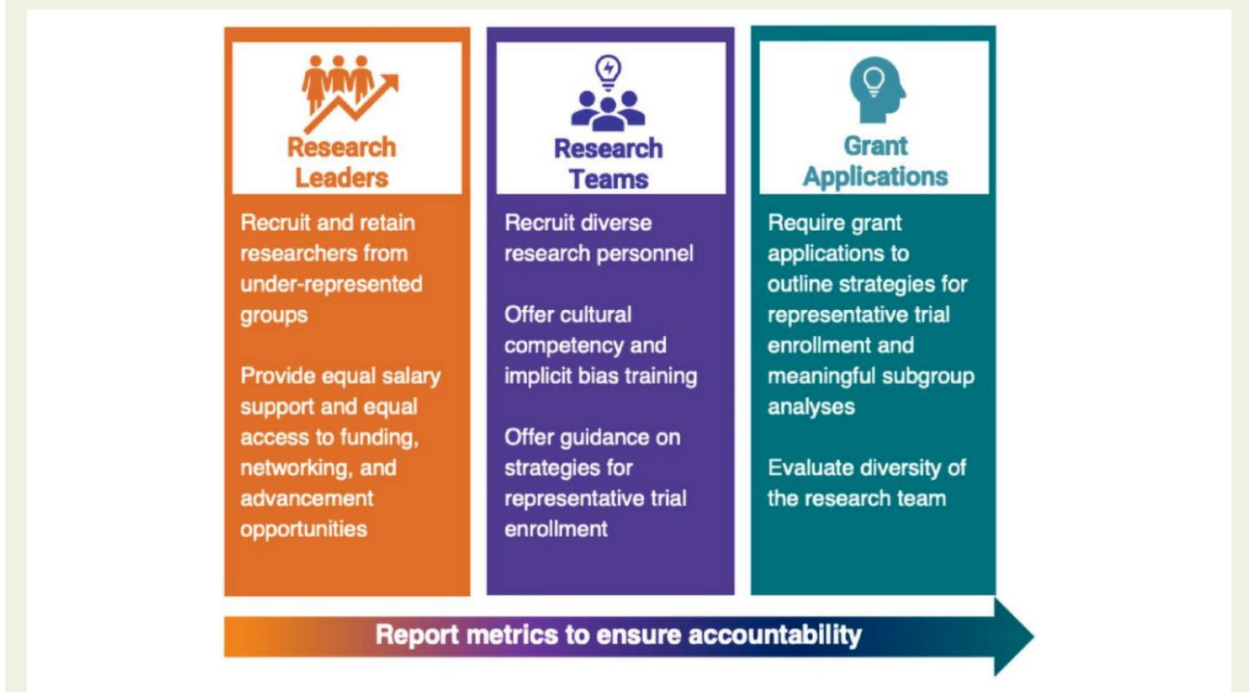


2 **Figure 1** Benefits of representativeness in cardiovascular clinical trials.



**Figure 2** Under-represented groups in cardiovascular randomized clinical trials.

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**Figure 3** Institutional strategies to improve representativeness in the cardiovascular trial enterprise.

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1 **Table 1** Justification scheme for eligibility criteria being considered for an RCT. *Adapted from*  
 2 *Van Spall HGC, Toren A, Kiss A, Fowler RA. JAMA 2007<sup>1</sup>*

<b>Adequate justification for exclusion</b>	<b>Inadequate justification for exclusion</b>
<p>Lack of consent</p> <p>Trial participation is likely to cause harm</p> <ul style="list-style-type: none"> <li>- There is unacceptable or known risk of harm from the intervention</li> <li>- There is unacceptable risk of harm from withholding the intervention (i.e. allocation to placebo)</li> </ul> <p>Individual is unlikely to receive benefit from the intervention</p> <ul style="list-style-type: none"> <li>- Individual is unlikely to have the condition of interest or a phenotype that will respond to the intervention</li> <li>- Individual is not at risk for the outcome during the follow-up period</li> <li>- Individual is at imminent risk of death or the outcome (i.e. unmodifiable risk)</li> </ul> <p>Effect of intervention will be difficult to establish</p> <ul style="list-style-type: none"> <li>- Individual is unlikely to adhere to the trial protocol</li> <li>- Individual has a cointervention that will influence the treatment effect</li> <li>- Individual has a comorbidity that will make the treatment response difficult to detect</li> </ul>	<p>Is not an adequate justification for exclusion</p> <p>AND</p> <p>Exclusion is based on <math>\geq 1</math> of the following factors</p> <ul style="list-style-type: none"> <li>- Age</li> <li>- Sex or gender</li> <li>- Sex-specific conditions (menstruation, pregnancy, lactation)</li> <li>- Race, ethnicity, culture, or religion</li> <li>- Spoken or written language ability</li> <li>- Educational background</li> <li>- Socioeconomic status</li> <li>- Cognitive ability</li> <li>- Physical ability or disability</li> <li>- Chronic health condition</li> </ul>

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**Table 1.** Adequate and inadequate justification for excluding individuals from RCTs. Adapted from Van Spall HGC, Toren A, Kiss A, Fowler RA. JAMA 2007. <sup>1</sup>

**Figure 1.** Justification for increasing representativeness of under-represented groups in cardiovascular randomized clinical trials

**Figure 2.** Under-represented groups in cardiovascular randomized clinical trials

**Figure 3.** Factors associated with under-representation of certain demographic groups in cardiovascular trial participation

**Central illustration.** Barriers to under-enrollment of diverse populations in cardiovascular clinical trials and strategies to achieve representative enrollment