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Research paper

## Protection by inclusion: Increasing enrollment of women in cardiovascular trials

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### ABSTRACT

Despite differences in biology that influence disease incidence, drug metabolism, and response to therapies, women remain under-enrolled in cardiovascular clinical trials. Estimates regarding treatment efficacy and safety are derived from male-predominant trial populations, with inadequate balance between sex subgroups for meaningful analysis on sex-specific treatment effects. Treatment strategies for women, particularly women of childbearing years, are derived from trials with predominantly men participants, from lower quality, observational studies, or anecdotal evidence. Guideline recommendations for women who are pregnant or lactating are typically based on opinion as there is little evidence to guide them. In this review, we discuss trial design factors independently associated with the under-enrollment of women, identify possible strategies to increase the enrollment of women in trials, and suggest multi-level actions that could close sex-based research disparities. Recruiting and retaining women trialists, independently associated with increased enrollment of women and Black, Indigenous, and Persons of Color (BIPOC) participants, and diversifying research teams may be effective approaches. Modifying trial design by eliminating default sex-specific exclusion criteria, developing patient-centered consent and participation processes, incorporating pragmatic follow-up schemes, and incorporating sex/gender analysis into trial planning may also increase the enrollment of women participants. Journals and funding bodies should require trials to report participant to prevalence ratios, sex-disaggregated trial flow, and sex-treatment interactions. Healthcare systems can help create research-ready cultures that both enhance patient engagement in trials and expedite end-of-trial knowledge translation.

### 1. Introduction

While cardiovascular disease is a leading cause of death among women [1], the randomized controlled trials (RCTs) that inform care under-enroll women relative to sex distribution of disease. Trials do not consistently account for sex-based biological differences and are often inadequately powered to test for sex differences in treatment effect. Despite recommendations by regulatory and funding institutions to promote sex enrollment in cardiovascular RCTs [2], women remain under-enrolled relative to disease prevalence, with ensuing knowledge-gaps in optimal drug dosing, treatment efficacy, and treatment safety. Strategies to increase enrollment of women proportionate to disease prevalence remain to be tested but may include addressing trial design

factors associated with under-enrollment of women, adopting adaptive enrollment schemes, and including patient-centered processes for consent and trial participation. Journals should require reporting on sex-specific participant-prevalence ratios and meaningful analysis of sex differences, including testing for sex-treatment interactions.

### 2. The rationale for representative inclusion of women in RCTs

Representativeness in a well-designed and adequately powered clinical trial can help ensure that 1) the estimated treatment effect both efficacy and safety reflect treatment response in patients living with the disease and 2) subgroup differences are explored meaningfully. Treatment effects established in RCTs with primarily White men may not

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reflect the heterogeneous treatment responses evident when broader demographic groups are included in trials. For example, there are sex differences in the burden of cardiovascular risk factors and in physiology, response to interventions, and drug metabolism [3]. Sex-specific conditions such as polycystic ovarian syndrome, gestational diabetes, hypertensive disorders of pregnancy, and pregnancy loss are associated with an increased risk of cardiovascular disease [1]; and traditional cardiovascular risk factors and comorbidities differentially influence cardiovascular risk in women than men [1]. Additionally, women have differences in cardiovascular physiology including smaller left ventricles, reduced stroke volume, and decreased coronary artery diameters than men [4,5]. Women respond differently to cardiovascular pharmacologic treatment due to sex differences in pharmacokinetics [1,6], and may have different procedural and device complication rates, partly related to devices designed for male anatomy [7]. However, efficacy and safety estimates for most cardiovascular interventions are based on men-predominant trial populations and knowledge regarding sex-specific differences often relies on observational data which take years to accrue after the end of a trial. Approvals for drugs and devices have historically not required representation of women proportionate to disease prevalence nor reporting of sex-specific treatment effect [8].

### 3. Under-representation of women in RCTs

Despite the implications of biological differences on the efficacy and safety of interventions, women have long been under-enrolled in RCTs. This is partly due to a historic characterization of male anatomy and physiology as standard within research and the female body as complicated and vulnerable due to fluctuating hormones and child-bearing potential. Research using animal models – which underpin human clinical research – has historically relied on male subjects for this reason [9]. This characterization of male anatomy and physiology as the standard upon which inferences should be based has been adopted readily in clinical trials. For example, among 317 RCTs in Heart Failure with reduced ejection fraction, only 25% of participants were women, with no change in temporal trends between 2000 and 2019. More than 70% of the trial under-enrolled women relative to disease prevalence (participant-prevalence ratio < 0.8) [10]. Similarly, women remained under-represented in cardiometabolic drug trials between 2008 and 2017 [11]. Women are even under-represented in exercise and sports physiology trials [24].

Without an adequate evidence base in women, drug dosing and estimates of treatment efficacy and safety are derived primarily from men. Women in clinical settings, including those pregnant and lactating, may be offered treatment that has a different efficacy or safety profile than evident in clinical trials; in some cases, potentially harmful treatment may be offered, and beneficial treatment withheld [1,10,12,13]. While meaningful sex-specific analysis requires the sample size of each group to be adequate and balanced, trials are often inadequately powered for sex-specific analysis. Sex subgroup analysis, when reported, rarely tests for sex-treatment interactions [6,10].

Women with childbearing potential, those pregnant or lactating, and those from marginalized groups including Black, Indigenous, and People of Color (BIPOC) are particularly susceptible to trial under-enrollment [12–14]. Trials that exclude pregnant and lactating women due to a protection-by-exclusion mentality often also exclude those with child-bearing potential, and these exclusion criteria are independently associated with the under-enrollment of women in RCTs, even for conditions that primarily affect older adults [1,10,12]. Sex specific exclusion criteria are often unjustified in the context of the trial that applies them [13]. Results from trials in non-pregnant women cannot be safely extrapolated to pregnant women due to differences in physiology and drug metabolism. In fact, most cardiovascular therapies have no clinical trial safety or efficacy data to support their use in pregnant or lactating women [13], and major guideline documents designate most treatments for these populations as ‘C’ [14]. This “protection by exclusion”

philosophy also extends to exercise trials, such that recommendations for physical activity in healthy pregnant and lactating women are not guided by high quality evidence [24]. Pregnant and lactating women are thus deprived of the benefits of modern-day therapies and interventions that improve outcomes in other groups. In this context, pregnant women may be safer as trial participants receiving careful monitoring than subject to untested or ineffective therapies in clinical settings. Indeed, trial participants in both placebo and intervention groups appear to have better outcomes than their counterparts who are not enrolled in trials [13].

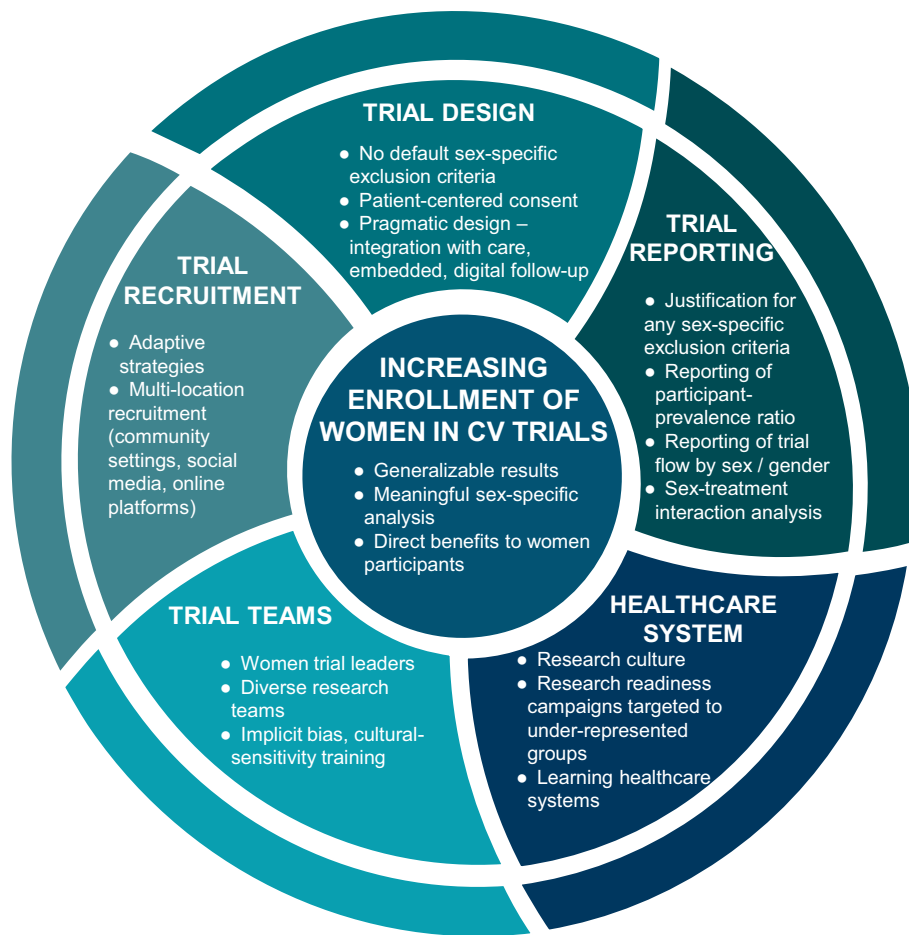
### 4. Strategies to increase enrollment of women in RCTs

Factors associated with under enrollment of women based on analyses of HF RCTs published in high-impact journals over 2 decades include men-only trial leadership teams, sex-specific eligibility criteria, and recruitment in ambulatory settings [8]; addressing these (Fig. 1) may improve the enrollment of women in trials. The presence of women trial leaders is independently associated not only with increased enrollment of women, but also of BIPOC participants [10,15]. The reasons for this are unclear, but may relate to the research questions that women investigators seek to answer (possibly of more relevance to diverse participants), the associated diversity of team members that steer the trial or recruit patients into it [16], and more patient-centered trial design elements that minimize research burden on participants [17,18]. Steps to increase the recruitment and retention of women trialists may include implementing objective, equal-opportunity processes for mentorship, sponsorship, research funding, salary support, publications, and career advancement [19]. Medical education on sex-differences in cardiovascular health and the need for representative enrollment may encourage the emerging era of clinical trialists to achieve research equity for patients living with cardiovascular disease.

The use of sex-specific exclusion criteria in phase III trials should be limited to cases in which they are justified. The blanket exclusion of women in childbearing years should no longer be considered ethically justifiable. The exclusion of pregnant or lactating women should be limited to trials with interventions that have preceding evidence – rooted in biological plausibility, animal models, or observational data – of harm to the fetus or the breastfeeding child [12]. Pregnancy and lactation should not automatically be combined into a single exclusion criteria as some drugs that may be teratogenic are not secreted into breastmilk [12]. If there is uncertainty around including pregnant or lactating women, trial teams can involve maternal-fetal medicine specialists so they can lend their expertise to the decision-making process.

The under-enrollment of women in trials with drug or device/surgery interventions [8] may reflect a need for more patient- and family-centered discussion around trial participation to obtain consent from women. There is some evidence that women may be more risk averse and less inclined to consent to RCT participation [20]; the under-enrollment of women in trials of drug, device, and surgical interventions relative to health service interventions [10] may be related to perceptions of risk, for example, although there is no direct data to support this [9].

Recruitment and retention strategies should be tailored to women and under-represented groups. Recruitment in ambulatory settings is independently associated with under-enrollment of women in heart failure RCTs [10], which may be related to barriers in approaching or engaging women as trial participants in these settings. Trials should engage patients as research partners to incorporate their perspectives into the recruitment and trial design process [17–19]. Cultural and socioeconomic factors must be considered in recruitment strategies, and frontline personnel must demonstrate cultural competence and cultural humility in their interactions with patients. Online and social media platforms as well as community-based recruitment strategies that target places frequented by women – grocery stores, community centers, places of worship – may be strategic. Providing options for remote follow up or



**Fig. 1.** Increasing the enrollment of women in cardiovascular trials. Strategies undertaken at the society/healthcare systems and trial level can promote the enrollment of women in cardiovascular randomized control trials. Representative enrollment of women in trials provides numerous benefits.

extended clinic hours may ease the research burden on women who may rely on hourly wages or provide caregiver roles [1,21]. Providing reimbursement for costs related to participation, including transportation and childcare costs could promote enrollment. When targets for enrollment have not been met, adaptive recruitment schemes, which allow ongoing trials to modify their recruitment process to meet enrollment goals, can be considered [22].

Funding bodies and journals must require trials to report the participant to prevalence ratio (PPR) and outline the strategies undertaken to enroll women proportionate to the sex distribution of a disease. When the PPR is beyond 0.8–1.2 in the region of recruitment, justification must be provided. Authors should report the sex of patients approached, eligible, consented, and included in the study, which could help limit bias and provide insight into factors involved in the ongoing underrepresentation of women [10]. Funding bodies and journals must require authors to undertake analysis of sex as a biological variable, including subgroup analysis that tests for treatment effect modification by sex [21]. Trialists should incorporate sex into the design, analysis, and discussion of the study, explore the implications of sex on the generalizability of the results, and provide justification when sex-specific analysis is lacking.

Healthcare systems must create a research-ready culture to enhance the engagement of patients in research. Systems that integrate research with everyday care and capitalize on digital health can facilitate the rapid adoption of research findings into clinical practice (learning healthcare systems) and also increase the participation of traditionally under-represented groups [10,15] in research. Healthcare systems can

conduct educational campaigns to promote research acceptance and research readiness among patients. Electronic health records (EHR) can be used to screen patients and decrease research burden on frontline staff. EHR or administrative databases can be used for outcome assessment and follow-up so as to minimize burden on trial participants [23]. These and other pragmatic design elements that decrease research burden on patients may facilitate enrollment of representative populations and improve trial generalizability.

The historical and current underrepresentation of women in cardiovascular trials has created knowledge gaps, limited the generalizability, and exacerbated disparities in healthcare. While strategies to close the gap in trial representation remain to be tested in well designed-studies, observational data points to important factors that must be addressed to confront research inequities and make a tangible difference in the lives of women worldwide.

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#### Credit statement

HGCV was invited to author the editorial. LF and HGCV drafted and edited the manuscript. MK edited the manuscript. HGCV supervised the work. All authors approved the final version.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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