

Clinical Trial Equity: From Design and Patient Recruitment to Investigator Opportunities

A multipronged approach is required to improve gender inclusivity in clinical trials and increase female representation in academia and senior clinical roles.

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Cardiovascular disease is the leading cause of mortality worldwide. In 2019 alone, 35% of all deaths in women were due to cardiovascular disease.¹ Differences have been recognized between men and women in etiology, disease progression, management strategies, efficacy of interventions, and cardiovascular outcomes.²⁻⁹ It is therefore necessary to have equal and equitable participation of women in clinical trials to ensure adequate understanding of the sex- and gender-specific differences in pathophysiology and response to interventions—and their influence on outcomes. Even after correction for sex-specific prevalence, women are underrepresented in drug trials for heart failure and coronary artery disease.¹⁰ It has been posited that inclusion and exclusion criteria of trials may favor men.¹¹ In this article, we consider the potential barriers to equitable inclusion of both sexes in clinical trials, as well as the underrepresentation of women in academia and senior clinical roles.

THE DESIGN OF CLINICAL TRIALS

In order to draw meaningful conclusions from clinical trials and allow generalizability, there must be adequate numbers of patients who are representative of the disease population recruited to and retained within the trial. Historically, women have been underrepresented

in clinical trials, and indeed, several large trials in cardiovascular disease—including the Multiple Risk Factor Intervention trial¹² and the United States Physicians Health study¹³—exclusively studied men. In 1985, the United States Public Health Service Task Force on Women's Health reported that women's health care was compromised by the lack of research focusing on women's health.¹⁴ Despite this, prior to 1993, there was neither obligation on researchers to include women in clinical trials nor obligation to analyze results by gender. In 1993, the National Institutes of Health (NIH) recommended that women should be included in clinical trials in "the same proportions as in the [United States] population having the disease entity being studied" and required all investigators funded by the NIH to include women as well as men in their trials.¹⁵

Certain exclusion criteria, such as pregnancy, breast-feeding, and being of childbearing age, are sex-specific and thus may potentially reduce participation in clinical trials. Historically, this was due to the classification of pregnant women as a "vulnerable population," implying that they did not have the capacity to make informed decisions regarding their health.¹⁵ Although there are concerns regarding the teratogenicity of medications in pregnancy, as well as the ability of medications to cross into breastmilk, being of childbearing age in and

of itself should not be a barrier to inclusion in clinical trials. Furthermore, pregnancy and breastfeeding need to be considered in the context of each trial rather than used as a blanket exclusion criterion. Examination of the screening logs for clinical trials may be beneficial in identifying whether sex-biased study criteria contribute to the underrepresentation of women in clinical trials. If women are being screened out of clinical trials based on inclusion and exclusion criteria, these should be examined to ensure there is a robust rationale for sex-biased inclusion and exclusion criteria.

RECRUITMENT TO CLINICAL TRIALS

Participation in clinical trials is likely influenced by both patient- and trial-related factors, including potential investigator bias. Screening logs of clinical trials may play a role in helping identify potential barriers to inclusion. If lower female enrollment is due to fewer women being referred for screening, the underlying motivation for this needs further examination. Are researchers less likely to consider women for screening in clinical trials and/or are women patients less likely than men to consider participation in clinical trials? Diagnostic patterns have the potential to influence recruitment into clinical trials. In the field of ischemic heart disease, several studies have shown that the diagnosis may be less commonly considered in women than in men.¹⁶⁻¹⁸ Therefore, if clinicians are not considering the diagnosis or there is a delay in consideration of the diagnosis, this may act as a barrier to referring the patient for inclusion in the trial.

Preconceived ideas on the part of referring clinicians may also lead to lower referral of women for consideration of inclusion in clinical trials. It is recognized that a clinician's belief as to whether or not a patient will benefit from an intervention influences recruitment into clinical trials.¹⁹ In the field of acute coronary syndrome (ACS), early data suggested that women may not benefit from invasive angiography,^{20,21} and later it was shown that it is high- or low-risk ACS that influences outcomes rather than sex.²² However, potential bias with regard to the belief that women do not benefit from invasive strategies may lead to preferential inclusion of men in intervention-based trials. Furthermore, from a physician perspective, practice setting, knowledge of the clinical trial, and interaction between the physician and researcher has been shown to influence the physician's decision to discuss clinical trials with patients.²³⁻²⁶

From a patient perspective, female patients are more likely to consider the opinions of friends and family members when deciding to participate in clinical trials.^{27,28} In trials where consent is time-sensitive, this support and perspective may not always be available to

allow women to consider participation. Studies investigating female participation in cardiovascular disease trials are limited. From the available data, motivators for participation in clinical trials include personal health benefits, interest in research/promotion of science, and societal benefits.^{29,30} Women were also less willing to participate in clinical trials than men because they perceived a higher risk of harm³¹; there are also perceived logistical barriers, such as transport to clinical trial sites for follow-up.³⁰

Other potential barriers to participation in clinical trials include time commitments to follow-up, particularly for women with additional family and childcare commitments. In countries with well-resourced and centralized health care systems, registry-based randomized clinical trials may help overcome some of these barriers, particularly where the clinical endpoints are binary, such as death or readmission to hospital.

INVESTIGATOR OPPORTUNITIES

Despite an increased intake of female medical students over the years, the paucity of women in the cardiology field at a senior clinician or consultant level is well established.³² During the progression from medical student to senior clinician, the number of female doctors declines due to a multitude of reasons, varying from personal to systemic. Academic cardiology is similar, if not worse, than clinical cardiology in terms of female representation and the obstacles to career progression, with a further decline in female representation from clinician to researcher.³³

THE CURRENT SITUATION

In a cross-sectional study from 2008 to 2020, women accounted for only 10% of authorship in trials for pivotal FDA-approved cardiovascular drugs.³⁴ A multitude of factors contributing to this disparity have been suggested, with different types of contributory bias classified as individual, systemic, and (perceived) lower performance, as described by Wittman et al.³⁵ Adding to this situation is the lack of visible female leadership in cardiology academia—"you can't be what you can't see."³⁶

It is not just the lack of female authorship or researchers being less successful in obtaining research grants; there is also a paucity of women editors and representation in research steering committees. Balasubramanian et al examined female representation in major cardiology journals according to the h-5 index over a 20-year period.³⁷ Between 1998 and 2018, they found no female editors-in-chief for United States cardiology journals and only one female editor-in-chief for

a European cardiology journal. On steering committees, women continue to represent as low as 11% of members—and this has remained unchanged throughout almost 20 years.³⁸

The presence of fewer female principal and chief investigators negatively influences the diversity of recruited participants and early career female researchers.³⁹

The “Why”

If we consider the field of research grants across various medical specialties, female researchers are less likely to be awarded grants than researchers who are men.³⁵ Witteman et al divided the bias in this field as individual, systemic, and (perceived) underperformance.³⁵ Individual bias refers to conscious or unconscious gender bias by the reviewer toward the applicant. Female authors are disadvantaged to begin with because conference abstracts and manuscripts are more likely to be accepted when author identities and gender are unknown.^{40,41} Systemic bias refers to the advantage men have as researchers due to a better start line from previous publications, grants, etc, which strengthens their academic track record. This has also been alluded to by Van Spall et al.³³ Research submitted by a woman is more likely to receive stronger criticism than when submitted under a man's name. The resultant effect is that female applicants submit weaker grant applications, leading to the appearance of underperformance despite equal ability.³⁵ This also translates and cumulates into the successful male researcher achieving leadership status because “success begets success.”

In addition to the types of bias mentioned previously, a lack of self-promotion and self-underreporting of achievements by women is also contributory. In an interesting experiment, Reuben et al studied negative sex stereotypes by conducting a simple arithmetic task as the basis for hiring an individual.⁴² Men were more likely to be hired as the chosen candidate—especially if the performance on the arithmetic task was self-reported, as they tend to overreport their performance compared to women with similar achievements. An unusual type of bias is “benevolent sexism,” where women are wrongly overlooked for research leadership and collaboration opportunities because they may have familial responsibilities,³³ ignoring the presence and effect of systemic bias. In addition, even when female researchers are acknowledged to be successful, they are sometimes considered to be more hostile and less objective than their successful male counterparts. This ambivalent opinion could lead to exhibition of bias toward women.⁴³

WHAT CAN BE DONE TO IMPROVE THE CURRENT SITUATION?

Professional research organizations, universities, health boards, professional societies, journals, and individuals all need to work together to improve and solve the current situation. Van Spall et al identified four themes for professional research organizations to work on to improve the current paucity of women in research: education, funding, advocacy, and partnership.³³ They also suggested a 5-year plan to reduce the gender gap in leadership of clinical trials.

Nonprofit organizations such as Women As One, founded in 2019 by internationally renowned cardiologists and researchers Drs. Roxana Mehran and Marie-Claude Morice, promote female talent in medicine and offer opportunities.⁴⁴ In addition to being a platform for networking and collaborating with similar professionals, the organization has been instrumental in setting up clinical- and research-based programs and awards, such as the CLIMB initiative and Escalator awards.

Grant funders should ensure that focus is shifted from the scientist to the science for which the funding is requested.³⁵ This requires systematic protocols and policies to ensure that the different types of bias can be prevented. Early career identification of research interest in female trainees with the introduction of female mentors to help guide and navigate the trainee is another solution that has been partially addressed by the Women As One mentoring pilot project.

Industry also has a role to play in offering solutions. For example, industry members organized the first worldwide female cardiologists advisory board virtual meeting.⁴⁵ This offered a platform for women in cardiology to discuss career progression and difficulties at the early, mid-, and late-career stage from 15 countries in Europe, the Middle East, and Africa.

CONCLUSION

To draw meaningful conclusions from clinical trials and allow physicians to provide true evidence-based care to their patients, it is imperative that the full spectrum of the population is adequately represented in clinical trials. Although this article focuses on gender- and sex-based equity, it is equally important to ensure equity at a racial and socioeconomic level within trials. In order to understand how to increase enrollment of women in clinical trials, further understanding of the motivators, facilitators, and barriers to participation is required. Furthermore, not only are women underrepresented in trials, but there is also underrepresentation in academia and senior clinical roles. There is no single or simple solution to increase the number of women

as senior clinicians and researchers. A multipronged approach at various levels from the individual to institutional level is required. Acknowledging that the problem exists is the first and one of the most important steps. ■

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