

EDITORIAL COMMENT

Participation of Women in Clinical Trials

Not Yet Time to Rest on Our Laurels*



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From the stories of workplace impropriety and sexual misconduct allegations, a movement emerged as a supportive platform for women to share their experiences in solidarity. This movement's call for action has challenged all fields to examine institutionalized power dynamics and gender biases through a feminist lens. Advancing sex and gender considerations in the health care field can add to this growing movement.

In the 1990s, the U.S. Food and Drug Agency's (FDA's) Office of Women's Health established a specific program dedicated to support FDA research and development activities related to improving women's health (1). Their mandate is to improve clinical study designs and procedures to better identify and evaluate possible sex differences in FDA-regulated products. As a response to various interest groups advocating for adequate representation of women in cardiovascular clinical trials, the FDA, as well as other agencies (i.e., National Institutes of Health [2], Canadian Institute of Health Research) established policies focused on greater participation of women in clinical trials to strengthen science and guarantee quality and generalizability of biomedical research, breaking the ceiling of health inequity.

Reports of FDA drug approvals showed that women's participation in clinical trials has progressively increased compared with reports from the

1990s that demonstrated a consistent underrepresentation of women (<20%) (3-5). Although women's participation increased to 45% for new drugs approved between 2010 and 2012 (5), inclusion varies widely by indication and has been the lowest in cardiovascular trials (3-5).

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In this issue of the *Journal*, Scott et al. (6) report on the participation of women in 36 pivotal cardiovascular disease (CVD) drug trials with FDA approval between 2005 and 2015 and on the influence of sex on study results in terms of safety and efficacy, using data publicly accessible at [Drugs@FDA](#). The CVD areas explored were atrial fibrillation, coronary artery disease, acute coronary syndrome/myocardial infarction, heart failure, hypertension, and pulmonary arterial hypertension. During this period, the overall percentage of women participants in the trials analyzed was 34% and the proportion per trial ranged from 22% to 81% (mean per trial = 46%) across different cardiovascular areas. When considering the percentage of women in the trial divided by the percentage of women in the disease population (participation prevalence), women in hypertension, atrial fibrillation, and pulmonary arterial hypertension trials were well represented. Conversely, low enrollment (24%) and low participation prevalence of women among participants were observed in ischemic heart disease and heart failure trials, the most common cardiovascular conditions affecting women (7). Hazard ratios for primary efficacy endpoints were similar among the sexes for 14 of the 36 studied drugs' reports with clinical outcomes data. In the 15 trials on antihypertensive drugs assessing softer outcomes, that is, reduction in blood pressure, no sex differences in outcomes were observed. An analysis of safety was reported only for antithrombotic drugs, which did not detect any sex

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differences in bleeding events. To explore the impact of sex-biased inclusion criteria on the low proportion of women enrolled, the proportion of screened participants by sex was provided. Although this information was only available for 5 trials, the authors concluded that screening failure did not appear to be a contributor to the under-representation observed.

The optimistic results portrayed by this FDA report for hypertension, atrial fibrillation, and pulmonary arterial hypertension trials are dampened significantly by the continued under-representation of women in heart failure and ischemic heart disease drug trials (6). Indeed, the inadequate participation of women in clinical trials could result in several significant issues, including male-patterned inclusion criteria, sex-biased outcomes measurements, inadequate data analysis, and the missed opportunity to transfer results in clinical practice. The estimation of adequate representation of women in trials is highly dependent on reliable measures of disease prevalence; unfortunately, obtaining such estimates can be fraught with detection bias and variations with regard to case definition. For example, diagnostic criteria for heart failure with or without preserved ejection fraction are unclear, and these clinical entities may be difficult to distinguish at the population level. Moreover, no obstructive coronary artery disease may be misdiagnosed in women and therefore not represented in trials. Additionally, the epidemiology of CVD is strongly age-dependent; however, FDA reports consider age-specific distribution inconsistently in the proportion of women in the disease population, which may lead to an erroneous assessment of sex distribution.

A contribution to the continued low representation of women is the eligibility criteria that often reflect a male pattern of disease, especially in heart failure and ischemic heart disease drug trials. For example, in heart failure trials, ejection fraction $\leq 40\%$ and glomerular filtration rate < 30 ml/min/1.73 m² were eligibility criteria that consistently excluded women (8). Patient complexity is very often underestimated in randomized controlled trials, and the impact of patients' multiple comorbidities on efficacy and safety results cannot be ignored. The inclusion criteria in randomized controlled trials impose homogeneous clinical characteristics for men and women, and may be responsible for the lack of sex differences in efficacy outcomes.

Except for trials testing antithrombotic drugs associated with high bleeding event rates, adverse event rates were too small to allow meaningful sex-stratified analyses. Bleeding rates with antiplatelet

TABLE 1 Interventions to Address the Low Inclusion of Women in Trials and to Obtain Women-Specific Results

Pitfalls in Drug Clinical Trials	Proposed Interventions
Knowledge and awareness of sex and gender Knowledge gap in terminology, use of sex and gender as synonymous	Clarify the use of the terms sex and gender through educational intervention among health providers, researchers, and general population
Pre-screening/screening Gender-related barriers for screening Day care Elderly Access to care	Promote awareness on gender-dimension Policies to support women in day-life (e.g., adequate child care during time spent as a research participant, assistance for elderly included in the study)
Inclusion male-pattern criteria	Inclusion criteria that consider sex differences in pathophysiology Age Glomerular filtration rate Body size Biomarkers/diagnostic criteria
Study methodology/analysis of data No adjustment for relevant covariates Sample size lead to underpowered results	Pre-specified subgroup analyses Adjusted analyses with term for sex*drug interaction in all trials Adequate power for efficacy and safety analyses
Editorial policy/research output dissemination Lack of specific editorial requirements for sex-specific reporting in clinical trials	Journal-specific checklist for sex-specific reporting (i.e., specify the number of women in the trial, all primary and secondary endpoints by sex, discuss generalizability in both sexes)

drugs compared with clopidogrel (reference group) were similar among sexes despite a prior observational trial having reported a higher bleeding rate for women among clopidogrel users for acute coronary syndrome (9). There are many examples of drugs removed from the market in phase 4 studies because of adverse events in women, but most phase 3 trials are not powered to ascertain adverse events.

Although the FDA reports a reassuring lack of sex differences in drug efficacy and safety, the likelihood that these results are less likely to be generalizable to women should be of immediate concern. Given frequent reliance on subgroup analyses for definitive conclusions, future trials must plan to include a reasonable proportion of women in order to obtain adequate power to better assess if sex differences exist or not (10). Strategies including adequate sample size, pre-specified sex-based stratification analysis, and the measurement of gender-related factors are encouraged to achieve equality in health care for women and men.

Lastly, sex is identified as a biological variable defined by characteristics encoded in DNA, such as

reproductive organs, whereas gender is a complex construct that captures behavioral, cultural, and psychological traits linked to biologically human males and females through social context (11). Thus, among the hypothesized barriers to participation of women in research, gender-related factors, such as caretaking roles and low socioeconomic status, should be considered as main barriers to enrollment and women's willingness to participate in clinical trials.

The analysis of Scott et al. (6) exposes the successes and failings of clinical trial design for FDA approval over the last decade. Their report signals that we are still far from providing equitable cardiovascular health care for women, given the under-representation of women in heart failure and ischemic heart disease drug trials (12). Even if some cardiovascular areas have displayed significant achievements in women representation and sex-stratified analyses, there is still room for improvement in ischemic heart disease and heart failure, with an expected rise in incidence in the upcoming years. Specific interventions can help the researchers, health care providers, and their patients

empower and target the pitfalls and caveats of current clinical trials (Table 1).

In conclusion, as scientists of the 21st century, we admire the efforts of women worldwide that fight sex and gender disparities across their lifespan in every dimension of social life. Even though progress has been made toward a higher participation of women in pivotal clinical trials, it is still not time to rest on our laurels. On the slipstream of the FDA effort, patients, researchers, and health providers can take action by addressing the alarming gaps in quality and equitable health care for women (12). Our mandate as health providers and researchers should be to catalyze the energy and advance awareness that sex and gender in clinical trials really does matter.

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