

VIEWPOINT

# Sex Disparities in Cardiovascular Device Evaluations



## Strategies for Recruitment and Retention of Female Patients in Clinical Device Trials

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### ABSTRACT

Women have historically been underrepresented in clinical trials evaluating cardiovascular devices. Existing initiatives through government agencies have made some progress, but contemporary rates of female clinical trial participation leave much room for improvement. This position paper provides a narrative review and investigates reasons for the underrepresentation of women in cardiovascular trials. The observed differences in safety and/or effectiveness of devices in women warrant a campaign to increase their trial participation with the aim of better understanding and improving outcomes. The authors propose a multifaceted approach to increasing female enrollment through the development of a national public awareness and education campaign aimed to inform women, clinician-providers, and clinical research personnel of these differences. Finally, the authors visit some barriers relevant to women and recommend ways to facilitate their participation in clinical trials through multistakeholder engagement. (J Am Coll Cardiol Intv 2019;12:301-8) © 2019 by the American College of Cardiology Foundation.

Cardiovascular disease (CVD) takes the lives of 400,000 women in the United States every year, more than all cancers combined, making it the leading cause of death (1). Despite significant declines in overall CVD mortality, reliable evidence supporting access and timely delivery of optimal treatment for women lags significantly behind that of men, resulting in troubling trends in outcomes (2). Even though the prevalence of CVD in men and women is similar, use of cardiovascular (CV) procedures and devices such as diagnostic

cardiac catheterization, stents, and implantable defibrillators is far higher in men (3,4). A number of studies of various CV devices have uncovered significant sex-stratified differences in outcomes (5-10). The juxtaposition of evidence suggesting a risk-treatment bias has placed medicine at an impasse where investments must be made to identify and improve outcomes for women with CVD.

Improving outcomes and ensuring that women with CVD receive the best available care requires a foundation of reliable evidence. Unfortunately, for

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**ABBREVIATIONS  
AND ACRONYMS****CV** = cardiovascular**CVD** = cardiovascular disease**FDA** = U.S. Food and Drug  
Administration**NIH** = National Institutes of  
Health

decades, women have been underrepresented in clinical trials throughout CV medicine (11). Outcomes from predominantly male cohorts have driven guidelines that are not sex specific. In CV device trials, sex distribution is largely skewed compared with disease prevalence, with men constituting 70% to 80% of enrollees, resulting in small sample sizes of women and low statistical power for identifying meaningful sex-related outcomes (12). As a result, the majority of influential differences in sex-specific outcomes are uncovered largely as a result of post hoc analyses or systematic reviews, calling into question the reliability of the evidence.

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This call to action aims to halt the perpetuating cycle of female underrepresentation in CV studies, through a comprehensive multistakeholder engagement and awareness campaign, and streamlining clinical trial design to ensure more robust sex specific data (**Central Illustration**).

**REPRESENTATION AND GOALS**

The authors are members of the Women in Innovation subcommittee of the Society of Cardiac Angiography and Intervention, representing expertise in interventional and structural cardiology, clinical trials, and academic research organizations. AdvaMed represents the device industry and is a vital partnering stakeholder in implementing strategies to increase female recruitment in industry-sponsored clinical trials. The writing group requested that AdvaMed independently review and provide comments on the paper. The authors had sole responsibility for the content, drafting, final editing, and submission of the paper.

This position paper is intended to review root causes of underrepresentation of women in CV trials and to outline a multistakeholder (including clinicians, academics, regulators, government funding agencies, societies, and the device industry) education plan to address the sex-based recruitment gap in CV clinical trials. This paper was endorsed by the Society for Cardiovascular Angiography and Interventions in August 2018.

**REASONS FOR UNDERREPRESENTATION OF  
WOMEN IN CV TRIALS**

Patient participation, particularly of women, in CV clinical trials is challenging and is lower in the United States compared with the rest of the world, partly as a result of a decline in U.S. investigator engagement in

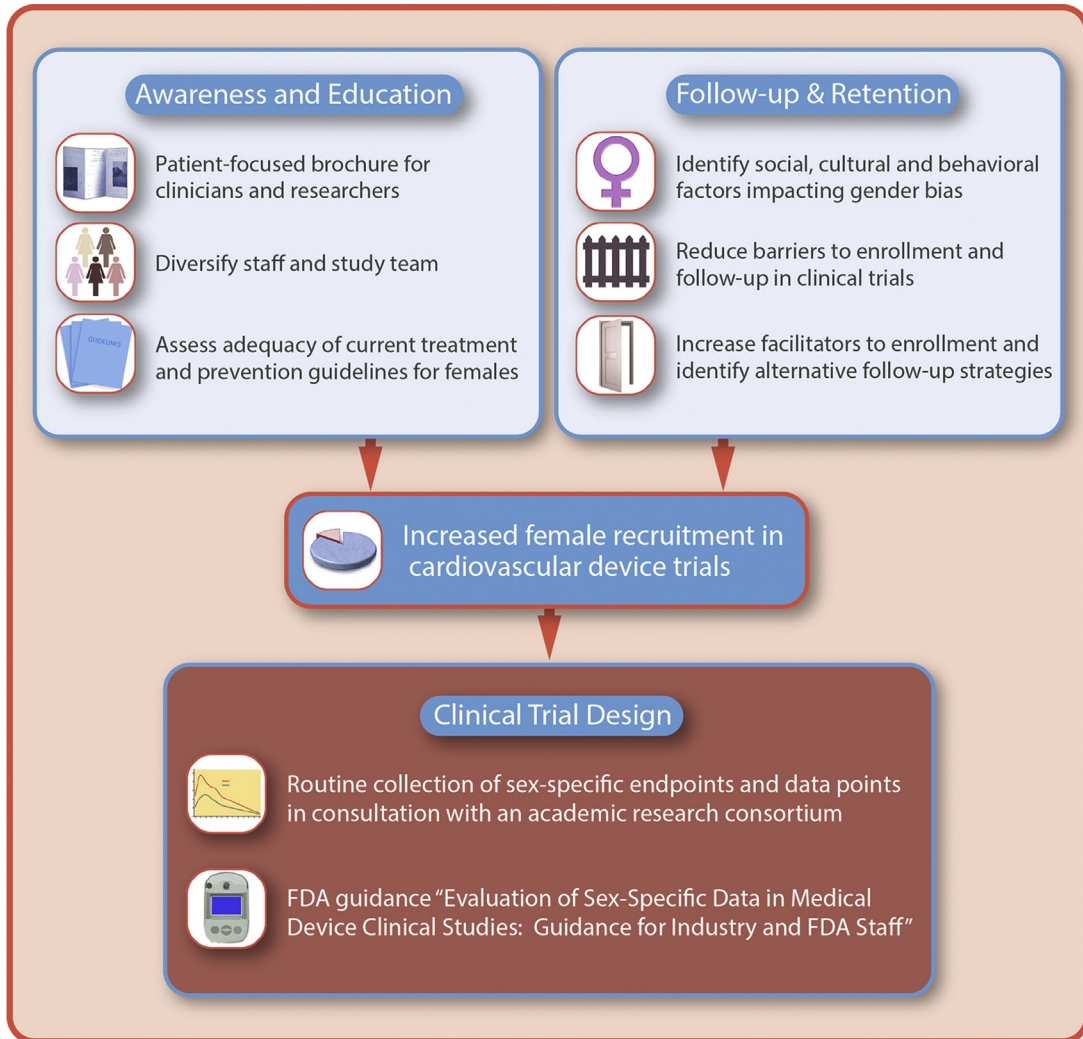
clinical research. Moreover, the proportion of women participating in clinical trials in the United States has only increased for government-sponsored trials because of mandated enrollment targets (13,14). In this context, active recruitment and retention of women in CV trials continues to stagnate. Economic stability, environment, education, community and social context, and the health care system are all important factors influencing CV health in women (15-17). These factors also play an important role in decision making when it comes to clinical trial participation. Understanding and addressing the complex socioeconomic determinants of health is fundamental to increasing women's willingness to participate in CV clinical trials. Recently, the National Institutes of Health (NIH) Office of Research on Women's Health published a comprehensive review identifying major obstacles to female participation in clinical trials (18), and although not specific to CV trials, much of the evidence supports similar contributing factors.

**RISK AND DECISION MAKING.** Women tend to have more risk-averse behavior than men in making decisions, a difference that is amplified under stress (19). Inherent in clinical trials, the process of randomization (20-24) and the fear of adverse health effects from trial participation (20,25,26) amplify risk-averse behavior and negatively influence their willingness to enroll. Therefore, emphasizing that clinical trials are closely monitored for safety and rely on a reliable foundation of standards of care to establish new evidence may provide an effective means to allay fears of risk and randomization.

**COMMUNICATION AND EDUCATION.** Fundamental differences in the approach to communication related to decision making may further contribute to sex disparities in trial participation. Women are more likely to report that their decisions are influenced by friends, family, or researchers, and they are also more likely to make decisions on the basis of general altruistic considerations (27). Although patient autonomy is paramount, informed decision making for women will often include a greater network of trusted individuals, including family and friends. Therefore, educational and awareness campaigns must include a broader sphere of influential individuals, aiming to demystify clinical research methods and to emphasize the broader societal benefits.

**TRIAL BURDEN.** As primary caregivers, women are particularly vulnerable to study burden, and the impact of follow-up requirements on sex bias continues to be challenging in CV trials. A contemporary large-scale study from a high-volume U.S. academic

### CENTRAL ILLUSTRATION Recommended Next Steps to Improve Female Cardiovascular Outcomes Through Clinical Trials



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FDA = U.S. Food and Drug Administration.

health system examined patient- and trial-specific factors associated with participation in CV randomized controlled trials through patient screening logs (28). Patient-specific predictors of trial nonparticipation were age  $\geq 65$  years and female sex, whereas trial-specific predictors included lack of compensation, longer follow-up duration, and intensive testing. In another survey of women who declined to participate in a CV trial, transportation issues and adverse health effects were the most common reasons (29). Enrolling women is also affected by conditions that may limit their personal autonomy.

Therefore efforts to reduce the patient burden of clinical trials (i.e., number of in-person follow-up appointments, number of tests) or providing additional infrastructure support, such as tokens or financial support for transportation, will help increase the number of female patients willing to participate (29). Although Institutional Review Boards are leery of undue influence to encourage enrollment in CVD trials, transportation tokens and ancillary services have been successful in trials of human immunodeficiency virus infection (30), and current regulations should be relaxed to address the

**TABLE 1 Vision, Goals, and Objectives From “A Vision for 2020 for Women’s Health Research”**

Goal 1: Increase sex differences research in basic science studies.
Goal 2: Incorporate findings of sex differences in the design and application of new technologies, medical devices, and therapeutic drugs.
Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women.
Goal 4: Create strategic alliances and partnerships to maximize the domestic and global impact of women’s health research.
Goal 5: Develop and implement new communication and social networking technologies to increase understanding and appreciation of women’s health and wellness research.
Goal 6: Use innovating strategies to build a well-trained, diverse, and vigorous women’s health research workforce.

legitimate barriers to female enrollment. Indeed, reimbursement for reasonable expenses, compensating participants for their time and recruitment incentives should be given greater consideration (31).

**INVESTIGATOR ENGAGEMENT.** A lack of awareness, leadership, and engagement on the part of investigators may be the leading causes of poor enrollment. Whether by choice or omission, a minority of cardiology subspecialists are women. In the case of interventional cardiology, which likely is the single most important source of patient enrollment in device trials, the fraction is minute. In the United States, only 4.5% of interventional cardiologists are women, and among academic cardiologists in general, fewer than 20% women ever achieve leadership roles (32). The current female cardiology constituency faces a steep climb to close the known gap in sex disparities in CV outcomes, in referrals to CV device-related procedures, and in enrollment in clinical trials (12,33). To address the ongoing disparities, we outline a multistakeholder national educational plan led by clinicians and academics, supported by their societies and their device-industry partners, that enforces established NIH and U.S. Food and Drug Administration (FDA) governmental initiatives.

#### EXISTING INITIATIVES AND TRIAL DESIGN RECOMMENDATIONS

A number of government-driven initiatives have been implemented to address the sex gap in clinical research; although a step in the right direction, adoption has been limited and remains inadequate. The NIH Office of Research on Women’s Health published a strategic plan, “Moving Into the Future With New Dimensions and Strategies for Women’s Health Research,” highlighting 6 goals (34) (Table 1). Goal 1 embodies the need for a call to action as it aims to

increase sex-specific research in basic science studies. Goal 2 specifically addresses medical devices and the incorporation of sex differences in the design and application of new devices. Accordingly, this review provides sufficient compelling evidence to warrant expanding female sex representation in device trials, to more reliably establish or refute differences in CV medical devices. Progress toward goal 2 will be instrumental in achieving goal 3, which allows for personalized prevention, diagnostics, and therapeutics for women (35). With appropriate and urgent action, reducing the outcomes gap for women’s CV health is an achievable goal.

The NIH Revitalization Act of 1993 (Public Law No. 103-43) was enacted as a response to the underrepresentation of women in clinical research. The Office of Women’s Health was established within the FDA 1 year later to further help shape policy. In 1994, the Center for Devices and Radiological Health developed a policy to address the possibility of sex bias in the review process for new medical devices (35). An FDA document published in 2013 titled “Collection, Analysis, and Availability of Demography Subgroups for FDA-Approved Medical Products” reported that 88% of pre-market approval applications included sex analysis, but these analyses were present only 63% of the time in device labeling or summaries of safety and efficacy data (36).

The 2014 FDA guidance document “Evaluation of Sex-Specific Data in Medical Device Clinical Studies: Guidance for Industry and FDA Staff” (37) provides further sex-specific recommendations for device evaluation. Specifically, the FDA’s guidance requires a statistical analysis plan that includes a sex-specific analysis. A systematic review of 78 high-risk CV devices that received premarket approval from the FDA between 2000 and 2007 found that 34 (28%) of 123 studies did not report the sex of enrollees. On average, when sex distribution was reported, men constituted 67% of the population, and there was no increase in the enrollment of women over time (12). Although the FDA requires a sex-specific analysis in the statistical analysis plan, the actual reporting of outcomes on the basis of sex remains inadequate at 48%, with only modest impact since its implementation in 2013 (38). Among studies of devices in heart failure, women have been grossly underrepresented. Randomized controlled trials evaluating implantable cardioverter-defibrillators include only 10% to 30% female patients (39,40), partially because of the higher prevalence of heart failure with preserved ejection fraction in women (41). Still, implantable cardioverter-defibrillators are used disproportionately more frequently in men (32.3 per 1,000, n = 65,917) for

primary prevention compared with women (8.6 per 1,000, n = 70,504) (multivariate hazard ratio: 3.15; 95% confidence interval: 2.86 to 3.47), even after consideration of the prevalence of heart failure with reduced ejection fraction (42,43). For industry-sponsored and investigator-initiated device trials, the FDA also requires a protocol section dedicated to the recruitment of women and minorities and encourages enrollment in trials that approximates the prevalence of disease by sex. Despite these requirements, the status quo is perpetuated. To facilitate female recruitment, the FDA provides a social media toolkit and fact sheets for women (Table 2). Although positive steps have been taken among various agencies and organizations in clinical trial data analysis, lower female enrollment in CV device trials persists, limiting the ability to detect female-specific nuances and outcomes. Clinicians, the FDA, industry, and patient advocacy groups all have critically important roles to play and must actively assist in and assume responsibility for adequate female representation and reporting in clinical trials.

**PATHWAYS FOR IMPROVING CLINICAL TRIAL PARTICIPATION: RECOMMENDATIONS FOR NEXT STEPS**

The challenges in interpreting sex-specific outcomes in CV device trials resulting from underrepresentation underpin the call to action for a multifaceted and multistakeholder national action campaign (Central Illustration). This campaign aims to overcome barriers to access and implement facilitators to enhance female participation in CV device clinical research and complement existing programs intended to address trial design considerations for sex-specific analyses. The primary focus of the campaign is to confront the burdens of trial participation, to simplify trial design and follow-up strategies, address patients' distrust of researchers, the lack of understanding of the clinical trial process, and fears of risk associated with randomization. The proposed approach to reduce existing gaps in female participation is to engage clinicians, academics and industry partners through AdvaMed to commit to the national dissemination and implementation of established regulatory guidelines for clinical trials.

**CLINICAL TRIAL FOLLOW-UP AND RETENTION STRATEGIES**

Creative solutions that reduce barriers and engage facilitators in trial recruitment can effectively improve enrollment and retention of female patients

**TABLE 2 Tools for Recruiting Women to Clinical Trials**

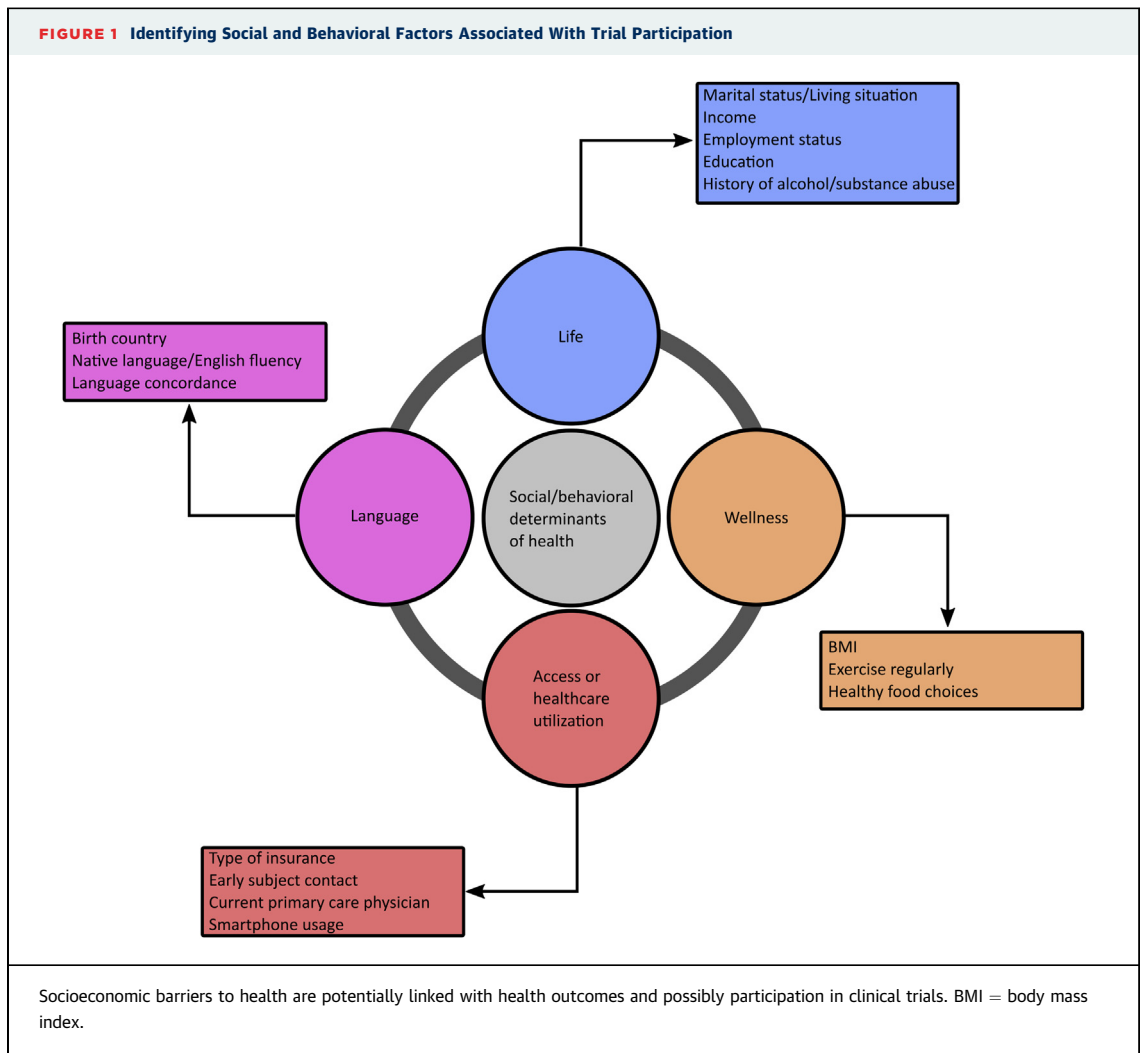
Document Title	Link to Documents	Description
FDA Office of Women's Health: "Women in Clinical Trials: Partner Toolkit"	English/Spanish	Sample tweets, Facebook posts, and blog posts for consumer audiences
Women in Clinical Trials: fact sheets	Various languages	Important facts for women wishing to enroll in clinical trials
Women in Clinical Trials: poster	English/Spanish	—
NIH Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research	Webpage	Comprehensive set of tools for increasing female enrollment in clinical research
Society for Women's Health Research: Successful Strategies for Engaging Women and Minorities in Clinical Trials	PDF	White paper on enrolling women in clinical trials

in device trials (Figure 1). Study burden along with cost and time commitment are the most cited barriers to trial participation (26). Alternative follow-up strategies that encourage participation and retention of women and minorities are an imperative. Specific examples include fewer protocol-required follow-up visits, phone follow-up or home visits by a nurse coordinator, flexibility to accommodate weekend hours, and allowing visits at alternative locations (25,44). In a society in which technology is omnipresent, there is an opportunity to use phone applications, online follow-up options, and telemedicine as alternatives to frequent on-site visits. Technology can also play a larger role in amplifying the throughput of screening, recruitment, and retention by using artificial intelligence and electronic health records (45-48). Finally, permitting primary care providers to perform some of the follow-up requirements and be reimbursed for study-related tests would further decrease study burden and increase compliance and primary care provider engagement in the trial process.

**AWARENESS AND EDUCATION CAMPAIGN**

A broad-based public education campaign, targeting female patients and their support networks, clinician-providers, and clinical research personnel, will heighten awareness of the need and relevance of boosting female engagement in CV device trials.

**EDUCATION OF PATIENTS.** Distrust of researchers, lack of knowledge and understanding of the clinical process, and fear of risk and random treatment assignment can be addressed through staff diversity and an education campaign. Women, especially minorities, are more likely to distrust the medical



system and have a negative attitude toward clinical trials (49,50). Patient-focused educational material to demystify the underlying principles of clinical investigation and emphasize the fundamental use of optimal guideline recommended standards of care upon which clinical investigations are based would reduce fears of participation.

Clear communication with easy-to-understand language (44) through phone calls, text messaging (51,52), e-mail, and social media (53,54) has also been effective. Further engagement and education through community members and organizations also fosters trust (51,55). Last, marketing strategies will help expand reach, with the most effective methods being posters, flyers, direct mailings, and especially social media (56,57).

**EDUCATION OF CLINICIANS AND RESEARCHERS.** A toolkit for clinicians and researchers highlighting

the vital benefits of participating in clinical trials, the importance of sex-specific analyses (including same-sex comparisons of investigational device vs. controls), and the implications on future guideline recommendations is paramount to the success of the campaign. Solutions to eliminating bias in clinical trial enrollment must include educational efforts for those who are responsible for conducting research, such as carrying out the informed consent process to ensure balanced recruitment and the value of sex as a primary variable in studies (58,59). Assessing the adequacy of current guidelines used to treat and diagnose CVD in women is essential to increase awareness and ensure that outcomes are optimized. Our recommendations remain broad because there is no one-size-fits-all approach. The best practices in enrollment and recruitment will need to continually evolve in the changing face of CVD in women.

## STAKEHOLDER ENGAGEMENT

The campaign will not succeed unless clinician investigators and industry partners prioritize eliminating sex disparities in the design and reporting of clinical trials. The FDA and the NIH have produced the guidelines necessary for addressing sex disparities. The most effective mechanism for addressing these disparities is for clinician and industry partners to voluntarily step up and take responsibility for adhering to the guidelines. The time has come to take conscious ownership in breaking the endless status quo and take decisive action to improve outcomes and provide equal care for our female patients.

## CONCLUSIONS

Continued scientific advancements are creating a new age in which personalized medicine contributes to improved outcomes. It is essential that sex be considered in treatment selection. Although advances have been made in some areas (e.g., structural heart therapies), decades of female and minority underrepresentation in CVD clinical trials have led to uncertainty in the benefit/risk assessment of device therapies and in best treatment recommendations,

which are currently based on performance evaluated primarily in men. As evidence for differences in sex-based outcomes accumulates, we can no longer rely on underpowered sex subanalyses to guide treatment for women. Higher female participation with routine collection of sex-specific data in clinical investigations is essential to inform best treatment and has become an urgent imperative.

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