Exclusion of women from clinical trials has its origins in the centuries-old concept of protecting women and children from harm. The logical result of this effort was that women of childbearing age were barred from participating in most medical research. Unfortunately, this reasonable, if somewhat paternalistic, effort to avoid harming fetuses by not enrolling pregnant patients in early-phase drug trials was overenthusiastically expanded to a virtual ban on all women in clinical trials. Additional reasons for excluding women from research studies include the real and perceived challenges of “controlling” for cyclic hormonal effects on outcomes and the widely held assumption that any results derived from male-only research could be applied to women.

Sex-based medicine traditionally has been thought of as the study and treatment of conditions affecting only men or only women, such as reproductive health and sex-specific cancers. Only in the past decade or so have researchers widely recognized the many biological differences between the sexes. Sex-based differences in natural history of disease, epidemiology, pathophysiology, diagnostic accuracy of tests, response to therapy, and outcomes have all been identified in a range of diseases and conditions previously thought to be “gender neutral.” Despite findings in 1985 from the US Public Health Service Task Force on Women’s Health Issues that excluding women from clinical studies had led to a lack of knowledge about women’s biology and that this deficiency had compromised the health of women, male domination in clinical trial enrollment continued.

To address the deficiency of knowledge about women and health, in 1993 the National Institutes of Health began to require that federally funded clinical trials include women and minorities unless their exclusion was clearly justified and that trials be designed and carried out in such a manner that sex-specific results (SSRs) could be validly analyzed. Eight years later, the National Academy of Sciences Institute of Medicine published its report, Exploring the Biological Contributions to Human Health: Does Sex Matter? This report concluded that sex differences must be researched at all levels, from the cells and chromosomes to whole organisms, if we are to identify the biological and physiologic differences between women and men. Further, the report states that “Understanding the basis of these sex-based differences is important to developing new approaches to prevention, diagnosis, and treatment.”

One important step in this effort to provide the best data for both sexes is to design clinical trials to include both men and women and to report results by sex.

Rogers and Ballantyne in this issue of Mayo Clinic Proceedings review 400 Australian studies published from 2003 through 2006. They report that a shocking 6% (23) of the studies did not even list the sex of the participants, and half of the investigators of those studies could not supply this information when asked. Further, 10% of the trials, for unclear or unspecified reasons, did not enroll any women, despite studying conditions affecting women. That investigators can still submit manuscripts without including the sex of the participants and that journals accept them for publication without comment is both worrisome and indicative that the vital need for sex-specific research and reporting is still not widely appreciated.

Almost three-quarters of the half-million participants in published reports were women. On the surface, this fact seems reassuring. However, approximately two-thirds of these women were involved in trials studying “female conditions,” whereas three-quarters of the men participated in research on diseases affecting both men and women. For example, 55% (219,865/401,801) of women studied were enrolled in one of 3 large sex-specific epidemiologic studies of cervical pathology, hysterectomy rates, and osteoporosis treatment patterns. The authors refer to this phenomenon as “biological essentialism”; that is, research in women emphasizes “female issues,” such as pregnancy and reproduction. Thus, this article suggests that much of the medical research in women has a focus similar to that of popular women’s magazines—breasts and sex. Research involving men includes a more diverse range of health concerns.

The relatively high number of women included in the Australian clinical trials is also explained by the authors’ broad definition of clinical trials. They included articles based on registry data, administrative claims databases, and observational trials, which supply valuable information but require little, if any, additional effort to include women. Instead, these studies retrospectively analyze patient information from data sets that happen to include many female patients. Randomized clinical trials require...
active recruitment and enrollment of participants, and women have been shown to have different, and frequently more, barriers to participation in trials than men.\textsuperscript{6} Randomized clinical trials are considered the best type of scientific evidence, to which observational studies are an important complement. After we have answered the experimental question about the efficacy of a particular therapy or procedure in the more idealized randomized trial setting, observational data tell us about its benefit and effectiveness in the “real world.” To ensure high-quality evidence-based health care, we must not only include adequate numbers of men and women in research but report SSRs also. This practice is especially important for large observational studies, as results can help inform our clinical practice.

The data reported by Rogers and Ballantyne on the current state of sex-specific reporting show there is much room for improvement. Of the studies of men and women reviewed, 93\% did not provide sex-specific analysis. It is disappointing to find that, as recently as 2006, sex-specific reporting and rates of inclusion of women in clinical trials were still appallingly low. In fact, in large trials involving the study of pharmaceuticals, the percentage of sex-specific reporting was a dismal zero.

We observed the same phenomenon in a recent review of cardiology clinical trials where only 25\% of all studies reported results by sex.\textsuperscript{7} As heart disease is the leading cause of death in women, it is dismaying that data from cardiovascular clinical trials are so limited. Unexpected sex-based differences have been found in the epidemiology of many diseases, such as lung cancer, other non-sex-specific cancers, degenerative joint disease, and depression and mental health disorders, leading us to conclude that the lack of sex differences should not be assumed and instead must be systematically studied. Further, we agree with Rogers and Ballantyne that, because of reporting that is inconsistent or lacking, these types of analyses to assess levels of SSRs are quite cumbersome and require intensive literature review and data analysis when done after publication.

Heightened awareness among investigators, authors, reviewers, and journal editors of the importance of enrolling and reporting data for both men and women in clinical trials will inform efforts to achieve optimal care of all patients. The International Committee of Medical Journal Editors\textsuperscript{8} recommends that investigators describe their selection of study participants, including controls, clearly (eg, eligibility, exclusion criteria, description of the source population). The committee states, “Because the relevance of such variables as age and sex to the object of research is not always clear, authors should explain their use when they are included in a study report; for example, authors should explain why only subjects of certain ages were included or why women were excluded. The guiding principle should be clarity about how and why a study was done in a particular way.”\textsuperscript{9} Perhaps it is time for this recommendation to be made a mandate and for journal editors to either require that manuscripts include sex-specific data to be considered for review or at least to make such data available online. The “author information” section of Circulation suggests providing “sex-specific and/or racial/ethnic-specific data when appropriate, in describing the outcomes of epidemiologic analyses or clinical trials; or specifically state that no sex-based or racial/ethnic-based differences were present.”\textsuperscript{10} The Journal of the American College of Cardiology uses nearly identical wording,\textsuperscript{10} but substitutes “gender-specific” for “sex-specific.” However, this requirement is not emphasized to submitting authors or to journals’ peer reviewers and is not a consistent practice in recent publications, even when female participants are included in sufficient numbers to provide this reporting.\textsuperscript{3,10}

It is time to recognize that women are complex biological creatures just as are men. All clinical studies should strive to include equal numbers of female and male participants or to at least reflect the prevalence of the condition of interest by sex. In older populations, this could appropriately include a preponderance of women. A recent analysis of clinical trials used for Medicare national coverage decisions found that, although 58\% of Medicare beneficiaries are women, women make up only 25\% of participants in the clinical trials reviewed.\textsuperscript{11} Until we are able to make this leap, women will continue to be marginalized in clinical trials of diseases that affect them in numbers equal to men.

We hope that this editorial and the work that has preceded it serve as a clarion call to researchers, authors, reviewers, and journal editors to include sex-specific reporting in all clinical trials that include more than 50 participants. Analyzing data by sex for conditions or treatments affecting both men and women is the only way we will be able to begin to provide optimal care for all patients and is a critical step toward the ultimate goal of “individualized medicine.”

Sharonne N. Hayes, MD
Division of Cardiovascular Diseases
Women’s Heart Clinic
Mayo Clinic
Rochester, MN

Rita F. Redberg, MD, MSc
Division of Cardiology
Women’s Cardiovascular Services
University of California, San Francisco