When Separate Is More Equal

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WOMEN CONSTITUTE SLIGHTLY MORE THAN HALF the population of the United States, but biomedical research has yielded less information on their health than that of men. Despite efforts in the past 2 decades to correct the balance, clinical practice and treatment of diseases other than those occurring primarily or exclusively in women are disproportionately based on research using male models of disease and male participants.

Male bias in research is implicit, and its effects are subtle but pervasive. It is seen more clearly when the entire landscape of health research is surveyed. This overview was taken by a recent Institute of Medicine (IOM) committee and summarized in the report *Women's Health Research: Progress, Pitfalls, and Promise*.[1] The report pointed to progress in the conduct of studies specifically involving women and their greater inclusion as research participants. However, it also noted that women are still underrepresented in the design, conduct, and analysis of studies and that these gaps have limited the utility of their findings for improving women's health.

Inadequate Basic Science Underpinning

The prototype disease model at each stage of research is often a male model. Animal models inform basic understanding of disease. A review of 2000 studies published in 2009 using animal models reveals substantially greater use of male than female animals.[2] This imbalance was especially noteworthy in research informing diseases that are actually more common in women. For example, in neuroscience studies, 5.5 male animals were used for every 1 female animal. More than 55% of samples testing animal models of anxiety and depression disorders failed to include any female animals even though such disorders are twice as common in women as in men.[2]

Inadequate Participation in Studies

At later stages of research, observational studies, including prospective cohort studies, inform understanding of determinants of disease onset and shape the questions addressed in more resource-intensive clinical trials. An analysis of cancer research articles published during 2006 in 8 high-impact journals found far fewer female participants relative to the percentage expected on the basis of sex ratios in incidence of the specific cancer.[3] The underrepresentation of women was greater in studies that were performed without government funding.

Trials performed exclusively or primarily in men cannot determine if a drug found to be safe and effective will be so for women, or whether a drug that does not work well in men might actually benefit women. Exclusion criteria based on a male model of a disease may unintentionally create samples that have a larger proportion of men and enroll female participants who are unrepresentative of women with that disease. For example, clinical trials in cardiovascular disease often use inclusion criteria regarding age and presenting symptoms that are more typical of male than of female patterns of disease.[4] Such criteria result in data more informative about the treatment of cardiovascular disease in men than in women.

Inadequate Enforcement

For many years women were excluded from clinical trials because of concerns that a trial could expose a fetus to harm if a woman was pregnant or became pregnant, and concern that hormonal fluctuations associated with women's menstrual cycles could complicate responses to treatment. In 1986 the National Institutes of Health (NIH) began mandating inclusion of female participants, and guidelines were further strengthened in the 1993 NIH Revitalization Act.[5] In this same year, the Food and Drug Administration (FDA) reversed earlier guidelines barring women of reproductive age from clinical trials, encouraging inclusion of women in phase 1 and 2 trials and requiring it in efficacy studies.[6] These guidelines produced a substantial gain in women's participation in studies. Guidelines alone, however, have not achieved parity. Government Accountability Office (GAO) analyses of NIH research and FDA applications have consistently found inadequate proportions of women in funded trials.

Even when women are included in clinical research studies, the data are often not analyzed and reported separately for female participants. A 2001 GAO report on FDA poli-

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cies stated that a third of documents did not present data according to sex.[7] This failure likely increases women's risks of drug complications, as evidenced by the GAO finding that 8 of the 10 drugs that had most recently been taken off the market had more adverse effects in women than in men.[8]

The problem is not the overall participation of female participants, but rather the uneven distribution of women across studies. In recent years women have constituted more than half of all participants in federally funded clinical research.[9] However, many female participants are in women-only studies such as the Women's Health Initiative and in studies of breast, ovarian, or cervical cancer. Women continue to be underrepresented in studies of diseases such as cardiovascular disease, cancer, and HIV/AIDS.[3,10]

Possible Suggestions

Stricter enforcement of existing federal regulations regarding enrolling women in federally funded clinical research would help but will not solve the problem. Current regulations do not affect participation in non–government-funded studies and cannot ensure sex-specific analyses in all funded studies. Although the FDA has enforcement mechanisms, the NIH, the Agency for Healthcare Research and Quality, and other government funders do not have sufficient authority to ensure analyses and reporting of sex-specific data. These agencies require inclusion of women and can evaluate progress in enrollment. However, data analysis and publication generally occur in the final year or beyond; by the time an agency receives a final report, grant funds have been expended and there is no hold on the investigators.

The IOM committee[1] evaluating women's health research identified complementary publication guidelines as a more comprehensive and readily administered way to help ensure adequate sex-specific analyses. If sex-specific analyses are required for publication, researchers will be more likely to design studies that yield applicable data. Although useful for all studies, the recommendation made by the committee was somewhat narrower (and more easily implemented). The IOM committee recommended that the International Committee of Medical Journal Editors and editors of other relevant journals develop guidelines requiring reports of clinical trials to present outcomes separately for male and female participants, except for those studies involving conditions that affect only one sex.

Addressing Objections

This recommendation is likely to engender considerable debate. Requiring that results be reported for both men and women can have unintended costs along with intended benefits. Most notably, this recommendation may increase sample size and therefore the cost of some trials. Studies that present a compelling rationale for why separate analyses are not justified could be exempted, although an explicit model of men's and women's health and clear criteria will be needed to ensure that exemptions are granted fairly and judiciously. Over time, the requirement may encourage efforts to design new techniques for pooling data across studies and relieve the burden on each individual study.

Even if the requirement for separate analysis for men and women in clinical research studies increases the burden on researchers and the cost of some studies, the alternative is to continue practices that clearly shortchange progress in women's health and may also hamper progress in men's health. It is preferable to conduct adequately powered studies that will yield knowledge that will help both men and women than to do more studies that systematically provide poorer information for more than half the population.

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Editor's Note: The IOM recommendation " . . . that the ICMJE and editors of other relevant journals develop guidelines requiring reports of clinical trials to present outcomes separately for male and female participants . . . " is well taken. However, that addresses only a post hoc opportunity: the numbers and types of women and men participants is long cast, and based on personal experiences at least, the numbers of women in many trials are insufficient to be analyzed separately.