New Policies Signal Changing Attitudes on Sex Differences Research: An SWHR[®] Perspective

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Abstract

The Society for Women's Health Research has long advocated that research studies on diseases that impact men and women should consider sex as a fundamental variable. Thankfully, this attitude seems to be evolving. Recently, the National Institutes of Health (NIH) reported that it will issue new policies on the inclusion of female animals and cells in preclinical medical research. We look forward to working with the NIH and the Office of Research on Women's Health as they develop new policies that require grant applicants to report their plans for including a balance of male and female animals and cells in preclinical studies as appropriate.

Introduction

THE SOCIETY FOR WOMEN'S HEALTH RESEARCH (SWHR[®]) believes that the U.S. National Institutes of Health (NIH) policy should require relatively equal proportions of male and female animals and cells in preclinical studies as appropriate, or require the proportion of male and female models used to investigate specific diseases be representative of the disease prevalence in the general population. Second, the NIH should require all investigators to describe how sex-specific reporting and/or analysis will be conducted within their grant applications. Third, the NIH should develop mechanisms to track successful inclusion of females and males in all stages of preclinical and clinical research. Fourth, the NIH should require grantees to report and, when appropriate, analyze their data by sex as part of grant progress reporting to the agency and in all published results resulting from NIH funding. Finally, the NIH should consider enhancements to the review process, such as the addition of ad hoc reviewers when appropriate and training for study section reviewers.

SWHR has long advocated that research studies on diseases that impact both men and women should consider sex as a fundamental variable; however, historically the medical community has disagreed. Thankfully, this attitude seems to be evolving. Recently, the NIH reported that they will issue new policies on the inclusion of female animals and cells in preclinical medical research. In a commentary published in the May 15 issue of *Nature*, NIH Director Francis Collins and Office of Research on Women's Health Director Janine Clayton Austin acknowledged that while scientists "know more about the role of sex and gender in medicine, there has not been a corresponding revolution in experimental design and analysis in cell and animal research."¹

The new policies, which will be rolled out in stages beginning this October, will require grant applicants to explain how they plan to include female cells and animals in preclinical studies that impact both men and women. This is the largest step taken by a federal agency to support and encourage investigation of biological sex differences since the NIH Revitalization Act of 1993, which mandated the inclusion of women and minorities in all human subject research sponsored by the NIH. These achievements are a direct result of advocacy efforts by SWHR and other women's health research advocates to educate policymakers, as well as the medical and scientific communities, regarding the existence and importance of sex differences in health and disease.

A Legacy of Advocacy

SWHR, widely considered to be the thought leader in research on biological differences in disease, has been dedicated to transforming women's health through science, advocacy, and education since 1990. Our organization has been committed to the inclusion of women and minorities in clinical trials and sex differences research and was one of the driving forces behind both the NIH Revitalization Act of 1993 and the 2001 Institute of Medicine report "Exploring the Biological Contributions to Human Health: Does Sex Matter?" which reported that "every cell has a sex" and that biological sex matters "from womb to tomb."² SWHR has worked with congressional champions, federal health and research agencies, and federal offices of women's health to ensure that females are included in all phases of medical research and that any differences found are translated into medical practice. We believe it is critical that our country's leaders understand the importance of sex differences research

and that we make it part of our mission to educate and serve as a resource for both congressional leaders and federal health agency leaders on these important issues.

SWHR has worked with congressional leaders as they ensure that the NIH places appropriate emphasis on the importance of sex differences research within the agency and on ClinicalTrials.gov, the nation's resource for all clinical trial information. Recently, many members of Congress sent an inquiry to the Government Accountability Office asking that the agency re-examine women's inclusion in NIH-sponsored trials.³ Additionally, we have championed the Research for All Act of 2014 (HR 4879) in the advocacy community so that research is designed from the beginning, where appropriate, to ensure that sex- and gender-related data are reported and analyzed as new drugs and medical devices are developed. The legislation directs the NIH to determine, with the input of experts in the field, when it is appropriate for basic research projects to include both sexes and issue guidelines to ensure the inclusion of both sexes and the analysis of sex differences. Importantly, the bill mandates that the NIH consult with scientific and medical experts and relevant organizations in the development of a policy that is based on a consensus of experts who have been working in this field for years.⁴

Some Progress but Not Enough

There is still much work to be done to ensure that biological sex differences research is truly integrated into medical research and the medical community. SWHR believes that the first step toward truly personalized medicine is the incorporation of sex and gender differences as mainstream variables in all medical research, and that all federal health agencies should take steps to address these differences.

We look forward to working with the NIH and the Office of Research on Women's Health as they develop new policies, training modules, and initiatives around the inclusion of female animals and cells and appropriate analysis. SWHR believes that the NIH policy should require relatively equal proportions of male and female animals and cells in preclinical studies as appropriate or require that the proportion of male and female models used to investigate specific diseases be representative of the disease prevalence in the general population. We know that incorporating sex as a basic variable is not appropriate for every study and that the NIH should define those exceptions to not unduly burden researchers. SWHR believes that some areas where equal representation of males and females is unwarranted are studies that only affect one sex, studies in disease models where one sex is not viable, and studies where the disease does not manifest in one sex.

Further, we recommend that the NIH consider adopting additional methods to further support and encourage sex differences reporting and analysis in preclinical studies. The NIH should require all investigators to describe how sex-specific reporting and/or analysis will be conducted within their grant applications. Third, the NIH should develop mechanisms to track successful inclusion of females and males in all stages of preclinical and clinical research. Fourth, the NIH should require grantees to report and, when appropriate, analyze their data by sex as part of grant progress reporting to the agency and in all published results resulting from NIH funding. Finally, the NIH should consider enhancements to the review process, such as the addition of ad

hoc reviewers when appropriate and training for study section reviewers.

Translational Implications

Currently, inclusion of women is not required at phases 1 and 2 of NIH-funded human subject trials when critical safety and dosage issues are addressed. This is an area where much improvement needs to be made. We know that 80% of the drugs taken off the market between 1997 and 2000 "had disproportionately adverse effects on women, including a cardiovascular drug that actually caused heart failure in women."⁵ Without consideration of sex differences at these early stages of research, the impact that new drugs or treatments will have on women cannot be completely understood, potentially jeopardizing their health. SWHR believes that the inclusion of female cells and animals in preclinical studies, along with the inclusion of women in early human subjects clinical trials, will shed light on vital sex differences. We are committed to working with both the NIH and the private sector to increase the representation of women in these trials.

These differences are critical in aiding the U.S. Food and Drug Administration (FDA) as it reviews and makes approval decisions regarding new drugs, devices, and biologics. SWHR has worked in collaboration with congressional leaders to pressure the FDA to place a greater focus on the analysis of sex differences in the evaluation of new drugs. In a recent letter, 15 female senators called for greater analysis of sex differences in the evaluation of new drugs at the agency.⁶ SWHR believes that the FDA should require that research that accompanies an application for a new drug, device, or biologic have the appropriate representation of women and minorities in all phases of research. Further, we believe the FDA should disallow or disapprove applications that do not have enough women to draw the relevant conclusions, do not provide the required analysis for safety and effectiveness by sex, or do not include women and minorities at levels in proportion to the disease prevalence in those populations. The agency has a responsibility to guarantee the safety and effectiveness of any medical product—drug, device, or biologic—that is available in the U.S. Until the FDA prioritizes the inclusion of women and minorities in all trials and ensures that appropriate analyses are conducted prior to review, they are failing in this responsibility.

Conclusion

SWHR is pleased to see a more intense focus on biological sex differences. We stand ready to work with congressional leaders, federal health and research agencies, and scientists across the country to ensure that women are represented at every stage of medical research and that sex differences analysis is appropriately prioritized in medical research. SWHR will soon be publishing a white paper to inform and educate researchers on the importance of incorporating sex as a fundamental and important variable in their research. We look forward to working with other women's health advocacy groups and the medical and research community to ensure that sex differences are recognized as a fundamental variable in all research.

Disclosure Statement

No competing financial interests exist.

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