

Chairman Lamar Alexander
Ranking Member Patty Murray
Senator Richard Burr
US Senate Committee on Health, Education, Labor & Pensions
428 Dirksen Office Building
Washington, D.C. 20510

August 18, 2015

Dear Chairman Alexander, Ranking Member Murray, and Senator Burr

The Endocrine Society and the Society for Women's Health Research (SWHR®) were extremely excited to review the report on Innovation for Healthier Americans¹ and learn of the formation of a bipartisan initiative to improve processes at the Food and Drug Administration and National Institutes of Health. Our organizations recognize that this document is an important effort to identify issues and improve upon the process of delivering cures to America's patients. We applaud the Senate HELP Committee for their work and appreciate the opportunity to continue to provide feedback on how to implement transformative change to more efficiently bring cures to the public.

While the Innovation for Healthier Americans report contains many commendable initiatives, our societies are concerned that the document lacks language to codify a process to include sex differences in basic research at the NIH. This is an imperative provision for achieving meaningful reform. As we and others have noted, biomedical research has historically utilized male research subjects disproportionately, creating a significant gap in knowledge regarding the extent to which disease processes and underlying physiology are influenced by biological sex^{2,3}. The lack of inclusion of females in pre-clinical basic research has resulted in an increasing number of treatments that have had more adverse effects in women and in some cases resulted in medications being pulled from the market.

¹ http://www.help.senate.gov/imo/media/IInnovation_for_Healthier_Americans.pdf Accessed April 15, 2015

² [Endocrine Society Letter to Bipartisan Group of Women Senators on Sex Differences in Preclinical Research](#)
- May 12, 2014. Accessed February 8, 2014.

³ New Policies Signal Changing Attitudes on Sex Differences Research: An SWHR® Perspective. Ritter Leslie, Grant Emily, and Carter Christine L.. Journal of Women's Health. September 2014, 23(9): 717-719.
doi:10.1089/jwh.2014.1506.



The NIH has recognized this gap and announced policies to balance the study of males and females in preclinical research⁴. With this announcement, the NIH has begun to take steps towards achieving equity in biomedical research, but it has yet to implement these policies. Therefore, legislation is necessary. We fully support the NIH in this endeavor and we believe that the Senate HELP Committee could provide the NIH with an incentive to prioritize these policies while holding NIH accountable to ensure their full development implementation. The attached document "Codifying a Process to include Sex Differences in Basic Research within NIH" contains proposed language that would give NIH the authority to implement the policies it is already planning to advance.

We believe that any overarching strategy to "ensure that America remains the world's leading global innovator in medicine, and in the process also ensure that our nation's patients have access to the most cutting-edge medical products" should advance the science of sex differences so that we can achieve cures for the entire population. We hope that you will include the attached provision in legislation related to the Innovation for Healthier Americans Report. Thank you for your time and consideration. We look forward to working with you to advance the biomedical research enterprise in a truly transformative way.

Sincerely,

Lisa Fish, MD
President
Endocrine Society

Phyllis Greenberger, MSW
President and CEO
Society for Women's Health Research

⁴ J.A., Collins, F.S. NIH to balance sex in cell and animal studies. Nature. 509, 282-283 (2014)

Codifying a Process to include Sex Differences in Basic Research within NIH

Background

More than anything, “good science” is at the heart of basic clinical research. It is imperative that data collection be both reproducible and generalizable, because it is this data that leads to important discoveries and breakthroughs. As a result, reproducible and generalizable data requires that all stages of the biomedical research cycle include a consideration of sex differences in research subjects where appropriate. A significant component of the rigor and completeness in research is the investigation of sex specific effects. Despite decades of awareness of the issue, females are still inadequately represented in many clinical trials. Additionally, sex differences are still not routinely considered as a critical variable in basic biological studies. This critical inconsistency in the biomedical research pipeline can have serious consequences. For example, of the 10 drugs that were withdrawn from January 1, 1997 through 2001, 8 posed greater health risks for women⁵. The consideration of sex is an important biological variable and therefore must be incorporated into preclinical research.

The Office of Research on Women’s Health’s (ORWH’s) Strategic Plan, published in September 2010, included as its first goal to “increase sex differences research in basic science studies.” It noted that “an expanded conceptual framework is needed that explores variations due to sex as an integral part of the search for knowledge across the entire research spectrum, beginning at the most basic laboratory level.”

In May 2014, NIH Director Collins and ORWH Director, Jeanine Clayton published a comment in *Nature* indicating the agency was developing “policies that require applicants to report their plans for the balance of male and female cells and animals in preclinical studies in all future applications, unless sex-specific inclusion is unwarranted, based on rigorously defined exceptions.” This commentary set the stage for NIH’s positive steps towards implementing a new policy to require grant applicants to describe their plans to include sex as a biological variable in research.

In June 2015, NIH released a notice (NOT-OD-15-102) and guidance document detailing their expectations for the consideration of sex as a biological variable in medical research, to be in effect for the 2017 fiscal year funding. While the guidance does provide researchers with NIH’s expectations regarding the inclusion of sex as a biological variable; many questions remain on how it should be incorporated into research designs, analyses, and reports in both pre-clinical and human studies. We believe that codification of the recommendations below will guide agencies to provide clarity to researchers in the community, thereby ensuring that effective policies are implemented in a way that makes sense and is minimally disruptive.

⁵ <http://www.gao.gov/new.items/d01286r.pdf> Accessed May 20, 2014

Proposed Legislation

1. Authorize NIH to develop policies that require research applicants to report their plans for the inclusion of male and female cells and animals in preclinical studies in all ~~future~~ applications, unless sex-specific inclusion is unwarranted, based on rigorously defined exceptions. No later than one year after enactment of this legislation, NIH shall publish the final policy and detailed guidance for reviewers and prospective grantees on sex inclusion, and criteria for exclusion from the NIH policy.
2. The expansion of such current policies shall include plans for:
 - a. Investigators to prominently indicate the sex of their experimental model in their grant application, progress reports and journal articles.
 - b. Investigators studying one sex to provide justification as to why the study is limited to one sex as part of the grant reporting process and in published reports. When studying both sexes, investigators should report, and when appropriate, analyze their data by sex as part of grant progress reporting to the Agency and in published results.
 - c. Investigators to consider sex as a biological variable in relevant research on animals, cells, and human subjects.
3. Direct NIH to monitor compliance of sex and gender inclusion in all phases of research funded by the agency through data-mining techniques that are currently being developed and implemented. Encourage NIH to work with publishers to promote the publication of such research results.
4. Authorize the Director of the NIH to establish a Trans-NIH Working Group on Sex Differences in Research, which shall be comprised of representatives of each Institute and Center, the Office of Research on Women's Health, as well as appropriate members of the extramural scientific and academic communities and patient organizations as determined by the NIH Director.

The Working Group shall ensure appropriate implementation of the regulations proposed above; determine the progress of NIH's strategic plan on sex difference in research and ensure open collaboration between ICs on this matter. The Working Group shall provide a written report to the Director to be included in the NIH biannual report that details the inclusion of female cells and animals as well as advances in sex differences in pre-clinical research; the proportion of women and minorities as subjects in clinical research participant enrollment by trial phase and in all studies of human subjects; the proportion of studies that incorporate sex as a biological variable; and number of those studies which analyze data by sex as part of grant review, award, and oversight processes. This data should be reported by Institute and Center across the Agency.

5. The National Library of Medicine is urged to implement changes to Clinicaltrials.gov that will require users to input the number of participants that drop out of trials and break those participants out by sex/gender and race.

6. Authorize a regional Specialized Centers of Research on Sex Differences program, which would be a collaboration between ORWH and FDA. The purpose of the program is to “support interdisciplinary collaborations on sex and gender influences in health, and bridges basic- and clinical-research approaches. This program also facilitates training in sex and gender considerations in experimental design and analysis.”