

The Honorable Fred Upton, Chairman
The Honorable Diana DeGette
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515

February 10, 2015

Dear Mr. Upton and Ms. DeGette

The Endocrine Society and the Society for Women's Health Research (SWHR[®]) were extremely excited to review the 21st Century Cures Discussion Document. Having closely followed the 21st Century Cures initiative and provided input from its inception, our organizations recognize that this document is an extraordinary synthesis of stakeholder expertise and input. We applaud the 21st Century Cures team for their effort 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 21st Century Cures Discussion Document 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 National Institutes of Health (NIH). This is an imperative provision to meeting the goals of the path to 21st Century Cures. 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 sex¹. 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.

The NIH has recognized this gap and announced policies to balance the study of males and females in preclinical research². With this announcement, the NIH has begun to take steps towards achieving equity in biomedical research, but it has not implemented any of these policies. Therefore, legislation is necessary. We fully support the NIH in this endeavor and we believe that 21st Century Cures could provide the NIH with an incentive to prioritize and accountability to ensure the development and full implementation of these policies. The attached document

¹ [Endocrine Society Letter to Bipartisan Group of Women Senators on Sex Differences in Preclinical Research](#) - May 12, 2014. Accessed February 8, 2014.

² 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” contains proposed language for 21st Century Cures that would give NIH the authority to implement the policies that it is already planning to advance. This language could most appropriately be included in Title IV, Subsection A, of the 21st Century Cures discussion draft.

We believe that a necessary component of any overarching strategy to “build the foundation for 21st century medicine”, as 21st Century Cures is capable of doing, should advance the science of sex differences, so we can achieve cures for the entire population. We hope that you will include the attached provision in the 21st Century Cures Initiative. 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,



Richard J. Santen, MD
President
Endocrine Society



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

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

Background

More than anything, “good science” is at the heart of basic research. It is imperative that data collected be both reproducible and generalizable, because it is this data that leads to important discoveries and breakthroughs. The generalization of 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, women 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 women³. 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 that it 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.” They indicated that they would be rolling out these policies starting in October 2014. While NIH has initiated this process, we believe that codification of the recommendations below will provide guidance to the process.

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 draft policy via a notice of proposed rulemaking to allow for public comment and response. 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 and progress reports.

³ <http://www.gao.gov/new.items/d01286r.pdf> Accessed May 20, 2014

- b. Investigators studying one sex, should provide justification as to why the study is limited to one sex as a 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.
2. Direct NIH to monitor compliance of sex and gender inclusion in preclinical 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.
3. 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 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 to 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 females and advances in sex differences in pre-clinical research and include 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 of those studies which analyze data by sex as part of grant review, award, and oversight processes and this data should be reported by Institute and Center across the Agency.

4. 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.
 5. Authorize the Specialized Centers of Research on Sex Differences program, which is 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."