

August 2, 2024

The Honorable Diana DeGette
Committee on Energy and Commerce
U.S. House of Representatives
2111 Rayburn House Office Building
Washington, DC 20515

The Honorable Larry Bucshon
Committee on Energy and Commerce
U.S. House of Representatives
2313 Rayburn House Office Building
Washington, DC 20515

Dear Representatives DeGette and Bucshon:

The Society for Women's Health Research (SWHR)—a national nonprofit organization dedicated to improving women's health through science, policy, and education while promoting research on sex differences to optimize women's health—is pleased to provide response to your request for information on the Next-Generation Cures bill.

SWHR has a more than 30-year history of working to improve our nation's research enterprise by ensuring the inclusion of women across all levels of science and to deliver treatments to patients who need them, when they need them. As such, we appreciate your efforts to build upon the legacy of the *21st Century Cures* initiative to bring about innovation, advance scientific understanding, and spur the development of new treatments.

As you review stakeholder input on the future of this initiative, SWHR would like to provide the following comments for your consideration, some of which reflect similar feedback we provided on the *21st Century Cures 2.0* concept paper:

Enhance Research on Sex Differences and Sex as a Biological Variable (SABV)

The National Institutes of Health (NIH) Revitalization Act of 1993¹ directed the NIH to establish guidelines for the inclusion of women and minorities in clinical research. Going a step further, the NIH in 2016 released the guidance document, "Consideration of Sex as a Biological Variable in NIH-Funded Research," which highlighted NIH's expectation that researchers consider sex in the design, analysis, and reporting of studies involving vertebrate animal and human studies and noted that "strong justification from the scientific literature, preliminary data, and other relevant considerations, must be provided for applications proposing to study only one sex."²

¹ Public Health Service Act sec. 492B, 42 U.S.C. sec. 289a-2. Accessed at: <https://www.govinfo.gov/content/pkg/USCODE-2011-title42/pdf/USCODE-2011-title42-chap6A-subchapIII-partH-sec289a-2.pdf>

² National Institutes of Health (2016). Consideration of sex as a biological variable in NIH-funded research. Accessed at: https://orwh.od.nih.gov/sites/orwh/files/docs/NOT-OD-15-102_Guidance.pdf

SWHR was grateful that the *21st Century Cures Act* (PL 114-255) required NIH to provide guidance for reporting on sex differences within preclinical research and to consider, as appropriate, whether scientists and research institutions have complied with this reporting requirement when awarding any future grants. For, as was noted in the 2020 *Journal of Women's Health* article, "Sex as a Biological Variable: A 5-Year Progress Report and Call to Action,"³ "Integrating SABV into basic and preclinical research to identify potential differences in drug safety is far more efficient than discovering them during clinical trials or in postmarketing surveillance. Investments in preclinical research that consider SABV may also help avoid differential effectiveness outcomes."

Despite these important prior steps, SWHR believes that greater enforcement and accountability of the SABV policy is needed and that more could be done to integrate SABV into the broader biomedical research enterprise. For example, in November 2022, an article was published in *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*⁴ that examined whether the SABV policy was being considered in preclinical aging research. For the study, the authors searched for research articles that reported NIH extramural research funding support from January of 2020 through May of 2021, yielding 507 articles the authors felt were relevant to their analysis. While the authors note some limitations to their review, they ultimately found that "more than 50% of [National Institute on Aging]-funded studies published [from 2020 through 2021] are not considering SABV, despite the NIH mandate being in place since 2016." Specifically, the article shares the following statistics:

- Approximately half incorporated both sexes in the design of all or a subset of experiments (40.6% and 7.1%, respectively), while 43% reported single-sex data (30.4% male-only; 12.6% female-only), and 9.3% failed to specify sex at all
- Just 17.4% of male- or female-only experiments offered any justification as to why
- Of the articles that included both sexes in some or all experiments, only 46.3% reported comparisons between male and females

As part of the Next-Generation Cures bill, SWHR would like to see SABV prioritized across NIH Institutes and Centers, the U.S. Food and Drug Administration (FDA), and other research entities across the federal government. Steps you may wish to consider include directing NIH to provide information regarding compliance with the requirements laid out in the original Cures legislation and to provide an update on this process; calling for a U.S. Government Accountability Office (GAO) report to evaluate adherence to the NIH SABV policy since its implementation; conducting an evaluation on the use and prioritization of sex differences research across U.S. research agencies; expanding initiatives such as the NIH's Sex & Gender Administrative Supplement Program, which grants supplemental funding as an incentive to add a sex component to an existing research program; and considering whether journal articles and

³ Arnegard, M. E., Whitten, L. A., Hunter, C., & Clayton, J. A. (2020). Sex as a Biological Variable: A 5-Year Progress Report and Call to Action. *Journal of women's health* (2002), 29(6), 858–864. <https://doi.org/10.1089/jwh.2019.8247>

⁴ Carmody, C., Duesing, C. G., Kane, A. E., & Mitchell, S. J. (2022). Is Sex as a Biological Variable Still Being Ignored in Preclinical Aging Research?. *The journals of gerontology. Series A, Biological sciences and medical sciences*, 77(11), 2177– 2180. <https://doi.org/10.1093/gerona/glac042>

published research results that do not comply with SABV or Sex and Gender Equity in Research (SAGER) guidelines should be posted and linked in the National Library of Medicine.

Build Upon the Work of the PRGLAC Task Force

The *21st Century Cures Act* took an important step toward improving the health of mothers and their infants by calling for the establishment of the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to identify and address “gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies and the collaboration on and coordination of such activities.”⁵ The Task Force’s 2018 report to the Secretary of the U.S. Department of Health and Human Services (HHS)⁶ outlined a set of 15 recommendations to increase the inclusion of these populations in research, with the ultimate aim of improving knowledge and research on safe and effective treatments. Together, these steps could help inform women, their families, and health care providers about the potential effects of different treatments on both mother and baby.

Yet, despite the beneficial impacts these recommendations could have on moms and their babies for generations to come, most of the PRGLAC recommendations have not been fully implemented. Incorporating PRGLAC recommendations—and specifically those outlined in the *Advancing Safe Medications for Moms and Babies Act*—could accelerate the inclusion of these populations in clinical trials moving forward, leading to better outcomes for both mother and baby.

Therefore, SWHR supports the recommendation made by the Coalition to Advance Maternal Therapeutics (CAMT) in its response to the Next-Generation Cures request for information⁷ to include the following three PRGLAC recommendations in the Next-Generation Cures bill:

- **Require the FDA to remove regulatory barriers to the participation of pregnant women in clinical trials.** Congress requested in the *21st Century Cures Act* that FDA harmonize its regulations with the Common Rule to improve the inclusion of pregnant and lactating women in clinical research. The harmonization, which was supposed to be completed in 2019, is still in draft form. We urge you to include provisions in the Next-Generation Cures bill that would require FDA to issue final regulations in a timely manner relating to the protection of human subjects, including Parts 50 and 56 of Title 21, Code of Federal Regulations, with the latest regulations of HHS relating to the inclusion of pregnant women as subjects in clinical research.
- **Accelerate NIH research on the safety and efficacy of medications used during pregnancy and lactation.** We recommend the creation of a new program at NIH that

⁵ 114th Congress. 21st Century Cures Act. Congressional Record. 2016; 130 Stat, PL 114-255. <https://www.congress.gov/bill/114th-congress/house-bill/34/text>. Accessed July 18, 2024.

⁶ Task Force on Research Specific to Pregnant Women and Lactating Women. Report to Secretary, Health and Human Services, Congress. Bethesda, MD: NICHD; 2018. Available from: https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf. Accessed July 18, 2024.

⁷ Coalition to Advance Maternal Therapeutics. Response Letter on Next-Generation Cures Bill Request for Information; 2024. <https://safemeds4moms.org/wp-content/uploads/2024/07/CuresRFIResponseCAMT2024.pdf>. Accessed 31 July 2024.

provides dedicated funding to conduct priority research projects on existing medications and therapeutics prescribed to pregnant and lactating women, which are currently significantly underfunded. The new program should give preference to research applications demonstrating the following as it relates to pregnant and lactating women: an unmet medical need or gap in treatment, severity and prevalence of a specific disease or condition, and cost and availability of treatment or alternate treatments.

- **Educate stakeholders on opportunities for pregnant and lactating women to participate in clinical research.** We encourage you to provide funding for a new education campaign, developed in consultation with external subject-matter experts, that would make it easier for clinicians, patients, and families to identify research opportunities that exist for pregnant and lactating populations. The campaign should include information on registries and clinical trials that enroll pregnant and lactating women, how patients can enroll, and address common questions for clinicians and patients. All campaign information should be available via a public-facing website.

Further, SWHR encourages you to ensure that the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has adequate authority and resources to fully implement PRGLAC's recommendations.

Continue Efforts to Increase Diversity in Clinical Trials

The *21st Century Cures Act* placed an emphasis on diversity of clinical trial participants – both as part of the Precision Medicine Initiative and as part of its call for the NIH to develop policies to enhance the rigor and reproducibility of its research. SWHR encourages lawmakers to prioritize diversity within clinical trials in the Next-Generation Cures bill as well.

Women's representation in clinical trials has admittedly improved over the years. ClinicalTrials.gov data⁸ shows that women, on average, represent 41.2 percent of trial participants. However, looking within different fields of research reveals that problems with representation persist.

One analysis on clinical trials between 2000-2020 found that women are underrepresented in clinical trials in cardiology, oncology, neurology, immunology, and hematology.⁹ Women of color are also significantly underrepresented. According to a 2022 article in *Cell Reports Medicine*,¹⁰ in U.S. Food and Drug Administration (FDA) oncology trials over 2017-2020, the total percentage of participants (of which women comprised less than half) who were Black or African American ranged from 2-5 percent, and of Hispanic or Latino ethnicity from 4-6 percent

⁸ Vadali, M. More Data Needed, Study Shows Females Underrepresented in Key Disease Clinical Trials. Accessed 15 December 2022. <https://hms.harvard.edu/news/more-data-needed#:~:text=After%20examining%201%2C433%20trials%20with,of%20trial%20participants%20were%20female>

⁹ Steinberg JR, Turner BE, Weeks BT, et al. Analysis of Female Enrollment and Participant Sex by Burden of Disease in US Clinical Trials Between 2000 and 2020. *JAMA Netw Open*. 2021;4(6):e2113749. doi:10.1001/jamanetworkopen.2021.13749

¹⁰ Bierer, B. E., Meloney, L. G., Ahmed, H. R., & White, S. A. (2022). Advancing the inclusion of underrepresented women in clinical research. *Cell reports. Medicine*, 3(4), 100553. <https://doi.org/10.1016/j.xcrm.2022.100553>

(Black and African American individuals represent 12.1 of the U.S. population, and Hispanic or Latino individuals represent 18.7 percent of the population). Authors also noted that while sex and race are reported for these trials, the intersection of sex and race are not, which limits our ability to study important intersectional characteristics within trial populations. Additionally, the authors emphasize, “In addition to FDA-regulated trials, numerous reports confirm the underrepresentation of women of diverse racial and ethnic backgrounds in post-approval trials, NIH-supported trials, comparative effectiveness trials, vaccine trials, and others.”

Beyond diversity in clinical trials, the *21st Century Cures Act* also referenced enhancing workforce diversity. Workforce diversity can have implications on innovation, health disparities, trust, and the strength of the science itself.

Although women account for about half of medical graduates and doctoral recipients in the biological sciences, they are underrepresented at all levels of leadership in the biomedical field.¹¹ Women in research earn less¹² and receive less funding at the beginning of their careers.¹³ Women are also more likely to switch to part-time work, change careers, or leave the workforce. Furthermore, they disproportionately face sexual harassment and discrimination.^{14,15}

While efforts have been made to foster the next generation of researchers, address sexual harassment, and improve workforce diversity, there is more that could be done. SWHR’s previous suggestions¹⁶ on this topic have included:

- Urging federal agencies to consider the roles of sex and gender and sexual and gender minorities and how the current landscape may affect different populations (whether through implicit or subconscious bias or harassment) and how policies could resolve the disparities faced by these populations
- Establishing, sustaining, and enhancing partnerships with higher education institutions to improve talent pipeline initiatives
- Expanding partnerships to community colleges, technical colleges, and historically Black colleges and universities (HBCUs) to enhance training and credentials and recruit from traditionally underrepresented populations
- Establishing and/or encouraging employer-institution partnerships—including networking, mentorship, and job shadowing programs—at non-traditional institutions to enhance exposure opportunities for workers

¹¹ Clayton et al. Women’s Careers in Biomedical Sciences: Implications for the Economy, Scientific Discovery, and Women’s Health. *Journal of Women’s Health*, 2017. doi: 10.1089/jwh.2016.6012

¹² Scientists’ salary data highlight US\$18,000 gender pay gap. *Nature*. January 22, 2019.

¹³ Sege, Nykiel-Bub, Selk. Sex Differences in Institutional Support for Junior Biomedical Researchers. *JAMA*. 2015; 314(11): 1175-1177. doi: 10.1001/jama.2015.8517

¹⁴ Sexual harassment of women: Climate, culture, and consequences. National Academies (2018).

¹⁵ Funk and Parker. Women and Men in STEM Often at Odds Over Workplace Equity. Pew Research Center. January 2018. <https://www.pewresearch.org/social-trends/2018/01/09/women-and-men-in-stem-often-at-odds-over-workplace-equity/>

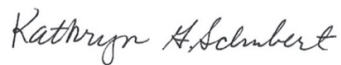
¹⁶ SWHR Comments to NIH UNITE Initiative Committees on Diversity in Biomedical Careers (2021).

https://swhr.org/swhr_resource/swhr-comments-to-nih-unite-initiative-committees-on-diversity-in-biomedical-careers/

The *21st Century Cures Act* marked an important point in time – representing a bipartisan desire from Congress to substantively invest in the acceleration of cures and the advancement of biomedical research. It funded innovative initiatives and examined how the U.S. research enterprise could be adjusted to foster scientific progress. We are glad to see renewed momentum around this initiative and appreciate your leadership to develop the Next-Generation Cures bill. Thank you for the opportunity to provide input and for your consideration of our comments.

If you have questions about the content above, or if you would like to discuss it further, please email me at kathryn@swhr.org. SWHR stands ready and willing to assist you and your teams as you move forward in this process.

Sincerely,

A handwritten signature in cursive script that reads "Kathryn H. Schubert".

Kathryn Schubert, MPP, CAE
President and CEO
Society for Women's Health Research