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August 21, 2020

### Submitted electronically to:

<https://grants.nih.gov/grants/rfi/rfi.cfm?ID=108>

Barbara Wold, PhD  
Bren Professor of Molecular Biology, Caltech  
Co-Chair, ACD Working Group on Enhancing Rigor,  
Transparency, and Translatability in Animal Research

Lawrence A. Tabak, DDS, PhD  
Principal Deputy Director, National Institutes of Health  
Co-Chair, ACD Working Group on Enhancing Rigor,  
Transparency, and Translatability in Animal Research  
Building 1, Room 126  
One Center Drive  
Bethesda, MD 20892-0160

Re: NIH NOT-OD-20-130: Enhancing Rigor, Transparency,  
and Translatability to Improve Biomedical Research Involving  
Animal Models

Dear Dr. Wold, Dr. Tabak, and members of the National  
Institutes of Health Advisory Committee to the Director  
Working Group on Enhancing Rigor, Transparency, and  
Translatability in Animal Research,

The Society for Women's Health Research (SWHR) is  
pleased to offer comments in response to the June 16  
Request for Information: Enhancing Rigor, Transparency, and  
Translatability to Improve Biomedical Research Involving  
Animal Models (NOT-OD-20-130).

SWHR is a 30-year-old national nonprofit dedicated to  
promoting research on biological sex differences in disease  
and improving women's health through science, policy, and  
education. SWHR is committed to ensuring that researchers  
consider the unique needs of women across all areas of  
health care and that sex as a biological variable (SABV) is  
incorporated within research involving animal models.

Until about 25 years ago, essentially all health research was  
conducted on men, due to the persistent idea that female  
hormonal cycles were too difficult to manage in experiments  
— including the fear of harming potential pregnancies — and  
that using only one sex would reduce variation in results. This  
exclusion of females in health research extended to research  
on female animals, cells, and tissue. Researchers assumed



they could simply extrapolate their male-only study results to females, a dangerous precedent that overlooked fundamental differences between women and men.

Given this history, SWHR is grateful for the National Institutes of Health (NIH) policy requiring grant applicants to consider SABV in vertebrate animal and human studies. Based on the 2016 policy, if grant applicants seek to study only one sex, they must offer strong justification. The implementation of the NIH Policy on Consideration of Sex as a Biological Variable in NIH-Funded Research (NOT OD-15-102) has been a positive catalyst for advancing SABV.

However, because the policy only requires that investigators consider the role of SABV in research designs, analyses, and reporting — and stops short of requiring it — there is variability in the testing and reporting of sex-difference findings in NIH-funded research.

With this in mind, SWHR is pleased to provide feedback on the use of SABV to enhance rigor, transparency, and translatability in order to improve biomedical research involving animal models. We provide recommendations across NIH-specified domains and topic areas below.

**Rigor and Transparency:** *The challenges of rigor and transparency in animal research and actions NIH can take to improve the quality of animal research including rigor and transparency.*

SWHR Recommendation: Institute policies to provide improved oversight and monitoring regarding the inclusion of SABV within animal research.

The 2016 NIH SABV policy would benefit from follow-up analyses and guidance for grant reviewers to ensure the policy is changing research culture and improving analysis and reporting. Implementation and oversight of the 2016 policy can and should serve as a model for future NIH efforts to improve reproducibility.

Current research shows the dominance of male subjects and ignorance of SABV persists. As compared to a 2009 study,<sup>1</sup> recent research indicates that significantly more preclinical articles published in 2019 included both sexes in the sample population. However, little progress has been made in analyzing study results by sex. Among studies that included both sexes as subjects, only 42% included sex-disaggregated analyses, down from 50% of articles in 2009.<sup>2</sup>

SWHR encourages the NIH to consider how best to build upon the successes of its 2016 policy to ensure that grant reviewers are well-trained in providing SABV oversight during that process. We also recommend the NIH engage in periodic monitoring of grant applications to ensure that the policy is being implemented as intended.

Finally, SWHR stresses the importance of not only including both sexes, but providing sex-disaggregated outcomes analyses. We encourage the NIH to train reviewers to look not only for the inclusion of both sexes, but for explanations as to how researchers plan to account for SABV within intended outcomes analyses, as appropriate to the overall goals of the study.

<sup>1</sup> Beery, A, Zucker, I. Sex bias in neuroscience and biomedical research. *Neurosci Biobehav Rev.* 2010;35(3):565-572.

<sup>2</sup> Woitowich, NC, Beery, A, Woodruff, T. Meta-research: A 10-year follow-up study of sex inclusion in the biological sciences. *eLife.* 2020;9:e56344. doi: 10.7554/eLife.56344



**Rigor and Transparency:** *How preregistration, the process of specifying the research plan in advance of the study and submitting it to a registry, would impact animal research including improving the quality of scientific research.*

SWHR Recommendation: We encourage the NIH to provide further explanation as to how preregistration within preclinical research will benefit the field without limiting researcher ability to explore unexpected results.

Regarding SABV, SWHR is concerned that overly rigorous preregistration requirements may limit the study of sex differences unexpectedly found during the course of research. SABV is important not just in the consideration of equal representation of female and male study subjects but also in the analysis of sex-disaggregated data. Should researchers not include SABV in planned outcomes analyses during the course of preregistration, they may be unable to complete secondary analyses to determine the magnitude and/or etiology of said differences.

Any preregistration requirements must maintain some level of researcher flexibility. This is especially true within the field of animal research, where important secondary analyses may be revealed in the course of investigation, versus clinical research, where preplanned secondary analyses are more common. Preregistration requirements, therefore, should be considered and developed in manners that support the different goals within preclinical and clinical research.

**Optimizing the Relevance to Human Biology and Disease:** *How to encourage researchers to select or develop animal models with high utility and design experiments that have external validity to the clinical populations.*

SWHR Recommendation: Expand 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.

Many drivers of academic research fall outside of the NIH's control, e.g., the financial considerations of funding one's own salary and laboratory operations as well as pressure to succeed in order to achieve career milestones such as tenure. Providing financial incentives and/or other types of research awards may incentivize researchers to take the inclusion of SABV a step further, as these awards may be included within a researcher's curriculum vitae and/or tenure application.

We encourage the NIH to consider implementing initiatives that may benefit researchers within their career and to incorporate these considerations into the creation of future supplemental funding and/or research award models.

SWHR Recommendation: The NIH should urge investigators to provide comprehensive reasoning behind animal model selection and fully explain why the selected model is the best choice to address the research questions proposed within the grant application. SWHR encourages the consideration of SABV within this process.

Regarding translatability, it is equally important to encourage the inclusion of female and male animals as it is to consider how well the animal model chosen is able to represent disease pathophysiology and progression.



For example, within animal models investigating osteoarthritis (OA), the extent to which certain animal models exhibit disease markers in both sexes varies. Within the destabilization of the medial meniscus (DMM) model, a surgical model of OA characterized by limited inflammation and slow disease progression in distinct stages, only male animals exhibit effects. In contrast, studies using the monoiodoacetate-induced model (MIA) of OA show effects in animals of both sexes.<sup>3</sup> It would be tempting to conclude that the MIA model is a superior choice; however, the mechanism behind this model leads to an overly-aggressive inflammatory disease progression that is less similar to OA human presentation.

Although this is not a satisfactory reason to study only one sex, it points to the importance of consideration of multiple factors in study design and the need for animal model selection to be fully explained within grant applications.

**Research Culture:** *How all researchers, including trainees, are educated in research design, statistical considerations, transparent research practices that are fundamental to rigorous animal research, and the role of the NIH in this training.*

**SWHR Recommendation:** Increase and improve training of researchers on SABV study design in preclinical and clinical research.

SWHR looks forward to the upcoming release of plans for NIH continuing education courses and materials on SABV, including “Bench to Bedside: Integrating Sex and Gender to Improve Human Health” and “Sex as a Biological Variable: A Primer.” The goals of both courses are commendable and we are hopeful that the NIH will continue to lead the way in providing educational materials for researchers.

SWHR encourages the creation of SABV materials aimed at scientists-in-training that student mentors and faculty members can include within their own graduate-level courses. Training the upcoming generation of biomedical research scientists in best practices for SABV will be crucial to standardizing these concepts within the field.

The NIH is able to play a major role in training for the next generation of scientists. Training modules should be generalizable to the largest extent possible. SWHR recommends partnering with relevant stakeholders (e.g., membership societies as well as professional interest groups, relevant nonprofits, etc.) to create more specific guidance within subdisciplines as appropriate.

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SWHR is grateful for the opportunity to provide feedback to the NIH on the best practices for enhancing rigor, transparency, and translatability to improve biomedical research involving animal models. We look forward to continued opportunities to collaborate with the NIH on this topic. If you have any questions, please do not hesitate to contact SWHR's Director of Science Policy, Melissa Laitner, PhD, MPH, at [melissa@swhr.org](mailto:melissa@swhr.org).

<sup>3</sup> Malfait, A.M., & Miller, R. E. (2020). Why we should study osteoarthritis pain in experimental models in both sexes. *Osteoarthritis and Cartilage*. doi:10.1016/j.joca.2019.12.008



Society for  
Women's Health Research

MAKING WOMEN'S HEALTH MAINSTREAM

Sincerely,

*Kathryn G. Schubert*

Kathryn G. Schubert, MPP  
President and Chief Executive Officer  
Society for Women's Health Research