

CONSIDERATION OF SEX AS A BIOLOGICAL VARIABLE IN NIH-FUNDED RESEARCH

The new National Institutes of Health (NIH) policy on consideration of sex as a biological variable <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html>, once approved by the Office of Budget and Management, will require investigators to include accounting for sex as a **biological variable** in the 'research strategy' section of the application.

This policy will apply to applications submitted on or after January 25, 2016.

Key points from the policy are the following:

1. The policy sets forth expectations that studying **both male and female vertebrate animals and humans** will improve the understanding of health and disease in men and women.
2. In the **Research Strategy section** of the NIH application, applicants are to
 - Explain how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans
 - Provide strong justification from the scientific literature, preliminary data, or other relevant considerations when proposing only one sex
3. NIH **review criteria** will include evaluation of the adequacy of the research plan in considering sex as biological variable.

NIH Definitions of Sex and Gender

NIH follows the Institute of Medicine report, *Exploring the Biological Contributions to Human Health: Does Sex Matter?* <https://www.iom.edu/Reports/2001/Exploring-the-Biological-Contributions-to-Human-Health-Does-Sex-Matter.aspx#sthash.byYBNt0V.dpuf>. "Sex is defined as a biological variable defined by characteristics encoded in DNA, such as reproductive organs and other physiological and functional characteristics. Women and men are characterized by both sex and gender. Gender refers to social, cultural, and psychological traits linked to human males and females through social context. In most cases, "sex" should be used when referring to animals. Both sex and gender and their interactions can influence molecular and cellular processes, clinical characteristics, as well as health and disease outcomes."

Preparing an Application: Things to Consider

Literature Review:

- Consider and describe how sex and gender may influence the research questions
- Conduct a review of the literature for human clinical literature and preclinical literature and look for any reported differences between males and females

- Differences in male and female data provide strong rationale for building consideration of sex into the research design and analyses of the data.

Note - The absence of data alone does not justify studying only one sex.

Research Design:

- The strategy for considering sex as a biological variable will depend on the context of the research question, existing knowledge about male and female biology and behavior in the field of research, and methodology.
- If insufficient sex-specific data are available, sex-specific hypotheses may not be possible. If sufficiently observed sex differences exist, a sex-specific hypothesis may be included.
- Consideration of effect size and power calculations to determine the number of samples/subjects in the study should be included in the experimental design, if applicable.
- If utilizing animal models, the experimental design and analysis sections should include if and how the female estrous cycle is relevant.
- When using both sexes, develop a data analysis plan that provides, at a minimum, for the collection of data disaggregated by sex.
- Include in the proposal, progress reports, and publications, the limitations of the findings that may arise from the samples, methods, and analysis used.

Reports and Publications:

- The sex of the research subjects and/or materials must be provided in reports and publications when possible.
- Include when sex differences are or are not detected in the analyses of the data.

Single-Sex Studies:

If single sex studies are proposed in the application, strong justification must be provided to justify studying only one sex. Justification for these studies may include

- Sex-specific conditions or phenomenon (e.g. ovarian or prostate cancer)
 - Acutely scarce resources (e.g. non-human primates)
 - Investigations where the study of one sex is scientifically appropriate and justified
- Note – Absence of evidence regarding sex differences in an area of research does not constitute strong justification for studying one sex.

Contact the IACUC Chair (Frank Jenkins fjenkins@pitt.edu), for inquiries and assistance when considering sex as a biological variable in NIH applications.

Additional Resources

NIH policy on consideration of sex as a biological variable

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html>

NIH Guidance

http://orwh.od.nih.gov/sexinscience/overview/pdf/NOT-OD-15-102_Guidance.pdf

Institute of Medicine Report on Sex and Gender

<https://www.iom.edu/Reports/2001/Exploring-the-Biological-Contributions-to-Human-Health-Does-Sex-Matter.aspx#sthash.byYBNt0V.dpuf>

NIH policy on Enhancing Reproducibility through Rigor and Transparency

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-103.html>

Nature Articles on the subject

<http://www.nature.com/news/policy-nih-to-balance-sex-in-cell-and-animal-studies-1.15195>

<http://www.nature.com/news/policy-nih-plans-to-enhance-reproducibility-1.14586>