Frequently Asked Questions for the Congressionally Directed Medical Research Programs (CDMRP) Directive on Sex as a Biological Variable (SABV) in Research

I. General CDMRP SABV Directive Questions

A. What is the purpose of the CDMRP directive on sex as a biological variable (SABV) in research?

The overarching goal of this directive is to ensure the appropriate inclusion of males and females across the spectrum of CDMRP-funded research, including basic, translational, and clinical research. Consideration of biological variables, such as sex, improves our understanding of health and disease in both men and women. The directive applies to vertebrate animals, humans and/or material of human origin, thereby complimenting the CDMRP directive on the Inclusion of Women and Minorities as Subjects in Clinical Research.

Full details on the directive, as well as the directive on the Inclusion of Women and Minorities as Subjects in Clinical Research, are available on the eBRAP website under the Funding Opportunities & Forms tab, in the Resources and Reference Material section.

B. Which studies are subject to the directive?

This directive applies to all applications for CDMRP-supported research involving vertebrate animals, humans and/or material of human origin where the sexes are known. **This includes studies using cadaveric specimens, tissues, cell lines, and/or data.** The directive applies to all applications for studies that will be supported by grants, cooperative agreements, R&D contracts, and Other Transaction Agreements.

C. Which studies are exempt from the directive?

The directive applies to all FY25 and beyond applications and awards. All applications received and awards made prior to 1 October 2024 are exempt from this directive. Beginning 1 October 2024, only applications with strong justification to study only one sex are exempt from the directive. Justifications may come from the scientific literature, preliminary data, or other relevant considerations for only studying one sex. Justifications will be evaluated for appropriateness during peer and programmatic review.

D. What is the difference between the CDMRP directive on SABV and the CDMRP directive on the Inclusion of Women and Minorities (IWAM) as Subjects in Clinical Research?

The CDMRP directive on the Inclusion of Women and Minorities (IWAM) as Subjects in Clinical Research applies specifically to studies performing clinical research involving human subjects, as well as biospecimens and/or datasets that can be linked to a specific individual, sex, ethnicity, or race. The directive on SABV applies to studies using vertebrate animals, humans and/or material of human origin, thereby encompassing studies performing basic, translational, and clinical research. Additionally, the SABV directive requires that both sexes be considered in the analysis plan whereas the IWAM directive is primarily focused on the populations recruited for participation. Thus, the SABV directive and IWAM directive are not mutually exclusive. Rather, both directives may apply to a project, although the SABV directive applies to a broader variety of projects. The SABV directive applies to all projects for which the IWAM directive applies.

E. What are some examples of strong justifications to exclude SABV?

Below are some potential examples of strong justifications to exclude SABV, but it is important to note that the peer reviewers will ultimately determine whether the strength of a justification is adequate for a proposed study. As such, using one of these justifications does not guarantee that it will be favorably reviewed during peer review.

1. Samples will be deidentified and sex will be unknown.

    a. This includes basic research studies using a commercially procured, deidentified cell line. However, if cells from multiple donors will be obtained and compared, and sex information is available, it may be appropriate to include SABV.

2. The disease/condition of interest affects only one sex (e.g., ovarian or prostate cancer, pregnancy).

3. The only animal model available/appropriate for use has sex-linked lethality, making only one sex available for study.

4. The small sample size to be used excludes the possibility of sex-based comparisons. (Appropriateness of the sample size will be evaluated by peer reviewers).

F. What are some examples of inadequate justifications to exclude SABV?

1. Prohibitive cost of studying both sexes.

2. Difficulty controlling for sex hormones or the female estrous cycle.

3. Unknown sex differences.

4. Sex-based phenotypic differences in animal models.

5. The lower percentage of women in the military.

II. Questions on SABV Information When Submitting CDMRP Applications/Proposals

A. What SABV-related information do I need to submit in my competing application/proposal?

All applicants are required to include a strategy for the consideration of SABV. The statement should include a brief discussion about the current consensus of the literature regarding sex differences relevant to the research area(s) of interest. The statement should also include details on how the study design and analyses will incorporate both sexes. It is strongly encouraged to include sufficiently powered statistical analysis for sex differences or explain why this is not warranted or feasible. Additionally, applicants should consider if and/or how the female estrous cycle is relevant for experimental design and analysis. For proposed single-sex studies, the statement should provide strong justification as to why a study in both sexes is not warranted (e.g., disease only affects one sex) or is not feasible (e.g., sex-linked lethality in only available model).

In addition, applicants are advised to include appropriate discussion regarding SABV in any other sections in the proposal that may be relevant (e.g., study design in the Project Narrative). Proposals including human subjects/materials should also reference the **'**CDMRP Directive on the Inclusion of Women and Minorities as Subjects in Clinical Research' for possible additional requirements.

III. How SABV is Considered in the CDMRP Peer and Programmatic Review Processes

A. How is SABV considered in peer and programmatic review?

Peer reviewers will be asked to evaluate how the proposed plan addresses SABV in the study design, the potential generalizability of findings to both sexes, and the proposed plan for data disaggregation and/or statistical analysis on the basis of sex. In the absence of a plan to address SABV, peer reviewers will evaluate the proposed scientific justification to exclude SABV or study only one sex.

When making funding recommendations, programmatic reviewers will consider the technical merit of the application, encompassing the plan to address SABV and the justification relative to the objectives of the study, as evaluated by the peer reviewers.

B. What happens if, during peer review, my plan for considering SABV is unfavorably reviewed?

Criterion weaknesses identified during peer review will be outlined in the summary statement. If concerns regarding an applicant's plan for considering SABV arise during peer review and the application is recommended for funding, the applicant will need to work with the Grants Officer/Grants Specialist at the US Army Medical Research Acquisition Activity (USAMRAA) and the Science Officer at CDMRP during award negotiations to ensure that the concerns are addressed prior to award. If the application is not recommended for funding, the applicant should carefully consider the concerns raised in the summary statement in subsequent submissions.