DEPARTMENT OF THE ARMY
HEADQUARTERS, U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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FCMR-CD 18 July 2024

MEMORANDUM FOR SEE DISTRIBUTION

SUBJECT: Congressionally Directed Medical Research Programs Policy: Sex as a Biological Variable in Research

1. References.

a. National Institutes of Health. Consideration of Sex as a Biological Variable in NIH-funded Research; NOT-OD-15-102 Guidance. Definitions of sex and gender are available at https://orwh.od.nih.gov/sites/orwh/files/docs/NOT-OD-15-102%20Guidance.pdf.

b. National Institutes of Health. Glossary of NIH Terms. Definition of basic research is available at https://grants.nih.gov/grants/glossary.htm#BasicResearch.

c. National Institutes of Health. Glossary of NIH Terms. Definition of translational research is available at https://grants.nih.gov/grants/glossary.htm#TranslationalResearch.

d. National Institutes of Health. Glossary of NIH Terms. Definition of clinical research is available at https://grants.nih.gov/grants/glossary.htm#ClinicalResearch.

e. White House Executive Order on Advancing Women's Health Research and Innovation available at https://www.whitehouse.gov/briefing-room/presidential-actions/2024/03/18/executive-order-on-advancing-womens-health-research-and-innovation/.

f. 2022 Demographics Profile of the Military Community available at https://www.militaryonesource.mil/data-research-and-statistics/military-community-demographics/2022-demographics-profile/

2. Purpose. To establish a Congressionally Directed Medical Research Programs (CDMRP) policy outlining requirements for the consideration of sex as a biological variable (SABV) in all CDMRP-funded research, across the full spectrum of basic, translational and clinical research to include clinical trials.

3. Definitions.

a. Sex and Gender. Sex is a biological variable defined by characteristics encoded in DNA, such as reproductive organs and other physiological and functional characteristics. Gender refers to social, cultural, and psychological traits linked to human males and females through social context. In most cases, studies of cells and animals should use the term “sex.” Both sex and gender and their interactions can influence molecular and cellular processes, clinical characteristics, as well as health and disease outcomes.

b. Basic Research. This policy uses the National Institutes of Health (NIH) definition of basic research: Systematic study directed toward greater knowledge or understanding of the fundamental aspects of phenomena and of observable facts without specific applications towards processes or products in mind.

c. Translational Research. This policy uses the NIH definition of translational research: Translational research includes two areas of translation. One area is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science.

d. Clinical Research. This policy uses the NIH definition of clinical research:

(1) Patient-oriented research. Research conducted with human subjects (or on material of human origins such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies.

(2) Epidemiologic and behavioral studies.

(3) Outcomes research and health services research.

4. Policy. The CDMRP expects researchers to study both males and females unless there is a strong justification from the scientific literature, preliminary data, or other relevant considerations for only studying one sex. Single sex studies may be appropriate for sex-specific conditions or phenomena, such as ovarian or prostate cancer, or when infeasible. The enclosures to this policy provide references for requirements to implement this policy into CDMRP-funded research.

5. Applicability. This policy applies to all applications and awards for CDMRP-supported research involving vertebrate animals, humans and/or material of human origin (e.g., cadaveric specimens, tissues, cell lines, and their derived data) where the sexes are known.

6. Background. Preclinical research studies tend to rely heavily on male animals and/or omit reporting the sex of animal subjects; this issue is particularly problematic in those studies intended to inform understanding of diseases and conditions affecting both sexes. Similar to randomization, blinding, sample-size calculations, and other research design elements, consideration of biological sexes is a critical component of rigorous experimental design. Failure to account for SABV may undermine the rigor, transparency and generalizability of research findings. Considering biological variables, such as sex, improves our understanding of health and disease in both men and women.

7. Authority. This policy is an internal CDMRP initiative guided by the Office of the Secretary of Defense for Health Affairs and the White House Executive Order on Advancing Women's Health Research and Innovation, which calls on agencies to, "...use their existing authorities to advance and integrate women's health across the Federal research portfolio, close research gaps, and make investments that maximize our ability to prevent, diagnose, and treat health conditions in women." Additionally, the Executive Order requires that agencies, "...develop or strengthen research and data standards that enhance the study of women's health across all relevant, federally funded research...."

8. Effective Date. This policy becomes effective immediately upon signature, beginning with FY25 applications and awards. All applications received and all awards made prior to 1 October 2024 are exempt from this requirement.

9. The eBRAP helpdesk is the technical point of contact for all questions related to uploading required reports or documents into eBRAP at help@eBRAP.org. The point of contact for all other questions is at usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@health.mil.

10. The point of contact for this policy is [redacted].

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SARAH B. GOLDMAN
Colonel, SP
Director

4 Encls
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CDMRP Award Applicants

Enclosure 1. Background and Relevant CDMRP Processes

CDMRP's mission is to responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, their Families, Veterans and the American public. CDMRP manages research programs directed by Congress in the Defense Appropriations Bill, encompassing over $18.5 billion between FY92 to FY24. CDMRP seeks paradigm-shifting research, solutions that will lead to cures or improvements in patient care, and breakthrough technologies and resources for clinical benefit.

In FY21, CDMRP established a policy on the Inclusion of Women and Minorities as Subjects in Clinical Research, which largely mirrors the NIH policy and guidelines on this topic. The policy requires that women and individuals from minority groups be included in all CDMRP-funded clinical research studies, unless there is a clear, justifiable rationale that it is inappropriate with respect to the health of the subjects or the purpose of the research.

Beginning in FY24, CDMRP implemented language in relevant funding opportunity announcements encouraging research on health areas and conditions that affect women uniquely, disproportionately, or differently from men, including studies analyzing SABV. Such research should relate anticipated project findings to improvements in women's health outcomes and/or advancing knowledge for women's health. In an effort to ensure applicants consider SABV in designing and analyzing their research projects, including basic, translational, and clinical research, CDMRP developed this current policy in consultation with the NIH based on the NIH's 2015 policy on SABV and subsequent lessons learned.

Research funded by CDMRP must take into account the known and as yet to be discovered sex differences in disease prevalence, symptomology, and outcomes as applicable. In addition to the sex differences found within specific diseases and conditions, there are well established and significant sex effects: on drug pharmacokinetics, pharmacodynamics, and efficacy; within basic physiology that affect device design and performance; and on psychosocial and behavioral parameters. Thus, researchers should consider sex differences at all stages of the research pipeline, from preclinical research and development to clinical trials, and for all types of health care solutions, from drugs or devices to quality of life recommendations. Of note, some CDMRP programs are specifically focused on diseases or conditions that only affect one sex, such as prostate cancer and ovarian cancer.

All CDMRP funding opportunity announcements require applicants to outline specific details if proposing animal or human subjects research, including but not limited to: study objectives; animal species, sex, strain, and models; clinical strategy; randomization and blinding procedures; study endpoints/outcome measures; recruitment plan or plan for acquiring animals, cell lines and/or human biospecimen samples; and inclusion/exclusion criteria.

All applications submitted to CDMRP funding opportunity announcements undergo a rigorous two-tier review process that includes a technical review followed by a programmatic review. All CDMRP-funded research involving new and ongoing research with animals, human anatomical substances, human subjects, or human cadavers must be reviewed and approved by the Office of Human and Animal Research Oversight prior to research implementation. This administrative review requirement is in addition to the local Institutional Animal Care and Use Committee (IACUC), Institutional Review Board (IRB), Ethics Committee, or equivalent review.

Enclosure 2. Application Requirements

In addition to CDMRP's application component requirements, including those outlined by the CDMRP policy on the Inclusion of Women and Minorities as Subjects in Clinical Research, this policy requires that all CDMRP applications include a strategy for considering SABV. For proposed single-sex studies, this strategy should provide strong justification as to why a study in both sexes is not warranted. Such exceptions may include a disease or condition that only affects one sex, or a research area where SABV consideration is not feasible, such as sex-linked lethality in the only available animal model of a disease or condition.

For studies that will consider SABV by including both sexes, applicants are expected to develop a data analysis plan prospectively that, at a minimum, will collect data disaggregated by sex. Applicants are strongly encouraged to incorporate a sufficiently powered statistical analysis for sex differences into their study 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 both single and dual-sex studies, applicants should include a brief discussion of previously published sex differences research relevant to the study proposed including reference to whether prior studies support, do not support, or are inconclusive as to whether there are significant differences. Applicants should acknowledge limitations in the applicability of findings that may arise from the samples, methods, and analyses used, in the research plan.

During application review, both peer and programmatic reviewers will evaluate how well SABV was considered in the proposal. Applicants should reference the specific review criteria listed in the funding opportunity announcement.

It is important to note that the following are not considered adequate justifications for conducting single sex studies: (1) cost, (2) lack of prior evidence regarding sex differences, (3) sex-based phenotypic differences in animal models, and (4) the lower percentage of women in the population affected by the disease or condition.

Of note, the percentages of female Service Members and Selected Reserve Members have increased over the past two decades. Women currently represent 17.5% of the DoD Active-Duty Force and 21.6% of the Selected Reserve Force. Additionally, CDMRP seeks to discover, develop, and deliver health care solutions for not only Service Members and Veterans, but also military Families and the general public.

Enclosure 3. Roles and Responsibilities

1. Principal Investigators and Organizations: Consider SABV when designing studies. Provide the required information regarding compliance with the study of SABV, including a SABV strategy and appropriate discussion in relevant sections in the proposal, such as the project narrative. In DoD reports and peer-reviewed publications, acknowledge limitations in the applicability of findings that may arise from the samples, methods, and analyses used and report sex-based differences and/or disaggregate data based on sex where possible.

2. Organizational Institutional Review Boards (IRB): When deemed necessary by the Office of Human Research Oversight (OHRO), provide IRB review exemption status for projects using deidentified cell lines or samples derived from humans, which do not constitute human subjects research (see *Guidance on OHRO Review Requirements for Research Involving the Secondary Use of Data/Specimens* in Enclosure 4). Research that constitutes human subjects research requires IRB and OHRO approvals and should align with the CDMRP policy on the Inclusion of Women and Minorities as Subjects in Clinical Research.

3. Organizational Institutional Animal Care and Use Committees (IACUC): Address ethical issues for projects using animals as described in the Code of Federal Regulations. More information about these requirements can be found at https://www.ecfr.gov/current/title-9/chapter-I/subchapter-A/part-2/subpart-C/section-2.31

4. Peer Review Panels: Evaluate the following application components, in addition to current CDMRP review practices.

    a. The proposed plan to address SABV in the study design and the potential generalizability of findings to both sexes.

    b. In the absence of a plan to address SABV, the proposed scientific justification to exclude SABV or study only one sex. Lack of prior evidence regarding sex differences does not constitute strong scientific justification to study only one sex.

    c. The proposed plan for data disaggregation and/or statistical analysis on the basis of sex.

5. Programmatic Panels: In making funding recommendations, 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.

6. CDMRP Staff: Provide PIs and organizational representatives with relevant resources, such as the written policy, frequently asked questions (FAQs) and guidance to address SABV in their applications and progress reports.

Enclosure 4. Additional Resources and References

Investigators should defer to CDMRP's guidance if differences between the CDMRP and NIH policies on SABV are noted.

1. CDMRP Policy on the Inclusion of Women and Minorities in Clinical Research at https://ebrap.org/eBRAP/public/Program.htm.

2. National Institutes of Health. Consideration of Sex as a Biological Variable in NIH-funded Research is available at https://orwh.od.nih.gov/sites/orwh/files/docs/NOT-OD-15-102%20Guidance.pdf

3. NIH ORWH "Sex as a Biological Variable Primer" Training Course at https://orwh.od.nih.gov/e-learning/sex-as-biological-variable-primer.

4. FDA Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs; Guidance for Industry https://www.fda.gov/regulatory-information/search-fda-guidance-documents/study-and-evaluation-gender-differences-clinical-evaluation-drugs

5. FDA Evaluation of Gender Differences in Clinical Investigations Guidance for Institutional Review Boards and Clinical Investigators https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-gender-differences-clinical-investigations

6. Guidance on OHRO Review Requirements for Research Involving the Secondary Use of Data/Specimens https://mrdc.health.mil/index.cfm/collaborate/research_protections/hrpo

7. The following articles and website may provide useful resources related to the consideration of SABV:

a. Arnegard ME, Whitten LA, Hunter C, Clayton JA. Sex as a Biological Variable: A 5-Year Progress Report and Call to Action. J Womens Health (Larchmt). 2020 Jun;29(6):858-864. doi: 10.1089/jwh.2019.8247. Epub 2020 Jan 22. PMID: 31971851; PMCID: PMC7476377.

b. Becker JB, Arnold AP, Berkley KJ, Blaustein JD, et al. Strategies and methods for research on sex differences in brain and behavior. Endocrinology. 2005; 146:1650-73.

c. Holdcroft A. Integrating the dimensions of sex and gender into basic life sciences research: methodologic and ethical issues. Gend Med. 2007; 4 Suppl B:S64-74.

d. Hughes, RN. Sex does matter: comments on the prevalence of male-only investigations of drug effects on rodent behavior. Behav Pharmacol. 2007;18: 583-589.

e. Kostas-Polston, EA, Bevans, M, Shea, TL, McGlothen-Bell, K, et al. Ensuring accountability for consideration of sex as a biological variable in research. Nursing Outlook. 2024; 72(4):102194.

f. McCarthy MM, Arnold AP, Ball GF, Blaustein JD, et al. Sex differences in the brain: the not so inconvenient truth. J Neurosci. 2012; 32:2241-7.

g. Nieuwenhoven L, & Klinge I. Scientific excellence in applying sex- and gender-sensitive methods in biomedical and health research. J Women's Health. 2010; 19: 313-321.

h. Prendergast, BJ, Onishi KO, Zucker I. Female mice liberated for inclusion in neuroscience and biomedical research. Neurosci Biobehav Rev. 2014;40:1–5.

i. Ritz SA, Antle DM, Côté J, Deroy K, et al. First steps for integrating sex and gender considerations into basic experimental biomedical research. FASEB J. 2014; 28:4-13.

j. Gendered Innovations web resources: http://genderedinnovations.stanford.edu/methods-sex-and-gender-analysis.html Accessed May 15, 2015.

8. The following may provide useful literature review tools and resources related to the consideration of SABV:

a. Jenkins M & Wilson J. (2012). Finding the Evidence: A Sex-and Gender-Specific Medicine (SGSM) PubMed Search Engine Tool. Lubbock: Texas Tech University School of Medicine Health Sciences Center. (Instructions for accessing the database can be found here: http://genderedinnovations.stanford.edu/methods/Workshop_B_LWBSHI_Search_Engine.pdf).

b. Oertelt-Prigione S, Gohlke BO, Dunkel M, Preissner R, Regitz-Zagrosek V. GenderMedDB: an interactive database of sex and gender-specific medical literature. Biol Sex Differ. 2014; 5:7.

c. What a Difference Sex and Gender Make: A Gender, Sex and Health Research Casebook, (Canadian Institutes of Health Research, Institute of Gender and Health) http://www.cihr-irsc.gc.ca/e/44734.html.