Defense Health Agency

Congressionally Directed Medical Research Programs
Directive

March 24, 2025

DHA R&D CDMRP

SUBJECT: The Congressionally Directed Medical Research Programs Directive on Sex as a Biological Variable in Research

References: See Enclosure 1.

1. PURPOSE. This Congressionally Directed Medical Research Programs (CDMRP) directive establishes requirements for the consideration of sex as a biological variable (SABV) in all CDMRP-funded research.

2. APPLICABILITY. This directive 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.

3. IMPLEMENTATION. 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. This requirement extends across the full spectrum of basic, translational and clinical research to include clinical trials. Single sex studies may be appropriate for sex-specific conditions or phenomena, such as ovarian or prostate cancer, or when infeasible. See Enclosure 3 for requirements to implement this policy into CDMRP-funded research.

4. CANCELED DOCUMENTS. This directive replaces the "CDMRP Policy on Sex as a Biological Variable in Research" signed July 18, 2024.

5. RESPONSIBILITIES. See Enclosure 2.

6. PROCEDURES. See Enclosure 3.

7. PROPONENT AND WAIVERS. The proponent of this directive is the Director, CDMRP. When applicants are unable to comply with this directive, the applicant's rationale will be evaluated by the peer review panel.

8. RELEASABILITY. Cleared for public release. This directive is available on the Internet from the CDMRP website at: https://cdmrp.health.mil/ and is also available on the Electronic Biomedical Research Application Portal at: https://ebrap.org/eBRAP/public/Program.htm.

9. EFFECTIVE DATE. This directive is effective upon signature.

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MARK G. HARTELL
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Director

Enclosures
1. References
2. Responsibilities
3. Procedures

Appendix:
1. Additional Resources

Glossary

ENCLOSURE 1

REFERENCES

(a) Guidance on OHRO Review Requirements for Research Involving the Secondary Use of Data/Specimens https://mrdc.health.mil/index.cfm/collaborate/research_protections/hrpo.
(b) CDMRP Directive on the Inclusion of Women and Minorities in Clinical Research at https://ebrap.org/eBRAP/public/Program.htm.
(c) Code of Federal Regulations. Title 9–Animals and Animal Products is available at https://www.ecfr.gov/current/title-9/chapter-I/subchapter-A/part-2/subpart-C/section-2.31.
(d) 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.
(e) 2022 Demographics Profile of the Military Community available at https://www.militaryonesource.mil/data-research-and-statistics/military-community-demographics/2022-demographics-profile/

ENCLOSURE 2

RESPONSIBILITIES

1. DIRECTOR, CDMRP. The Director, CDMRP will ensure compliance and implementation of this CDMRP directive.

2. PRINCIPAL INVESTIGATORS (PI) AND ORGANIZATIONS. PIs and organizations will:

   a. Consider SABV when designing studies;

   b. 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;

   c. 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 in DoD reports and peer-reviewed publications, where possible.

3. ORGANIZATIONAL INSTITUTIONAL REVIEW BOARDS (IRB). IRBs will provide IRB review exemption status for projects using deidentified cell lines or samples derived from humans, which do not constitute human subjects research, when deemed necessary by the Office of Human Research Oversight (OHRO), in accordance with Reference (a). Research that constitutes human subjects research requires IRB and OHRO approvals and should align with Reference (b).

4. ORGANIZATIONAL INSTITUTIONAL ANIMAL CARE AND USE COMMITTEES (IACUC). IACUCs will address ethical issues for projects using animals in accordance with Reference (c) Chapter 1, Subchapter A, Part 2, Subpart C, Section 2.31.

5. PEER REVIEW PANELS. Peer reviewers will evaluate the following 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 justification to exclude SABV or study only one sex.

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

6. PROGRAMMATIC PANELS. In making funding recommendations, programmatic panels 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.

7. CDMRP STAFF. CDMRP staff will provide PIs and organizational representatives with relevant resources, such as the CDMRP directive, frequently asked questions, and guidance to address SABV in their applications and progress reports.

ENCLOSURE 3

PROCEDURES

1. BACKGROUND.

a. 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.

b. 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.

c. 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 IACUC, IRB, Ethics Committee, or equivalent review.

d. 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.

e. 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 directive in consultation with the NIH in accordance with Reference (d) and subsequent lessons learned.

2. GENERAL INFORMATION.

a. 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.

b. Similar to randomization, blinding, sample-size calculations, and other research design elements, consideration of biological sexes is a critical component of rigorous experimental design.

c. Failure to account for SABV may undermine the rigor, transparency and generalizability of research findings.

d. Considering biological variables, such as sex, improves our understanding of health and disease in both men and women.

e. Clinical research, including interventional clinical trials, observational clinical studies, and research with human biospecimen samples or other medical information/datasets, is important for translating health care solutions from the bench to the bedside.

f. 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.

g. 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.

h. 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.

i. Some CDMRP programs are specifically focused on diseases or conditions that only affect one sex, such as prostate cancer and ovarian cancer.

j. It is important to note 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;

(4) The lower percentage of women in the population affected by the disease or condition.

(a) The percentages of female Service Members and Selected Reserve Members have increased over the past two decades. As noted in Reference (e), 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.

2. APPLICATION AND AWARD REQUIREMENTS.

a. In addition to CDMRP's application component requirements, including those outlined in Reference (b), this directive requires all CDMRP applications include a strategy for considering SABV.

b. 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.

c. For studies that will consider SABV by including both sexes, applicants will develop a data analysis plan prospectively that, at a minimum, will collect data disaggregated by sex.

d. 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.

e. Applicants should consider if and/or how the female estrous cycle is relevant for experimental design and analysis.

f. For both single and dual-sex studies, applicants will 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.

g. Applicants should acknowledge limitations in the applicability of findings that may arise from the samples, methods, and analyses used, in the research plan.

h. 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.

i. In DoD reports and peer-reviewed publications, funded investigators will 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.

APPENDIX

ADDITIONAL RESOURCES

(a) CDMRP Frequently Asked Questions for Directive on Sex as a Biological Variable in Research at https://ebrap.org/eBRAP/public/Program.htm.
(b) NIH ORWH "Sex as a Biological Variable Primer" Training Course at https://orwh.od.nih.gov/e-learning/sex-as-biological-variable-primer.
(c) FDA Study and Evaluation of Sex Differences in the Clinical Evaluation of Drugs; Guidance for Industry at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/study-and-evaluation-sex-differences-clinical-evaluation-drugs.
(d) FDA Guidance for Institutional Review Boards and Clinical Investigators on the Evaluation of Sex Differences in Clinical Investigations at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-sex-differences-clinical-investigations.
(e) 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.
(f) 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.
(g) 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.
(h) 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.
(i) 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.
(j) Prendergast, BJ, Onishi KO, Zucker I. Female mice liberated for inclusion in neuroscience and biomedical research. Neurosci Biobehav Rev. 2014;40:1–5
(k) National Institutes of Health. Consideration of Sex as a Biological Variable in NIH-funded Research; NOT-OD-15-102 Guidance. Definition of sex is available at https://orwh.od.nih.gov/sites/orwh/files/docs/NOT-OD-15-102%20Guidance.pdf.
(l) National Institutes of Health. Glossary of NIH Terms. Definition of basic research is available at https://grants.nih.gov/grants/glossary.htm#BasicResearch.
(m) National Institutes of Health. Glossary of NIH Terms. Definition of translational research is available at https://grants.nih.gov/grants/glossary.htm#TranslationalResearch.
(n) National Institutes of Health. Glossary of NIH Terms. Definition of clinical research is available at https://grants.nih.gov/grants/glossary.htm#ClinicalResearch.

GLOSSARY

PART I. ABBREVIATIONS AND ACRONYMS

CDMRP	Congressionally Directed Medical Research Programs
IACUC	institutional animal care and use committee
IRB	institutional review board
OHRO	Office of Human Research Oversight
PI	principal investigator
R&D	research and development
SABV	sex as a biological variable

PART II. DEFINITIONS

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.

clinical research. 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.

Epidemiologic and behavioral studies.

Outcomes research and health services research.

sex. Sex is a biological variable defined by characteristics encoded in DNA, such as reproductive organs and other physiological and functional characteristics. Sex can influence molecular and cellular processes, clinical characteristics, as well as health and disease outcomes.

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.