DEPARTMENT OF THE ARMY
HEADQUARTERS, U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
810 SCHREIDER STREET
FORT DETRICK, MARYLAND 21702-5000

FCMR-CD 2 November 2022

MEMORANDUM FOR SEE DISTRIBUTION

SUBJECT: Congressionally Directed Medical Research Programs Policy: Inclusion of Women and Minorities as Subjects in Clinical Research

1. References.

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

b. Frérot M, Lefebvre A, Aho S, Callier P, Astruc K, Aho Glélé LS. What is epidemiology? Changing definitions of epidemiology 1978-2017. PLoS One. 2018 Dec 10;13(12):e0208442.

c. Office of Behavioral and Social Sciences Research. Definition of behavioral and social sciences research is available at https://obssr.od.nih.gov/bssr-definition.

d. Stengel D, Neugebauer EA, Meenen NM. Outcomes research: definitions, methods and challenges in trauma and orthopaedic surgery. Trauma Surgeon. 2007 Sep;110(9):792-6.

e. Patient Safety and Quality: An Evidence-Based Handbook for Nurses, 2008.

f. Code of Federal Regulations. Title 45, Subtitle A, Subchapter A, Part 46 – Protection of Human Subjects. Definition of clinical trial is available at https://www.ecfr.gov/on/2018-07-19/title-45/subtitle-A/subchapter-A/part-46#46.102.

g. National Institutes of Health. Glossary of NIH Terms. Definition of phase 3 clinical trial is available at https://grants.nih.gov/grants/glossary.htm#ClinicalTrial.

h. Office of Management and Budget. Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity. Minimum categories for race and ethnicity can be found at https://www.govinfo.gov/content/pkg/FR-1997-10-30/pdf/97-28653.pdf.

i. Senate Report 115-290 (S. 3159), 2019.

j. H.R. 6157 - Department of Defense and Labor, Health and Human Services, and Education Appropriations Act, 2019 and Continuing Appropriations Act, 2019.

k. Health and Human Services Policy for Protection of Human Subjects, Code of Federal Regulations, Title 45, Part 46, 2018.

l. Federal Policy for the Protection of Human Subjects, Subpart A - 'Common Rule,' 2018.

m. The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 1979.

n. 21st Century Cures Act, PL 114-255, 2016.

o. The National Institutes of Health Revitalization Act of 1993, PL 103-43, 2017.

p. Department Of Defense Instruction 3216.02, Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and Supported Research, 2020.

2. Definitions.

a. Clinical Research. This policy uses the National Institutes of Health (NIH) definition of clinical research:

(1) Patient-oriented research. Research conducted with human subjects (or on material of human origin 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.

b. Clinical Trial. This policy uses the Common Rule definition of clinical trials and the NIH definition of phase 3 clinical trials:

(1) Clinical trial: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

(2) Phase 3 clinical trial: Study to determine efficacy of the biomedical or behavioral intervention in large groups of people (from several hundred to several

thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the interventions to be used safely.

c. Racial and Ethnic Categories. Office of Management and Budget (OMB) directive No. 15 is used to define minimum standards to maintain, collect, and present data on race and ethnicity. The standards have five categories for data on race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. There are two categories for data on ethnicity: “Hispanic or Latino” and “Not Hispanic or Latino.”

3. Authority. Congressional report 115-290, pages 213-214, which accompanied H.R. 6157, the 2019 Department of Defense Appropriations Act, directed CDMRP to develop a plan to ensure the appropriate representation of women and minorities in its extramural research in coordination with the NIH to account for genetic and biomedical differences between sexes, races, and ethnicities. The report specifies that CDMRP must ensure research contains the following requirements:

a. Representation of women and minorities in each clinical trial, as well as the data on specific challenges researchers face in seeking to include women and minorities in their studies.

b. Examination of biological variables, including the appropriate analysis of differential outcomes by sex, in clinical research.

c. Practice of making clinical findings, subgroup analyses, and data publicly available, as appropriate and applicable.

d. Requirements (including, but not limited to, programmatic controls) and updated guidelines to ensure the appropriate representation of women in clinical research. Outcomes should also be analyzed for potential sex differences.

4. Applicability. This policy applies to all applications for CDMRP-supported clinical research. CDMRP 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. Studies utilizing human biospecimens or datasets that cannot be linked to a specific individual, gender, ethnicity, or race (typically classified as exempt from Institutional Review Board [IRB] review) are exempt from this requirement.

5. Policy. The inclusion of women and individuals from minority groups and their subpopulations must be addressed across the lifespan of CDMRP-funded research. This requirement extends to all clinical research, including interventional clinical trials, observational clinical studies, and studies involving human biospecimens or datasets.

Inclusion on the basis of sex/gender, race, and ethnicity should be guided by the disease and scientific aims of the study.

6. Exceptions. The CDMRP Director is the approval authority for any exceptions and will consider the exclusion on a case-by-case basis. All requests for an exception will initially be submitted to the respective program manager for processing.

7. Effective Date. This policy becomes effective immediately upon signature. All awards made prior to 1 October 2020 are exempt from this requirement.

8. The enclosures to this policy can be referenced for requirements and definitions of relevant terms to implement this policy into CDMRP-funded research.

9. Technical questions related to uploading required reports or documents in eBRAP may be directed to the eBRAP Helpdesk by email at Help@eBRAP.org or by phone at 301-682-5507. All other questions may be directed to usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil.

GOLDMAN.SARAH.B.1107252360 Digitally signed by GOLDMAN.SARAH.B.1107252360 Date: 2022.11.04 13:26:20 -04'00'

SARAH B. GOLDMAN
Colonel, SP
Director

4 Encls
1. CDMRP Processes for Clinical Research
2. Clinical Research Application Requirements
3. Roles and Responsibilities
4. Additional Resources and References

DISTRIBUTION:
CDMRP Military and Civilian Staff
CDMRP Contractors
CDMRP Awardees
CDMRP Award Applicants

Enclosure 1. CDMRP Processes for Clinical Research

Clinical research, including interventional clinical trials, observational clinical studies, and research with human biospecimen samples or other medical information/datasets, is important for translating healthcare solutions from the bench to the bedside. All CDMRP-funded research involving new and ongoing research with human anatomical substances, human subjects, or human cadavers must be reviewed and approved by ORP's subordinate Human Research Protection Office (HRPO) prior to research implementation. This administrative review requirement is in addition to the local IRB, Ethics Committee (EC), or equivalent review.

Some CDMRP programs are specifically focused on diseases affecting women and/or minorities. The Breast Cancer and Ovarian Cancer Research Programs both offer clinical research-focused funding opportunities for female participants. The Prostate Cancer Research Program has been supporting research on the disproportionate incidence and mortality of prostate cancer in minority men since its inception in FY97. Disease disparities in kidney cancer, of which there is a higher incidence in African American and Native American populations, is an area of emphasis of the Kidney Cancer Research Program's strategic plan and funding opportunities. The Peer Reviewed Medical Research Program and the Lupus Research Program solicit for and support research in diseases/conditions that disproportionately or exclusively affect women and/or minorities, including lupus, heart disease, endometriosis, rheumatoid arthritis, and Rett syndrome.

CDMRP funding opportunity announcements included language encouraging inclusion of women and minorities in clinical trials since 2009. Consistent with the Belmont Report, "Ethical Principles and Guidelines for the Protection of Human Subjects," and Congressional legislation, special attention is given to inclusion of women and/or minorities in studies funded or supported by the USAMRDC. This policy is intended to promote equity in assuming the burdens and in receiving the benefits of human subjects research.

CDMRP requires clinical research applications to outline specific components related to the proposed human subjects research, such as details of the clinical strategy, appropriate study variables/endpoints, recruitment plan or the acquisition of human biospecimen samples, and inclusion/exclusion criteria. Clinical trial applications require an intervention plan (including study procedures and a clinical monitoring plan), detailed description of human subject recruitment and safety procedures that specifically address the target populations, anticipated enrollment counts at each study site, any potential barriers to accrual, and a data management plan. Importantly, the human subject recruitment and safety procedures description must include a justification related to the scientific goals of the proposed study for limiting inclusion of any group by age, ethnicity, race, and/or sex/gender. Within the inclusion/exclusion criteria for any proposed clinical study, the inclusion of women and minorities must be described and

an appropriate justification must be included if women and/or minorities will be excluded.

Clinical trial and clinical research applications undergo a rigorous technical review that evaluates against specific criteria. Guidelines are provided in each funding opportunity that instruct applicants on the information needed to support this thorough review. Additional information regarding the CDMRP program cycle is available on the CDMRP website at https://cdmrp.army.mil/about/fundingprocess.

Enclosure 2. Clinical Research Application Requirements

In addition to CDMRP's current requirements in funding opportunity announcements for clinical trial applications, all clinical research applications are required to have a strategy for the inclusion of women and minorities appropriate to objectives of the study, including a description of the composition of the proposed study population in terms of sex/gender, racial, and ethnic group, and an accompanying rationale for the selection of subjects (Figure 1-1).

Plans for the examination and analyses of biological variables and subpopulation data are required and will be evaluated as part of the application. Consistent with the 21st Century Cures Act, PL 114-255 and the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, analyses are required to be uploaded to clinicaltrials.gov for phase 3 clinical trials only.

During application submission, applicants are required to provide a *planned* enrollment table(s) with the proposed enrollment distributed on the basis of sex/gender, race, and ethnicity (see Public Health Service [PHS] Inclusion Enrollment Report, OMB No. 0925-0770, located at https://ebrap.org/eBRAP/public/Program.htm under "Resources and Reference Material.").

On applications selected for funding, PIs shall provide a *cumulative (actual)* enrollment table(s) (see PHS Inclusion Enrollment Report, OMB No. 0925-0770, located at https://ebrap.org/eBRAP/public/Program.htm under "Resources and Reference Material.") at the time of each Annual and Final Technical Progress Report submission, to describe progress toward enrollment goals, and report on challenges associated with including women and minorities in their studies. CDMRP staff will monitor and track the inclusion of women and individuals from minority groups when reviewing technical reports.

A valid design and analysis on the basis of sex/gender, race, and/or ethnicity as appropriate for the scientific goals of the study must be included in the research application with a proposed phase 3 clinical trial. Evidence of whether or not clinically important sex/gender and race/ethnicity differences are expected in the intervention effect should also be included. Considerations for existing evidence are described in more detail in Section IIB of the Inclusion of Women and Minorities as Participants in Research Involving Human Subjects National Institutes of Health policy. As described there, applicants should describe whether prior studies do or do not support the existence of significant differences, or if they neither support nor negate significant differences.

Phase 3 clinical trials include statistically significant numbers of human subjects to allow for analyses down to the gender and minority level. As opposed to earlier phases of clinical investigation establishing safety and dosing regimens, the aim of phase 3

investigations is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

Therefore, requiring plans for the valid design and analysis on the basis of sex/gender, race, and/or ethnicity and requiring entities conducting applicable clinical trials to submit results of valid analyses and outcomes by sex/gender, race, and ethnicity in clinicaltrials.gov is appropriate only at this phase. These requirements will be cited in the terms and conditions of all awards for grants, cooperative agreements and contracts supporting phase 3 clinical trials. If final analyses of sex/gender and race/ethnicity are not available at the time of the final technical progress report, a justification and plan ensuring completion and reporting of the analyses is required.

Regulatory Strategy

- IRB/EC approval
- HRPO approval

Project Narrative

- Research Strategy describing study population and detailed plan for recruitment.
- Describe the methods that will be used to recruit.
- Define each arm/study group of the proposed trial or clinical research study.

Human Subjects/Sample Acquisition

- Describe the study population (e.g., age ranges, gender, ethnic groups, and pertinent demographics).
- Describe criteria for inclusion/exclusion and provide detailed justification for exclusions.
- Provide a planned enrollment table(s) with the proposed enrollment distributed on the basis of sex/gender, race, and ethnicity using the PHS) Inclusion Enrollment Report (IER), OMB No. 0925-0770. The PHS IER is a fillable PDF form, which can be found at https://ebrap.org/eBRAP/public/Program.htm under “Resources and Reference Material.”
- Describe methods used for recruitment/accrual.
- Describe how subject-to-group assignments will be conducted (e.g., randomization, block randomization, stratified randomization, age-matched controls, alternating group, or other procedures).
- Inclusion of women and minorities in study – consistent with the Belmont Report and Congressional legislation, special attention is given to inclusion of women and/or minorities. Provide justification if women and/or minorities will be excluded from the study.
- Provide justification related to the scientific goals of the proposed study for limiting inclusion of any group.

- For phase 3 clinical trials only, describe plans for the valid design and analysis on the basis of sex/gender, race, and/or ethnicity as appropriate for the scientific goals of the study and describe whether or not clinically important sex/gender and race/ethnicity differences are expected in the intervention effect based on existing evidence.

Peer Review Criteria

- How well the inclusion, exclusion and randomization criteria meet the needs of the proposed clinical effort.
- How well the sample population represents the target patient population that might benefit from the research outcome.
- How well the applicant addresses the proposed plan for the inclusion of women and minorities for appropriate representation or justifies the limitation or absence.
- How well the applicant addresses the proposed exclusion of women and minorities on the basis that a requirement for inclusion is inappropriate with respect to the health of the subject or the purpose of the research.
- For phase 3 trials only:
    - How well plans for the valid design and analysis on the basis of sex/gender, race, and/or ethnicity as appropriate for the scientific goals of the study are described.
    - How well the application addresses whether or not clinically important sex/gender and race/ethnicity differences are expected in the intervention effect based on existing evidence.

Figure 1-1. Summary of CDMRP requirements for clinical research applications

Enclosure 3. Roles and Responsibilities

1. Principal Investigators and Organizations: Provide the required information on inclusion of women and minorities and their subpopulations in clinical research projects, and any required justifications for exceptions to the policy.

2. Organizational Institutional Review Boards (IRB): Address ethical issues as described in Section IX (1) for Principal Investigators. As the IRBs implement the Common Rule, they must ensure the equitable selection of subjects. More information about these requirements can be found at https://www.ecfr.gov/current/title-20/chapter-III/part-431/section-431.111.

3. Peer Review Panels: Evaluate the following in addition to current CDMRP review practices:

a. The proposed plan for the inclusion of women and minorities for appropriate representation or the proposed justification when representation is limited or absent.

b. The proposed exclusion of women and minorities on the basis that a requirement for inclusion is inappropriate with respect to the health of the subject.

c. The proposed exclusion of women and minorities on the basis that a requirement for inclusion is inappropriate with respect to the purpose of the research.

d. Plans for data analysis on the basis of sex/gender, race, and/or ethnicity in applications proposing phase 3 clinical trials, and whether or not data from prior studies strongly support significant group differences of clinical or public health importance. If so, the research plan must include plans to conduct analyses to detect significant differences in intervention effect in the relevant groups.

4. Programmatic Panels: Requires programmatic panels consider the technical merit of the application, encompassing inclusion of women and minorities and the justification relative to the objectives of the study as evaluated by the peer reviewers in making funding recommendations.

5. CDMRP Staff: Provide PIs and organizational representatives with relevant resources, such as a written policy, frequently asked questions (FAQs), forms and guidance to submit with their applications and progress reports. CDMRP staff will monitor and track the inclusion of women and individuals from minority groups in funded clinical trials and clinical research projects.

6. CDMRP Director: May approve the exclusion of projects on a case-by-case basis. In cases where it may be inappropriate to require a project to conform to these guidelines,

for reasons other than subject health, research purpose, or cost, the Program Manager may recommend exclusion of the project.

Enclosure 4. Additional Resources and References

Investigators should defer to CDMRP's guidance with differing guidance between CDMRP and NIH.

a. CDMRP Frequently Asked Questions (FAQs) for Policy on Inclusion and Women and Minorities at https://ebrap.org/eBRAP/public/Program.htm.

b. NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research at https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm.

c. Public Health Service Inclusion Enrollment Report, OMB No. 0925-0770 at https://ebrap.org/eBRAP/public/Program.htm.

d. NIH Application Guide Instructions for Completing Plans on the Inclusion of Women, Minorities, and Children at https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general/g.500-phs-human-subjects-and-clinical-trials-information.htm#2.4.

e. Food and Drug Administration Guidance for IRBs and Clinical Investigators on the Evaluation of Gender Differences in Clinical Investigations at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-gender-differences-clinical-investigations.