Human Subjects Research Resource

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Disclaimer: This informational resource does not supersede the application requirements described in the funding opportunity announcements and accompanying general application/submission instructions.

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INTRODUCTION

The Human Subjects Research Resource is developed for principal investigators (PIs) and applicant organizations who are proposing human subjects research funded through the Congressionally Directed Medical Research Programs (CDMRP). It is not intended to be an exhaustive compilation of human subject use regulations, but rather an informational resource for preparing an application. This document contains considerations related to required Department of Defense (DOD)-level regulatory reviews, factors that may impact study timelines, other elements to consider when designing research studies, and certain requirements PIs should be aware of if their application is funded.

DOD LEVEL REVIEW

Although no action is necessary until an application is recommended for funding, PIs should be aware at the time of application submission that ***all CDMRP-funded research involving prospective enrollment of human subjects, human data, certain human-derived cell lines, human specimens, human cadavers, or human cadaveric specimens must be reviewed for compliance with federal and DOD human subjects protection requirements. PIs must receive written approval by the USAMRDC Office of Human Research Oversight (OHRO) for such studies before using CDMRP funds towards them.*** Even projects that propose research that is deemed exempt according to the Code of Federal Regulations, Title 46, Part 104 (45 CFR 46.104) must be submitted to the OHRO for an administrative review and approval.

For extramural performers, OHRO staff will review submissions for the following. if applicable:

- Federal Assurance of Compliance
- Investigator Qualifications
- Compliance with the Single Institutional Review Board (IRB) mandate as outlined in 45 CFR 46
- Compliance with DOD unique requirements

Links to the relevant federal and DOD regulations, policies, and procedures are compiled here. Intramural performers will have additional regulatory requirements.

In-depth information regarding the policies and regulations that guide these processes, guidance for PIs, and submission forms and instructions are available on the OHRO website.

STUDY TIMELINE CONSIDERATIONS

The following elements may impact the timeline of conducting human subjects research for applications that are recommended for funding. As appropriate, PIs should consider the impact of these elements on their proposed study as they design their project and develop a Statement of Work (SOW). Failure to appropriately account for these considerations may impact review of the application and/or the study team's ability to complete the proposed study during the allotted period of performance for the award.

A. IRB and OHRO Review

As appropriate to the study, obtaining local IRB approval and submitting continuing reviews for IRB approval should be accounted for within the project timeline unless approvals are already in place prior to the start of the award period of performance. When developing the

SOW, PIs should include subtasks for local IRB submission and approval and obtaining OHRO approval. ***Allow up to 3 months within the study timeline to complete the OHRO review and approval process, which must occur after obtaining local IRB determination/approval for the study and before work on the CDMRP-funded study begins.*** Depending on the nature of the proposed study and the timing involved in obtaining the appropriate IRB approvals, this timeline may be different. When an application is recommended for funding, part of award negotiations may involve the PI discussing appropriate timelines with the CDMRP Science Officer assigned to manage the award and making any necessary revisions to the SOW. Detailed information about processes and regulations relevant to funded applications can be found in the Guide for Funded Investigators.

B. Risk to Human Subjects

The IRB will assign the risk designation for a study involving human subjects. Research designated as "no greater than minimal risk" may qualify for expedited IRB review under certain categories, which are found in 45 CFR 46.110. Research not meeting the expedited review criteria must undergo a convened IRB review, which may add time to the study timeline. Studies that are deemed "greater than minimal risk" may take additional time to gain both local and DOD level regulatory approval and may require additional effort and oversight throughout the award period of performance.

C. Exception from Informed Consent (EFIC) Research

If a PI proposes to conduct a clinical trial engaging trauma patients or other planned emergency research under the 21 CFR 50.24 provisions for exception from informed consent, they should ***plan for an additional 3-6 months for OHRO review and approval.*** OHRO review of EFIC studies includes requesting approval of a waiver of the requirements of United States Code, Title 10, Section 980 (10 USC 980) from the Army Surgeon General or a comparable DOD official.

D. Research Involving Multiple Performance Sites Within the U.S.

As of January 20, 2020, studies that involve multiple ***U.S. institutions*** engaged in cooperative research that has not been deemed exempt must rely on a single IRB to review and approve the portion of the research conducted at domestic sites in accordance with 45 CFR 46.114(b). ***This includes work with human data and/or human specimens that has not been/will not be deemed exempt.*** PIs are encouraged to coordinate across study sites early to develop a plan for how all collaborating sites will rely on a single IRB, which may be requested at the time of application. A research study that will utilize multiple performance sites will inherently take longer to obtain the necessary local IRB and OHRO approvals across all sites than a single-site study. Approval will be given on a site-by-site basis; however, the study team may choose to hold enrollment until all sites obtain the necessary approvals.

E. Research Involving International Performance Sites

In addition to host nation and local requirements, U.S. research regulatory requirements apply when DOD-funded research is conducted outside the U.S. Studies involving international sites, either completely or as a combination of U.S. and international sites, must adhere to the local institutional IRB or equivalent (e.g., an Ethics Committee) review policies and processes. Additionally, studies that include international sites are likely to require increased time for OHRO review and approval. PIs should plan to have the same clinical protocol, consent forms, etc., across all sites—national and international—to obtain OHRO approval.

F. Research Involving FDA-Regulated Products

Research regulated by the U.S. Food and Drug Administration (FDA), i.e., research evaluating the safety or effectiveness of drugs, devices, or in vitro diagnostics, must adhere to the Protection of Human Subjects and IRB requirements in accordance with 21 CFR 50 and 21 CFR 56, and 21 CFR 312 and/or 21 CFR 812, as applicable.

If the proposed research involves FDA (or equivalent international regulatory agency)-regulated drugs or medical devices, approval to proceed with the research must be obtained from the regulatory agency prior to initiating human subject enrollment. The funding opportunity announcement may set additional timelines/deadlines for regulatory application submission.

It is the responsibility of the PI to provide evidence from the IRB of record or the relevant regulatory agency if regulatory oversite is not required.

STUDY DESIGN CONSIDERATIONS

PIs should assess the potential impact of the following elements on their research project and ensure that their application materials reflect this consideration. Failure to appropriately account for these elements and/or develop feasible alternatives (e.g., articulating an alternative strategy if access to critical resources is lost) may impact review of the application and/or the research team's ability to complete the proposed study during the allotted award period of performance.

A. Collaboration with the Military Services and VA

The CDMRP encourages multidisciplinary collaborations among academia, industry, the military services, the U.S. Department of Veterans Affairs (VA), and other federal government agencies. These collaborations can leverage knowledge, infrastructure, and/or access to unique clinical populations that the collaborators bring to the research effort. Some CDMRP funding opportunity announcements will include additional language stating that the military service or VA collaborator should contribute both intellectual investment and research effort into the project rather than simply providing access to patients, data, and/or specimens.

B. Research Using VA and DOD Resources

Access to certain DOD or VA patient populations, resources, or databases may take a significant amount of time to obtain, and can often only be accomplished through collaboration with a DOD or VA investigator who has a substantial role in the research. PIs should be aware of which resources are available to them if the proposed research involves a non-DOD or non-VA investigator collaborating with the DOD and/or VA.

At time of application submission, the PI must demonstrate support for and access to the relevant population(s) and/or resource(s), which includes a letter of support from the DOD component or commander of military facilities for DOD-affiliated personnel, their data, and/or DOD facilities. A plan for maintaining access, as needed, throughout the proposed research will also be requested. ***If access is not granted at time of application submission, PIs should be aware that gaining access can take a significant amount of time, even for DOD or VA investigators, and thus should be considered when planning a study timeline***. CDMRP cannot not serve as a government sponsor for Data Sharing Agreements to access Military Health Systems data managed by the Defense Health Agency.

C. Women's Health Research

The CDMRP encourages research on health areas and conditions that affect women

uniquely, disproportionately, or differently from men. Such research should relate anticipated project findings to improvements in women's health outcomes and/or advancing knowledge for women's health. PIs should refer to the funding opportunity announcement for any specific requirements related to women's health.

D. Sex as a Biological Variable (SABV)

The CDMRP expects research 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. 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. PIs 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. The CDMRP Directive on Sex as a Biological Variable in Research and a Frequently Asked Questions document is available for additional information and considerations.

E. Research Readiness

Applicants are advised to ensure human subjects research, clinical research, or clinical trial applications include sufficient evidence to support the execution of the proposed research. This may be demonstrated through thorough review of the primary literature, analysis of completed and ongoing clinical research relevant to the study, assessment of key preclinical safety and efficacy studies, and/or inclusion of other preliminary data.

F. Rigor and Reproducibility

All projects should adhere to a core set of standards for rigorous study design and reporting to maximize the reproducibility and translational potential of clinical and preclinical research. The standards are described in Landis, S., Amara, S., Asadullah, K. et al. 2012. A Call for Transparent Reporting to Optimize the Predictive Value of Preclinical Research. *Nature* 490, 187–191. While these standards are written for preclinical studies, the basic principles of randomization, blinding, and sample-size estimation derive from well-established best practices in clinical studies.

G. Data Management

Data management planning should be an integral part of research planning. All CDMRP funded research is required to provide a data management plan that documents the decision process for capturing and preserving data for potential reuse. Each funding opportunity announcement and the associated version of the general application/submission instructions contain detailed instructions related to data management plan development. Additionally, all human subjects research will need to utilize an appropriate database to safeguard and maintain the integrity of the data collected. If required by a Regulatory Agency, a clinical trial must use a 21 CFR 11-compliant database and appropriate data standards.

H. Good Clinical Practice

As appropriate, applications should comply with the international ethical and scientific quality standards of Good Clinical Practice (GCP) for designing, conducting, recording and reporting human subjects research. GCP guidelines should be applied to clinical investigations that may have an impact on the safety and well-being of human subjects. Links to applicable laws enforced by the FDA and regulations relating to GCP and clinical trials can be found on the FDA website. The FDA also provides a variety of GCP educational materials.

I. Composition of Study Population

1. Inclusion of Women and Minorities

CDMRP requires women and individuals from minority groups be included across the lifespan of all CDMRP-funded clinical research studies unless there is a clear, justifiable rationale it is inappropriate with respect to the health of the subjects or the purpose of the research. PIs should address this directive when considering their population of study. PIs conducting phase 3 clinical trials will be required to submit results of analyses of group differences on the basis of sex, race and/or ethnicity to clinicaltrials.gov at the time of final report submission. PIs should refer to the CDMRP Directive on Inclusion of Women and Minorities as Subjects in Clinical Research and the associated Frequently Asked Questions document for additional information.

2. Research Involving Subjects Unable to Provide Informed Consent

In compliance with 10 USC 980, an individual not legally competent to provide informed consent (e.g., incapacitated individuals, cognitively impaired, minors) may not be enrolled as an experimental subject in a DOD-funded experiment unless participation in the research is intended to benefit each subject enrolled in the study, to include subjects enrolled in study placebo or usual care arms. ***Studies designed in a manner that permits all subjects to potentially benefit directly from medical treatment or enhanced surveillance beyond the standard of care can meet the 10 USC 980 requirements.***

J. Availability of Resources

Ensuring and maintaining access to appropriate resources necessary to conduct proposed research is a critical element driving the success of any project. Therefore, PIs should ensure that application materials demonstrate appropriate access to resources and that the research team is prepared to deal with challenges to maintaining that access. Additionally, if the possibility exists that the PI might move to a new institution before a funded study starts, or during the award period of performance, it is critical that the PI understands how such a move would impact access to study resources. A few of the common resources that PIs should pay particular attention to include:

- **Study Population –** The proposed study population should appropriately represent all targeted populations anticipated to benefit from the intervention or research outcome under investigation. Application materials should demonstrate access to the proposed study population and detail how enrollment and retention goals will be achieved.
- **Intervention –** PIs must demonstrate the availability of and access to the drug/compound, device, and/or other materials needed for the proposed research, as appropriate.
- **Personnel and Environment –** The study team's expertise and experience in all aspects of conducting the proposed research, including appropriate statistical analysis, knowledge of regulatory submissions, data management, etc., should be described in application materials. Any specialized equipment or infrastructure available at the facilities(s) conducting the study should also be clearly articulated.

REQUIREMENTS FOR FUNDED STUDIES

The following elements may be required of PIs when an application proposing human subjects research is recommended for funding.

A. Public Health Service Inclusion Enrollment Report

PIs conducting CDMRP-funded clinical research will be required to report enrollment on the basis of sex, race, and ethnicity. Reporting will occur annually and within the final technical report. Blank Inclusion Enrollment Report forms are available on the Electronic Biomedical Research Application Portal, eBRAP.org.

B. Inclusion of DOD-Specific Informed Consent Language

The following must appear in the consent form for human subject participation in a DOD-funded research study:

- A statement that the DOD is providing funding for the study.
- A statement that representatives of the DOD are authorized to review research records.
- In the event that Health Insurance Portability and Accountability Act authorization is required, the DOD must be listed as one of the parties to whom protected health information may be disclosed.

Additional information about submitting human subjects research protocols for OHRO review is available in the "Information for Investigators – Human Subjects Research" document on the OHRO website.

C. Posting of Informed Consent Forms (*clinical trials only*)

Studies that meet the definition of a clinical trial must post a copy of the IRB-approved informed consent form used to enroll subjects on a publicly available federal website (e.g., https://clinicaltrials.gov/, https://www.regulations.gov/). The informed consent form must be posted on the federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject.

D. Clinical Trial Registry and Data Upload (*clinical trials only*)

The CDMRP requires all funded Applicable Clinical Trials to register on https://clinicaltrials.gov/. When entering study identification information, include the eBRAP log number as a Secondary ID for the study with the following designation: "CDMRP-eBRAP Log Number" (e.g., CDMRP-PC25####). Ensure that "Congressionally Directed Medical Research Programs (CDMRP)" is entered as a collaborator for the study due to their role as a funding source. Additional instructions for registering a clinical trial and using clincaltrials.gov can be found here. As described in Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) and the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11), studies that meet the definition of an Applicable Clinical Trial (ACT) are also required to submit study result information to clinicaltrials.gov.

ADDITIONAL RESOURCES

More detailed information about the topics covered in this informational resource can be found at the locations listed below.

U.S. Army Medical Research and Development Command Website

- Office of Human Research Oversight (OHRO) – Prior to 1 July 2022, the OHRO was known as the Human Research Protection Office.
- Regulation, Policies, and Procedures
- Institutional Review Board Office (IRBO) – The IRBO only provides services for scientists and researchers assigned to the USAMRDC and serves as the primary IRB for USAMRDC subordinate institutes and laboratories.

Guide for Funded Investigators – This resource for CDMRP-funded PIs provides detailed information regarding various regulations and requirements that must be met after an application is recommended for funding.

General Application/Submission Instructions – These instructions provide specific directions concerning the funding opportunity announcement to which the application will be submitted.

eBRAP Funding Opportunities and Forms – This page contains the following items that were referenced in this document:

- Suggested SOW Format
- Example: Assembling a Clinical Research and/or Clinical Trial SOW
- Public Health Service Inclusion Enrollment Report
- Directive on Inclusion of Women and Minorities as Subjects in Clinical Research
- Frequently Asked Questions for Directive on Inclusion of Women and Minorities
- Directive on Sex as a Biological Variable in Research
- Frequently Asked Questions for Directive on Sex as a Biological Variable

DEFINITIONS

Human Subjects Research: A human subject is defined in 45 CFR 46.102 as a living individual about whom an investigator (professional or student) is conducting research. The investigator:

- Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

To help PIs determine whether a proposed study is considered human subjects research, the U.S. Health and Human Services Office of Extramural Research developed a decision tool to facilitate the decision-making process and ensure consistency with federal regulations.

IRB: According to 21 CFR Part 56.102, "IRB" means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act. Not all organizations may use the term "IRB" to signify their local board that

fulfills this role.

IRB Determination/Approval: The process involves a determination by the IRB that the investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

Exempt Human Subjects Research: Research activities in which the only involvement of human subjects will be in one or more of the categories found in 45 CFR 46.104 may be determined to be exempt from the IRB review and approval requirements of the Common Rule. In brief, the categories of human subjects research that may qualify as "exempt" include research on normal educational practices; educational tests, survey procedures, interview procedures, or observation of public behavior; research involving benign behavioral interventions in conjunction with the collection of information from an adult subject; and secondary research for which consent is not required.

Exemption status must be determined by the institution's IRB or a similarly named office, and official determination will be requested by OHRO review if an application is funded. Investigators must review their institutional requirements and guidelines for filing with the IRB.

Intervention: Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for the purpose of manipulating one or more health-related biomedical or behavioral processes or endpoints.

Examples include drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face- to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and diagnostic strategies.

Clinical Trial: A clinical trial is defined in 45 CFR 46.102 as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include a placebo or another control; see E. Intervention) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

Studies that do not seek to measure safety, effectiveness, and/or efficacy outcome(s) of an intervention are not considered clinical trials. Additionally, studies that retrospectively analyze data generated from previously conducted clinical trial(s) are also not considered clinical trials.

Clinical Research: For the purposes of CDMRP funding opportunities, research that meets the definition of a clinical trial is distinct from clinical research. Clinical research encompasses research with human data, human specimens, and/or interaction with human subjects. Clinical research is observational in nature and includes:

- Research conducted with human subjects and/or material of human origin such as data, specimens, and cognitive phenomena for which an investigator (or co-investigator) does not seek to assess the safety, effectiveness, and/or efficacy outcomes of an intervention. Research meeting this definition may include but is not limited to (a) mechanisms of human disease, (b) diagnostic or detection studies (e.g., biomarker or imaging), (c) health disparity studies, and (d) development of new technologies.
- Epidemiologic and behavioral studies that do not seek to assess the safety, effectiveness, and/or efficacy outcomes of an intervention.

- Outcomes research and health services research that do not fit under the definition of clinical trial.

Excluded from the definition of clinical research are in vitro studies that utilize human data or specimens that cannot be linked to a living individual and meet the requirements for exemption under 45 CFR 46.104(d)(4) of the Common Rule.

Observational studies are a type of study in which individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome (for example, no treatment is given). These are not considered to be clinical trials.

Award Period of Performance: The time period stated in the official award document that spans the specified start (Period of Performance Start) and end (Period of Performance Expires) dates of the funded project. The start date is not the date that the PI receives notification that their application has been recommended for funding. The award period of performance may begin before a PI receives all of the IRB and OHRO approvals necessary to start any proposed human subjects research.