



DEPARTMENT OF THE NAVY

NAVAEROMEDRSCHLAB
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IN REPLY REFER TO:
NAMRLINST 3900.3E

NAVAEROMEDRSCHLAB INSTRUCTION 3900.3E

From: Commanding Officer, Naval Aerospace Medical Research Laboratory

Subj: PROTECTION OF HUMAN SUBJECTS IN RESEARCH

Ref: (a) BUMEDINST 3900.6B, "Protection of Human Subjects"
(b) The Common Rule, "Federal Policy for the Protection of Human Subjects, 45 CFR 46"
(c) SECNAVINST 3900.39B, "Protection of Human Subjects"
(d) DoD Directive 3216.2
(e) NAVMEDCOMINST 6710.4
(f) NAVMEDCOMINST 6000.4
(g) SECNAVINST 5212.5C, Sec 3900

Encl: (1) Format for NAMRL Human Research Protocols
(2) Adverse Event Form

1. Purpose. To publish policies and assign responsibilities for protecting the rights and welfare of human subjects participating in human use investigation and research projects. To establish a Committee for the Protection of Human Subjects (CPHS) that will monitor the use of human subjects involved in research at the Naval Aerospace Medical Research Laboratory (NAMRL).
2. Cancellation. NAMRLINST 3900.3D is hereby canceled.
3. Scope. This instruction applies to the use of human subjects in any research, whether funded or unfunded and without consideration of funding source, conducted by NAMRL or its agents.
4. Policy. Protection of the rights and welfare of human research volunteers involved in investigational activities is a command responsibility that takes precedence over the responsibility to complete research programs.
5. Background. Protection of humans serving as subjects for research has been an evolving area of policy and law for nearly 50 years. References (a) through (g) set forth policies and guidelines to ensure the safety and welfare of human subjects. Reference (a) defines the conditions under which humans may be used in research activities subject to the regulation by the Navy Bureau of Medicine and Surgery (BUMED).
6. Definitions. For the purposes of this instruction the following definitions apply:
 - a. "Research" is defined as any systematic investigation designed to develop or contribute to generalized knowledge, to include any project, task, test, experiment, evaluation or similar undertaking in humans.
 - b. "Risk" is defined as the possibility of harm—physical, psychological, sociological, or other—as a consequence of any act that goes beyond the application of established and accepted methods or procedures that are in an individual's best interest, or increases the possibility of harm inherent in his/her daily life or occupation.

c. "Minimal Risk" indicates an anticipated risk of harm no greater in probability and magnitude than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

7. CPHS Membership

a. Composition. At least one committee member will fulfill each of the following categories (members may fulfill multiple categories):

- (1) Physician
- (2) Chaplain
- (3) Lawyer
- (4) Military Officer
- (5) Civilian Employee
- (6) Corpsman
- (7) An individual who is neither affiliated with nor in the immediate family of a person affiliated with NAMRL.

b. Quorum. At least five CPHS members fulfilling the requirements of reference (a) section 9.c. and 10.f. must be present for a protocol to be considered.

8. CPHS Responsibilities

a. The committee shall:

(1) Meet to review protocols at least once a month (if there are any protocols to be considered).

(2) Meet as soon as possible to consider all reports of adverse events that may be a result of using research volunteers in research or reports of research being conducted outside the prescribed framework of the CPHS, and forward results of such investigations with recommendations to the Commanding Officer (CO) for appropriate action.

(3) Conduct laboratory/field inspections of research involving greater than minimal risk to ensure compliance with this instruction (other methods of determining compliance may be used where physical inspection would be difficult or impossible).

(4) Conduct an annual audit of its policies and procedures for protection of human subjects to ensure that all are appropriate. This review will be forwarded, in the form of minutes to the CO.

b. The Chairperson shall:

(1) Conduct meetings and provide input to the recorder for the minutes of Committee proceedings for the CO's review.

(2) Review appropriate protocols and advise the CO whether they are exempt from CPHS review.

(3) Grant administrative approval to protocols that have been approved by the full committee, pending submission of identified modifications.

c. The Co-Chairperson shall:

(1) Fulfill all the duties of the Chairperson when the Chairperson is absent, ineligible to consider a protocol, or otherwise unavailable. Hereafter, whenever "Chairperson" is stated it shall mean "Chairperson" or "Co-Chairperson(s) of CPHS".

d. Committee Members shall:

(1) Attend meetings, or notify the Coordinator/Recorder when a meeting must be missed due to a schedule conflict so that meetings can be arranged when a quorum will be present.

(2) Keep informed on matters regarding the use of human subjects in human use research.

(3) Remain alert for instances of human use research that do not meet the requirements for protection of human subjects and notify the Chairperson or the CO.

9. CPHS Coordinator/Recorder

a. The Command shall appoint an individual (Coordinator/Recorder) to record the minutes of each CPHS meeting.

b. The Recorder is not a voting member of the CPHS.

c. If the appointed Coordinator/Recorder is unable to attend a CPHS meeting, a member of the CPHS will serve as ad hoc Coordinator/Recorder for that meeting. A member serving as Coordinator/Recorder will retain full membership rights.

d. The CPHS Coordinator/Recorder shall:

(1) Keep a list of all CPHS members and qualifications and their letters of appointment from the CO.

(2) Prepare and keep current a written protocol for CPHS procedures and guidelines (Standard Operating Procedures).

(3) Run the technical aspects of CPHS meetings, including:

(a) Determine if a meeting must be rescheduled due to a lack of a quorum.

(b) Assure that a meeting room is available.

(c) Ensure that all investigators receive notification of the deadline to submit protocols for consideration.

(d) Assign a protocol number to protocols submitted for initial review.

(e) Ensure that all CPHS members have copies of the protocols to be considered.

(4) Record minutes at meetings and compile typed minutes which include a record of the following:

(a) Members present.

(b) Discussion that occurred.

(c) Actions taken or decisions made.

(d) The count of the vote for approval, disapproval, or abstention for each protocol voted on.

(e) Exact and complete details of required revisions in proposals approved contingent upon revisions.

(f) A list of any protocols ruled exempt since the previous CPHS meeting.

(g) For joint research programs in which the NAMRL is designated as the activity having primary responsibility for protection of research volunteers, a specific statement that the final protocol approved by NAMRL has been verified to be the same protocol reviewed and approved by the other approving authority(s).

(5) Prepare letters to Principal Investigators (PI's) informing them of those parts of the minutes related to their protocol(s).

(6) Maintain CPHS files of paper documents, to include protocols submitted, results of reviews, changes to protocols, adverse reaction reports, meeting minutes, and other files the CPHS is required to maintain.

(7) Maintain a database of approved protocols in which will be recorded.

(a) The research protocol name, protocol number, work unit number, status (pending, active, or complete) and all investigators on the project.

(b) Dates of initial approval, continuing reviews, changes to protocol and completion of study.

(c) Standardized identification (Social Security number, if available) of volunteers participating in the protocol.

(d) Inclusive dates of participation of the research volunteers.

(8) Keep a record of pending CPHS matters and times for re-reviews and ensure that PIs are notified when they must submit protocols for continuing review.

(9) Update the CPHS format file on the central Command computer as required.

10. CPHS Review of Protocols

a. Exempted Review

(1) Only categories of research that are specified to be exempt by reference (a) will be exempt from policies and regulations pertaining to protection of research volunteers.

(2) Only the Chairperson may determine that a protocol is exempted from CPHS review. The criteria and authority for the exemption must be documented in a written statement signed by the Chairperson and approved by the CO prior to commencement of data collection.

b. Expedited Review

(1) Expedited review is no longer authorized.

c. Full Review

(1) All protocols that involve human subjects and have not been determined to be exempted from CPHS review must be reviewed and approved by a quorum of the CPHS.

(2) The CPHS will not approve any research protocol unless it fulfills all the requirements of reference (a).

(3) The determination of the CPHS will be made by majority vote.

(4) The committee will recommend one of the following actions to the CO, based on committee deliberations:

(a) Determine the protocol to be exempt from policies and regulations pertaining to protection of research volunteers.

(b) Approve the protocol as submitted.

(c) Approve the protocol if identified modifications are made.

(d) Disapprove the protocol, identifying the reason(s) for such action.

(5) For those protocols the CPHS votes to approve, the CPHS will make a determination of level of risk ("minimal risk", or "greater than minimal risk") and will provide a signature sheet with the dated signatures of all members who voted on the protocol. Protocols with multiple elements will be classified by the element of greatest risk.

(6) For those protocols the CPHS determines to be of greater than "minimal risk", the CPHS shall also make a determination as to whether the protocol falls within one of the categories specified by reference (a) as requiring Assistant Secretary of the Navy Research and Development and Acquisitions (RD&A) approval.

d. Continuing Review

(1) All protocols which have not been completed or terminated must be reviewed by the CPHS at least once a year, or more often if determined appropriate by the CPHS.

(2) Continuing review will include all the elements of initial review.

(3) Additionally, continuing review will specifically address the items specified for continuing review by reference (a) section 15.

(4) The CPHS shall evaluate the current balance of risk to research volunteers versus benefit from the study, and it will recommend suspension or termination of the human research protocol if it is judged sufficiently unfavorable or uncertain, or if investigators do not comply with requirements for protection of research volunteers.

(5) The documentation of CPHS continuing review will conform to the format recommended by reference (a) and will include a statement concerning the method of verification of information.

11. Principal Investigator's Responsibilities for Protection of Human Subjects

a. The PI shall ensure the following has occurred before data collection in a study can begin.

(1) A complete human research protocol, conforming to the format specified by enclosure (2) of reference (a) and to any format requirements determined by the CPHS, must be submitted to the CPHS.

(a) Reference (a) requires the protocol to describe the proposed study in sufficient detail in order to provide the CPHS with a clear and complete understanding of all work to be performed. Reference (a) sections 7, 8, 12, and 19 lists details required in all protocols as well as additional details required for certain types of protocols

(b) All protocols must include a statement that individual voluntary informed consent will be obtained from all subjects. The approved consent document will be included in the protocol and will follow the outline provided in reference (a).

(c) Any special circumstances for consideration, requests for waiver, or exemption from compliance with regulations should be clearly described in a cover letter to the submission along with any other issues that will assist the CPHS in assessing the merit and acceptability of the protocol.

(2) If the protocol involves a joint research program between more than one activity, the protocol should include a Cooperative Research Agreement (CRA) in which arrangements are made to avoid duplication of effort in the review process. Requirements for a CRA are specified in reference (a) sections 10.q, 11, and 14.

(3) The protocol must be either determined to be exempt from CPHS review, or approved by the CPHS after full review.

(4) If the CPHS approves the protocol, conditional on minor revisions, the following must occur:

(a) PI must submit to the Chairperson a correctly revised protocol with changes clearly marked and keyed to the revisions stated in the conditional approval letter.

(b) PI must submit to the Chairperson a signed statement that the PI has notified all co-investigators (listed by name, preferably with their signatures) about the changes and that all agree to accept and abide by the changes.

(c) The Chairperson (and any CPHS members who specified review privileges at the time of initial review) must determine that all the revisions specified by the CPHS are satisfied and provide a signed memorandum to that effect, or the revised protocol must be reviewed again and approved by the full CPHS (for major changes, full CPHS re-review is required).

(5) The CPHS recommendations have been reviewed and approved by the CO.

(6) If the protocol is determined to be "greater than minimal risk", the protocol has been reviewed and approved by BUMED.

(7) If the protocol is determined to require review approval from the Assistant Secretary of the Navy (RD&A), that approval must be obtained through the chain of command.

b. The PI shall not continue data collection in a study for more than one year after CPHS approval (or a lesser period if so determined by the CPHS) until continuing review has been completed, as detailed in section 10.d of this instruction.

c. It is the PI's obligation to provide the CPHS with copies of reviews of the protocol by an outside CPHS, communications from collaborating activities pertaining to human subjects, or any other information relating to CPHS concerns. These items should be provided to the CPHS as soon as possible after they are available, rather than being provided at the next regularly scheduled continuing review.

d. Prior to making a change in a previously approved protocol (including a change in personnel, such as the medical monitor), the PI shall submit a memorandum to CPHS specifying the protocol number and explaining the changes and their justification. This memorandum must include as enclosures copies of all sections of the protocol that are being changed (including Section III. Record of Changes to the Protocol) with the changes clearly marked. (For major changes, a full package should be submitted.) The PI shall not commence data collection under the changed protocol until one of the following have occurred:

(1) The changed protocol is determined to fall within the parameters of the originally approved protocol by the Chairperson.

(2) The changed protocol is determined to be exempted from CPHS review by the Chairperson, and this determination is documented and signed by the Chairperson and approved by the CO.

(3) The changed protocol is approved by the CPHS after full review and the CPHS recommendations are reviewed and approved by the CO. For "greater than minimal risk" studies, BUMED must also review and approve the changed protocol.

e. The PI shall assure that all investigators on a project have signed the Investigator Assurance Agreement. The Assurance Agreement format is specified in reference (a). The following special circumstances should be noted.

(1) If an investigator is added to the research effort after submission of the initial research protocol, a Supplemental Investigator Assurance Agreement must be prepared, signed, and submitted to CPHS before that investigator begins work on the project.

(2) If an individual's name is included as an author on a formal report for publication or presentation, the author is presumed to be an investigator.

(a) In an Investigator Assurance Agreement signature has not been obtained for that individual, the PI is required to provide written explanation to the CPHS why the Investigator Assurance Agreement has not been completed and the reason(s) for approval of the inclusion of the individual as an author.

(b) The CPHS may recommend, and the CO may require, removal of an individual's name as an author on any presentation, report, or publication if it is determined that the PI was negligent in obtaining and submitting a completed Investigator Assurance Agreement from the investigator in a timely manner, or if the investigator participated in research utilizing research volunteers, identifiable volunteer data, or identifiable specimens from volunteers prior to completing the Investigator Assurance Agreements.

f. Assure that all reasonable safety measures have been implemented to reduce risk to research volunteers.

g. Assure that all consent and data documents are stored in a fashion that protects the privacy of all participants.

h. Assure that a copy of the consent form and the information required by reference (a), section 14.e, are entered into each subject's medical or dental records. For "minimal risk" studies, in which the investigator does not have access to the subject's medical records, providing copies of these materials to the subject and requesting that he/she have them placed in their records is an acceptable alternative.

i. If a subject experiences an adverse reaction or event in the course of research, assure that it is reported directly to the Chairperson and to the CO within 24 hours by completing enclosure (2). Initial report may be by phone if a weekend or holiday will prevent timely delivery of the report form, in which case the form should be delivered the next working day. If the incident suggests any undue risk or harm to other subjects enrolled in the study, then research shall be suspended until the CPHS determines that it may continue.

j. Assure that, upon completion of a study, all consent forms and any documents on file with original signatures are transferred to the NAMRL central repository for storage.

k. Assure that, upon completion of a study, a summary report is sent to the CPHS briefly describing what was done, subjects who participated (listed by name, social security number, and experimental group if applicable) any adverse events, and the results of the study.

1. If an investigator is to be involved in any project not otherwise supported by NAMRL as a consultant and the involvement will be of a degree which will lead to co-authorship, the protocol must be submitted to NAMRL CPHS and ruled exempt or approved as detailed in section 10, prior to participation.

12. Department Head's Responsibilities for Protection of Human Subjects

Department heads shall:

a. Review CPHS submissions routed to them, and assure that these submissions conform to the required format and are well-written.

b. Ensure that research projects involving human subjects are not initiated or continued without the review and approval required by this instruction.

c. Ensure that research projects involving human subjects are not modified without the review and approval required by this instruction.

d. Ensure that no funds are obligated or expended for activities related to participation of research volunteers prior to obtaining CPHS approval for a protocol. The only exceptions to this restriction are specified in reference (a), section 21.

13. Commanding Officer Responsibilities for Protection of Human Subjects

a. The CO shall appoint the Chairperson, Co-Chairperson(s), and members of the CPHS by name, not position. Removal of the Chairperson, Co-Chairperson(s), or members may be accomplished only by the CO in writing.

b. CPHS appointment letters will specify the length of appointment, which shall be for no less than two and no longer than five consecutive years. Appointments should be staggered to ensure continuity. Previous members may be reappointed after a one-year hiatus.

c. It is desirable that the Chairperson or Co-Chairperson(s) have considerable research experience. Unless it is determined to be necessary, no individual shall be appointed to be simultaneously a member of both the CPHS and the Scientific Review Board (SRB).

d. The CO may appoint nonvoting consultants to the CPHS for review of a specific protocol as specified by reference (a), section 9.f.

e. By the first day of each fiscal year (1 October), the CO shall forward to BUMED a list of all CPHS members for that fiscal year.

f. The CO shall report any changes to the Committee during the fiscal year to BUMED as they occur.

g. The CO shall review the recommendations of the CPHS.

(1) If the CO agrees with it's recommendations:

(a) For protocols of no more than "minimal risk", he/she shall sign the Recommendations of Convening Authority and Determination of Approving Authority, with or without comment.

(b) For protocols of more than "minimal risk", he/she shall sign the Recommendations of Convening Authority with or without comment.

(2) If the CO disagrees with those recommendations, he/she may:

(a) Require additional safeguards or modifications that enhance protection of subjects.

(b) Require review of a protocol which the CPHS has determined to be exempt; or,

(c) Disapprove the protocol.

h. The CO shall ensure that a log of all research protocols he/she has approved, which is maintained by the CHPS recorder. This log will be available for inspection on request by higher authorities.

i. The CO shall forward two copies of CPHS submissions that have been approved via NHRC for review and for forwarding to BUMED for final review and approval. When approved, the originals are returned to NAMRL for filing with the appropriate research protocol.

j. The CO shall ensure that provisions are made for meeting space and sufficient administrative staff to support the CPHS review and record keeping duties.

k. The CO shall maintain a centralized repository at NAMRL in which, at the completion of research, the following will be stored:

(1) The original approved protocol with all approved modifications and the appropriate research proposal.

(2) All documents related to review for protection of research volunteers from research risks, including correspondence.

(3) All original signed consent forms.

(4) Other documents bearing original signatures.

(5) A two to five page executive summary of the research protocol, including the research objectives and the scientific results that were obtained.

(6) For each individual volunteer, a brief summary of the dates of participation, experimental exposure, the results obtained and a complete description of all untoward events, including all diagnoses, treatment, and final outcomes. (Note: A general statement that all subjects successfully completed the described proposal with no adverse events except as otherwise noted, along with a list of the names and social security numbers and dates of participation of the subject and any exceptions to the above statement will often suffice. If different groups in the study received different treatments, the group's membership must be noted.)

l. Microfiche copies are acceptable for permanent storage of all records, but electronic media storage is not.

m. The CO shall ensure that no funds are obligated or expended to support activities related to participation of subjects in a protocol prior to CPHS approval of the protocol.

n. The CO shall ensure that all significant adverse events likely to have been a result of a research volunteer's participation in a protocol are relayed to the Naval Health Research Center and BUMED within 24 hours of occurrence or within 24 hours of being reported.



MARY A. ANDERSON