DEPARTMENT OF THE NAVY
BUREAU OF MEDICINE AND SURGERY
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WASHINGTON DC 20372-5300

IN REPLY REFER TO
BUMEDINST 3900.6B
BUMED-26H
4 Oct 2001

BUMED INSTRUCTION 3900.6B

From: Chief, Bureau of Medicine and Surgery
To: All Naval Research Activities

Subj: PROTECTION OF HUMAN SUBJECTS

Ref: (a) NAVMEDRSCHDEVCOM 3900.2A
(b) SECNAVINST 3900.39B
(c) 32 CFR 219, "Protection of Human Subjects" of 1 Jul 01
(d) 10 USC 980 of 1 Oct 85
(e) DOD Directive 3216.2 of 7 Jan 83
(f) SECNAVINST 5212.5D
(g) OPNAVINST 5300.8B
(h) SECNAVINST 5211.5D

Encl: (1) Research Involving Investigational Drugs, Biologics, or Devices
(2) Research Involving the Unlabeled Use of Drugs and Biologics
(3) Research Involving Testing of Research Participants Suspected to be Infected with the Human Immunodeficiency Virus (HIV)
(4) Research Involving Physiological Stress

1. Purpose. This instruction administratively reissues reference (a) due to the disestablishment of the Naval Medical Research and Development Command to continue current policies in force as an interim measure pending substantial changes in Federal policy regarding the protection of volunteer human subjects in research. The instruction has not been rewritten, although administrative references have been updated and enclosures deleted.

2. Cancellation. BUMEDINST 3900.6A, NAVMEDRSCHDEVCOMINST 3900.2A, and BUMEDNOTE 3900 of 1 Oct 98.

3. Scope. This instruction applies to all research involving human research participants. Specifically:

a. The provisions of this instruction apply to:

(1) All studies, regardless of funding source, conducted at, by, or in collaboration with any naval activity.

(2) Contract research funded by naval activities.

b. The provisions of this instruction do not apply to research conducted under BUMEDINST 6000.12A, Clinical Investigation Program (CIP).

c. Nothing in this instruction is intended to limit the authority of a health care practitioner to provide emergency medical care under applicable law of the jurisdiction in which the care is provided.

d. Except as specifically indicated, nothing in this instruction is intended to limit the authority of unit commanders in the discharge of assigned duties or responsibilities.

4. Policy. Responsibility for the protection of volunteer human research participants is a responsibility for each command or unit involved with the research project. In all work governed by this instruction, the welfare of research participants is considered preeminent and, along with full compliance with applicable regulations, takes precedence over the needs of specific research programs. These requirements for protection of human research participants are minimum standards. While waiver of certain requirements of these regulations may decrease the cost, difficulty, or political or social complexity of performing a study, these reasons alone do not offer sufficient justification to waive protections afforded the volunteer research participant.

5. Background. Over the years, successive international declarations have been formulated that define the conditions under which humans may be used as subjects in research. The first attempt to set international standards was the Nuremberg Code of 1947. This Code was an outgrowth of the Nuremberg Trials of war criminals who performed experiments on prisoners and detainees during the Second World War. An important historical document in the U.S. is the Belmont Report - Ethical Principles and Guidelines for the Protection of Human Subjects of Research, produced by The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979. The three basic ethical principles discussed in the Belmont Report were respect for persons, beneficence, and justice which guide the ethics of research involving human participants. The essential elements in the protection of human research participants are: review of the research protocol by a Committee for the Protection of Human Subjects (institutional review board or other designation); determination that the benefits from the research outweigh the risks; approval of the protocol; implementation of all reasonable safety measures and means to reduce risk to research participants; provision of an easily accessible point of contact for research participants' rights and for care in case of research-related injury; and provision of informed voluntary consent by each research participant. These principles and procedures are the foundation upon which this instruction is based.

6. Delegation of Authority

a. Reference (b) assigns the Chief, Bureau of Medicine and Surgery (BUMED) approval authority for studies conducted by Navy activities or by contractors using Navy or Marine Corps personnel or employees of the Department of the Navy that do not require approval by the Assistant Secretary of the Navy (Research, Development, and Acquisition) (ASN(RD&A)).

b. Chief, BUMED has delegated approval authority to a medical or dental officer assigned to Naval School of Health Sciences, Bethesda for studies involving research participants supported by the Navy CIP and that do not require ASN(RD&A) approval.

c. Chief, BUMED has delegated approval authority to a medical or dental officer assigned to MED-26H for all studies involving research participants covered by this instruction that do not require ASN(RD&A) approval and are not part of the CIP.

d. Chief, BUMED has delegated to Commanding Officers, Naval Health Research Center and Naval Medical Research Center approval authority for studies involving research participants conducted by their respective commands and detachments, providing these studies involve no greater than minimal risk.

e. In all cooperative and contract research, the cooperative research plan or contract, as appropriate, will clearly define the responsibility and authority of all parties so the requirements for the protection of research participants will not be diminished.

7. Conflicting Regulations. Issues pertaining to protection of human participants who participate in research are in a state of evolution. This may result in confusion and apparent conflict in the applicable regulations. All personnel are advised that:

a. References (c) and (d) carry the force of law and supersede administrative directives and instructions.

b. In all cases, the regulation offering the greatest protection for the research participants will prevail.

c. If there are any significant conflict between regulations, requests for guidance should be forwarded to MED-26H.

8. Research Protocols

a. For each study involving human research participants, a research protocol will be prepared that fully describes the proposed study and its attendant risks.

b. The protocol will describe how appropriate anonymity will be maintained for any human samples or identifiable data collected or used.

c. The research protocol will contain a determination of the adequacy of the proposed sample size. This will be in the form of a statistical power calculation stated in terms of the hypothesis to be tested, or by other appropriate means. Calculations will be reviewed by the appropriate institutional review board (IRB) for the appropriateness of exposing research

participants to research risks relative to the likelihood the research results will adequately address the hypotheses under test. If sample size calculations are not warranted, explanation for omitting this aspect of the research protocol will be stated for review and consideration by the Committee.

d. The protocol will describe each study or procedure to be performed

(1) For each procedure or study, the protocol will include:

(a) A brief description of the procedure.

(b) A list of the most significant risks.

(c) Safeguards in place to minimize risk and deal with emergencies.

(d) A list of the total number of participants to be enrolled, whether military or civilian, male or female, and the age range of participants (the proposed number of human subjects that will be used in the studies must be specific).

(e) Justification to show studies in animals or in vitro systems could not address the hypothesis under test.

(2) Procedures that will be performed by other than naval institutions must have attachments showing an agreement by that institution to only use qualified personnel to perform the procedure. This agreement must include the dates of the planned study.

e. For each research protocol involving greater-than-minimal risk, a single appropriately qualified medical monitor, i.e., physician or dentist, military or civilian will be designated by name. This individual will be someone other than the principal investigator.

(1) The medical monitor is the individual responsible for medical aspects and the ongoing monitoring of the study.

(2) The medical monitor has the authority and responsibility to terminate exposure of research participants to research related risks whenever termination of exposure is medically indicated.

(3) The primary qualifications and experience of the medical monitor, and of each individual to whom medical monitor responsibility will be delegated, must be determined to be sufficient to meet all requirements for the safe conduct of the study.

(4) The designated medical monitor responsible for a research protocol may, on occasion (or as a part of a watch standing bill), delegate specific authority to other qualified medical monitors if he or she is not able to be present at a given time.

(5) In the absence of the medical monitor, the most senior military member and civilian staff member present will act in the place of the medical monitor to terminate exposure of research participants to research related risks whenever termination of exposure is considered in the best interest of the research participant.

(6) The principal investigator will ensure that any change of the medical monitor for an approved study will be reported to the IRB, and will submit the qualifications of the replacement medical monitor to the IRB for review.

(7) The designated medical monitor will ensure that the replacement medical monitor will be briefed regarding pertinent situations in the study to date. Formal transfer of responsibilities will be acknowledged in the form of a signed memorandum that will be filed in appendix D of the protocol.

(8) If a study does not warrant a medical monitor, a request for waiver of this requirement shall be forwarded to the appropriate authority following paragraph 23 of this instruction.

f. For studies that involve minors or third party permission, and are conducted outside the legal jurisdiction of the U.S., the research protocol will state the age of majority and the legal requirements for third party permission for the country, State, or area in question. In addition, the protocol will describe how the requirements of paragraph 9d are met.

g. For each protocol, the principal investigator will attach a cover letter when the protocol is initially submitted and when significant modification of the protocol is requested. The letter will clearly and completely describe any special circumstances for consideration, request for waiver or exemption from compliance with regulations (state requirement and reason for requested deviation), and any other issues that will assist the IRB in assessing the merit and acceptability of the protocol. The letter will include the location (page and paragraph numbers) of the elements for consideration in the protocol.

9. Voluntary Informed Consent

a. Voluntary informed consent shall be obtained for all research sponsored or conducted by a naval activity following reference (d). The elements of the informed consent process are detailed in references (b) and (c).

b. If it is not possible to obtain written informed consent, a waiver of this requirement may be requested following paragraph 23 of this instruction. This request for waiver must be clearly documented and justified in the protocol. Provided the described voluntary informed consent process meets the requirements of applicable guidance and the research exposure involves no more than minimal risk, waiver of the requirement for obtaining a signed consent document (but not waiver of the consent process itself) may be granted by the approving authority. In all cases

where the requirement for a signed consent document has been waived, investigators will document the consent process in writing following the requirements of paragraph 7 of reference (b). Waiver of the requirement to obtain a signed consent document in research involving research participants is not meant to be a routine procedure.

c. While it may be necessary to also obtain permission from a third party to conduct a study, especially in foreign locations, third party permission by itself is not sufficient to meet the requirements of these regulations.

d. The one exception to the requirement for individual voluntary informed consent is legally sufficient third party permission, as in the case of a minor or an incapacitated individual unable to give informed consent. Where third party permission is employed:

(1) Investigators are required to inform the actual participant in the research protocol about the procedures and implications of participation. This will be done to the extent that the participant is capable of understanding and to the extent that it is in the best interest of the participant. Comment will be made in the protocol concerning the intent of the investigator to provide information to the individual participant for whom third party permission is obtained.

(2) The IRB will consider and determine whether the assent of the actual participant is required for participation of that individual in the study. This determination and recommendation will be reflected in the minutes of the IRB meeting.

e. If third party permission is given by the parent of a minor or the legal guardian, next-of-kin, or other legally authorized third party representative of any individual, the following conditions must be met:

(1) The prospective participant in the research must be legally incapable of giving informed consent.

(2) The measures used in the research must be intended to be beneficial to the participant.

(3) Investigators must demonstrate that the individual providing permission is legally authorized to do so.

(4) The permission is legally effective in the locale(s) where it is obtained and the research exposure of the participant takes place.

f. The consent document will provide names and telephone numbers or other appropriate means of contact for the principal investigator and medical monitor if the research participant has a question that arises during or after the course of the study.

g. Foreign national participants and participants who are not fluent in the English language will be provided the informed consent process in their native language. All consent forms used must have an accurate and complete translation of the English version into the appropriate foreign language. This translation will be an integral part of the protocol and will be submitted with the original protocol for review. Willful failure to provide and use an accurate and complete translation will result in disapproval or termination of the research.

10. Institutional Review Board

a. Proposed studies involving research participants shall be reviewed by an IRB which meets at a minimum the requirements of references (b) and (c). This committee has been synonymously referred to as the Review Committee, Human Subjects Committee, Committee for the Protection of Human Subjects, or Advisory Committee for the Protection of Human Subjects. IRB is the preferred terminology. Following reference (e), IRBs in the Department of Defense do not have independent project approval authority, but make recommendations to the head of the research activity for approval.

b. The term of IRB members will be generally for a period of 2 years. Appointments should be staggered to ensure continuity.

(1) By the first day of each fiscal year (1 October) the convening authority of each IRB will forward to MED-26H a list of all IRB members for that fiscal year. This list will indicate the chairperson, alternate, or co-chairperson, and the representation of each committee member, e.g., physician, attorney, clergy, medical ethicist, officer, enlisted, civilian, community representative, etc..

(2) Changes to the committee occurring during the fiscal year will be reported to MED-26H as they occur.

c. A quorum of at least five members of the IRB who are eligible to vote on a specific research protocol will be required to convene a meeting and consider action on that protocol. The voting members of the IRB reviewing the specific research protocol must include:

(1) At least one member whose primary concerns are in scientific areas.

(2) At least one member whose primary concerns are in nonscientific areas.

(3) At least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(4) An individual member of the IRB may simultaneously fulfill more than one of the above criteria.

d. The determination of the IRB will be made by majority vote. Voting by IRB members will be recorded anonymously. The recommendation document will state the count of the vote for approval or disapproval.

e. An IRB convened at a foreign location will have at least one member appointed to the committee as a representative of the host government. This representative will be a non-voting member of the IRB, designated by the appropriate agency of the host government, and a national employee of the host government. This representative may not be an employee, contractor, or otherwise affiliated with the naval research activity because that would be a conflict of interest. The host government representative is authorized to participate in all IRB deliberations pertaining to studies conducted in the host country or involving host country nationals.

f. Consultants may be appointed to the IRB to supplement technical expertise required in a field that is not adequately represented by the IRB members present and eligible to vote on a specific research protocol. These consultants may be excluded from IRB deliberations, at the discretion of the IRB chair, and are neither eligible to vote nor considered in determining the presence of a quorum.

11. Basic Review and Approval Procedures. The basic procedures for review and approval of human research protocols are outlined below. Contractor funded naval research activities will ensure their respective institutional review mechanisms comply with the intent of these procedures.

a. Research protocols will be submitted in writing for each study involving research participants.

b. Approval of protocols involving research participants will be based upon a tiered review process.

(1) Studies involving no more than minimal risk will be reviewed by the IRB and will be approved by the head of the research activity. Oversight and second-level review responsibility for this process will be exercised by MED-26H.

(2) Studies involving greater than minimal risk will be reviewed by the IRB and will be forwarded to MED-26H for approval via by the head of the research activity.

(3) Requests for special handling, e.g., processing for approval in a time frame more rapid than possible under normal working conditions should be addressed to MED-26H.

c. The head of the research activity has the responsibility to establish a scientific review process that ensures proposed research has sufficient merit to warrant exposing research participants to research risks. This review is normally conducted by a committee having the title Scientific Review Committee or similar designation. The following comments pertain:

(1) Simultaneous assignment of an individual to membership on both the Scientific Review Committee and the IRB should be minimized to the greatest extent possible.

(2) The purpose and function of the IRB will not be combined with the purpose and function of a Scientific Review Committee.

(3) The IRB may make recommendations generally considered to fall within the purview of the Scientific Review Committee if these recommendations pertain to considerations for the protection of research participants.

d. It is the responsibility of the IRB and the IRB chair to ensure research protocols are reviewed and evaluated in strict compliance with all elements of pertinent laws, regulations, and guidance, and to establish a timetable for submission and review of research protocols.

(1) If a principal investigator submits a protocol for review and requests action from the IRB in less than the routinely allotted time, the principal investigator will provide justification for the request. The IRB chair may accept the submission for special review, or deny the request for special handling and treat the protocol as a routine submission. The principal investigator will be informed of the decision.

(2) If the IRB cannot complete action on a protocol in the time allotted, the IRB will inform the principal investigator of the reason for the delay and the expected completion date.

(3) The principal investigator and IRB chair will provide copies of the request for special handling, decision on the special handling request, and notification of delay in completion of IRB action to the convening authority.

e. Expedited review, as defined in paragraph 5q of reference (b), is not authorized.

f. No member of the IRB will vote upon or participate in the review of a research protocol in which he or she is materially involved or has a conflict of interest. Material involvement or conflict of interest includes managerial or leadership responsibility for the research protocol under review, principal or co-investigator status, or other conflicts of interest as determined by regulation or by the convening or approving authority. Persons with conflicts of interest may only be present at meetings during the time they are providing information requested by the IRB. Presence during the discussions or deliberations of the IRB is not authorized.

g. If the IRB convening or approving authority for a research protocol is involved as a principal or co-investigator for the protocol, or if any other conflict of interest exists, that individual is disqualified from taking official action. The protocol and all pertinent documents will be forwarded to the next higher echelon in the chain of command for action, along with a statement indicating the reason for disqualification.

h. Certain research protocols may be exempt from full IRB review.

(1) References (b) and (e) list categories of research which are exempt from policies and regulations pertaining to protection of research participants. It is the responsibility of the IRB to ensure exemptions are properly reviewed and justified in relation to both references (b) and (e) prior to initiation of the study.

(2) If there is any question whether a specific research protocol is exempt from review, the protocol shall receive a full IRB review.

(3) No research protocol involving children or fetal-related research will be exempt from full IRB review.

(4) If a research protocol is determined to be exempt from full review, the pertinent facts must be presented at the next regular IRB meeting for review and approval. A statement signed by the IRB chair is required indicating the criteria for exemption and the authority by which exemption is claimed. The IRB recommendation is approved by the approving official as part of the regular IRB minutes and forwarded to MED-26H for second-level review.

i. Investigators are required to provide sufficient detail in the research protocol so members of the IRB and other reviewers will have a clear and complete understanding of all work to be performed under the protocol. Failure to provide necessary detail will result in return of the protocol for revision, or result in disapproval.

j. All aspects of the welfare of a research participant related to his or her participation in a study will be considered as directly relevant to the issue of protection of research participants when a research protocol is reviewed. The following comments pertain:

(1) The exact role of investigators in clinical decision making or therapeutic intervention will be specified in the research protocol.

(2) Activities will evaluate all proposed research to ensure both the experimental exposure and related medical care a research participant may receive as an integral part of the study are scientifically, medically, legally, and ethically appropriate and correct.

(3) Review of research protocols will evaluate pertinent aspects of the research participants' proposed experimental exposure and related medical care, assess the ability of the medical system outlined in the research protocol to provide that medical care, assess the qualifications of the health care providers, and evaluate any other pertinent factors relating to the welfare of the participant.

(4) If any element of the protocol is found to be unacceptable, then consideration of the welfare of the research participant will preclude approval of or participation in the study unless all deficiencies are corrected.

k. Unless a research protocol is deemed exempt, full IRB review and subsequent approval of the protocol must be completed prior to either enrollment of any research participants, or collection or use of data or specimens derived from research participants. Local policy documents will clearly state that non-exempt research involving research participants will be reviewed by the IRB, regardless of perceived risk to research participants. It is the responsibility head of the performing or funding activity to ensure these policies are known and followed throughout their commands.

l. The minutes of the IRB will be forwarded to the approving authority, along with any recommendation for action by the convening authority. For each protocol, the minutes should anonymously reflect the IRB discussion. Minutes of the IRB meetings will be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions, including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of discussion of controversial issues and their resolution. The minutes will include anonymous statements describing the reason for each vote to disapprove or abstain from voting. These minutes will be retained permanently.

m. Upon review of a research protocol the IRB will determine the level of risk to the research participants and make a recommendation to the approving authority regarding approval.

n. Original signatures are required on all documents pertaining to the protection of research participants (research protocols, consent forms, review and approval documents, etc.). Photocopies and facsimile copies of signatures may be accepted for processing of documents and granting specified limited time approval to conduct research. Such temporary approvals will be authorized by the approving authority for a reasonable period of time necessary to obtain original signed documents. It is the responsibility of the principal investigator to obtain original signatures on the research protocol and investigator assurance agreement from all co-investigators and from the responsible department head or equivalent. The principal investigator is also responsible for ensuring informed consent documents are properly signed by each research participant (or the legally authorized representative), an investigator, and a witness. The IRB chair is responsible for obtaining original signatures of all committee members participating in the review of a given research protocol.

o. Specific review for legal sufficiency is required for research protocols where third party consent is necessary following paragraph 7 of reference (b). Final approval will be based upon the balance of risks to research participants and benefits of the study to the research participant. This review must be appropriately noted in the minutes of the IRB meeting.

p. The IRB will review investigator assurance agreements for completeness.

(1) The IRB will ensure all investigator signatures are provided on the agreement. Failure of the principal investigator to present an agreement with all required signatures may result in return of the research protocol without action.

(2) The IRB may consider a protocol without a completed investigator assurance agreement if the principal investigator provides an explanation why the necessary signatures are not included, as well as a timetable for obtaining the signatures.

(3) No investigator may participate in any research involving human research participants, or in the collection or use of data or specimens derived from such participants, prior to completion of the investigator assurance agreement and protocol approval.

q. The IRB will review every research protocol to determine if there is a research collaboration with an outside investigator or institution outside of the command responsibility of the approving authority. In all cases involving an outside collaboration, either a written cooperative research plan or a joint review agreement is required in which arrangements are made to ensure complete review and monitoring while minimizing duplication of effort, or the IRBs of all the collaborating institutions must review and approve the research separately.

r. After review of a research protocol, the IRB may either recommend approval of the protocol; recommend approval with explicit requirements for minor revision; return the protocol directly to the submitting investigator for specific major revision; or recommend the protocol not be approved. If a protocol is returned to the submitting investigator with recommendation for approval with minor revision, the following procedures will be followed:

(1) The minutes of the IRB will describe in exact and complete detail the requirements for the revision.

(2) If the protocol is revised by the submitting investigator exactly as described in the detailed requirements recorded in the minutes of the IRB, the chair may review these changes for compliance and, if correct and complete, forward the revised protocol as being recommended for approval. Further consideration by the full committee is not required. This is not considered expedited review.

(3) The IRB chair reviewing the minor revisions will attach a memorandum indicating the revisions to the protocol satisfy all requirements for revision determined by IRB review.

(4) If after review of the submitted revisions, the IRB chair believes the revised protocol should be resubmitted for full IRB review, he or she is authorized to do so.

(5) Failure of the submitting investigator to satisfy all revision requirements as noted in the minutes of the IRB, or the addition, deletion, or change of any other element in the protocol, will necessitate reconsideration of the revised protocol by the full committee.

(6) It is the responsibility of the principal investigator to submit a revised protocol for review of modifications as discussed above.

(a) Revisions to the protocol will include a signed statement from the principal investigator certifying he or she has informed all co-investigators about the changes to the protocol and all co-investigators agree to accept and abide by the changes. All co-investigators contacted must be listed by name.

(b) Demonstration of acceptance of the revisions by the signatures of co-investigators is strongly encouraged.

(c) Lack of documentation of agreement by all co-investigators will preclude acceptance of the revisions by the IRB and approving authority.

(7) Use of the procedures described in this section is at the discretion of the IRB. If used, the specific acceptance of this process by the IRB at the time of initial consideration or review of the protocol is required. This process should only be used for minor revisions. If required changes are major or complex, these procedures are not to be used and a revised protocol will be submitted for full review.

(8) If a principal investigator desires to modify an already approved protocol so that the changes remain within the parameters of the approved experimental design (e.g., withdraw a 5 cc blood specimen volume instead of the approved 10 cc specimen volume, exercise a participant for 10 minutes at the approved exercise intensity instead of 15 minutes at that intensity, etc.), these changes may be made by the principal investigator without submission of the protocol to the IRB for additional review. A record of such changes must be made in the protocol.

s. The recommendation of the IRB will be forwarded to the approving authority with the dated signature and typed name, business address and representation of each IRB member present at the meeting, and the dated signature of the IRB Chair.

t. Upon approval, the recommendation document will state the IRB assessment of the level of risk of the proposed research protocol, indicating it is either:

(1) Of minimal risk as defined by references (b) and (c).

(2) Of greater-than-minimal risk, but not requiring ASN(RD&A) approval per paragraph 12a(5)(a) of reference (b).

(3) Of greater-than-minimal risk which does require ASN(RD&A) approval.

u. For purposes of review and approval of research protocols involving multiple elements of varying risk, the entire protocol will be classified by the element of greatest risk.

v. Research protocols that are determined by the IRB to involve no more than minimal risk may be approved by the head of the activity provided they hold appropriate local approval

authority. A complete copy of the approved protocol, including all supporting documents, will be forwarded to MED-26H for second-level review. This will be done upon initial approval and after each approval for continuation of the research.

w. Research involving greater than minimal risk will be approved following this instruction and the requirements of higher authority.

x. Research protocols which require ASN(RD&A) approval must be submitted via the chain of command to the Chief of Naval Operations (N093 and N091) for forwarding to the ASN(RD&A) following reference (b). Correspondence must be endorsed by the Chief of Naval Personnel if Navy personnel will be participants, or by the Commandant of the Marine Corps (Attn: Chief of Staff for Manpower) if Marine Corps personnel will be participants. In all cases, Chief, BUMED should specifically comment on the balance of medical risks and benefits to research participants.

y. The requirements for protection of research participants represent minimum standards. Any higher authority in the chain of command is authorized to disapprove a research protocol or apply additional restrictions to any protocol. Lessening of restrictions is not authorized. An assessment of risk, the requirement for the protection of research participants, or disapproval of a protocol may not be downgraded or superseded in the chain of command review. In no case may the approving authority approve research without the recommendation for approval of the reviewing IRB. In the event of a dispute, all relevant information is to be forwarded through the chain of command to MED-26H for review and resolution.

z. Upon receipt of a research protocol with the recommendation of the IRB, the approving authority may:

(1) Accept the recommendation of the IRB.

(2) Require additional safeguards or additional modifications to the protocol that enhance the protections afforded research participants.

(3) Assign either a greater level of risk, an increased level of protection, or a greater requirement for monitoring or review than had been assigned by the IRB.

(4) Require review of a protocol which the IRB has determined to be exempt from review.

(5) Disapprove the protocol, despite the IRB recommendation to approve the protocol.

12. Responsibility for Protection of Research Participants in Research Involving More than One Activity. Research involving more than one activity must either involve a cooperative research plan or joint review agreement establishing specific arrangements to avoid duplication of

review effort, or the protocol must be reviewed and approved by every participating activity independently. In all cases, standards for protection of research participants and requirements for compliance with governing regulations will be maintained.

a. For collaborative research, one activity will be designated as having primary responsibility. Primary responsibility for protection of research participants means ensuring compliance with the provisions of this instruction and its references. The activity with primary responsibility must exercise responsibility even during phases of the research carried out by other activities. Continuity of primary responsibility is necessary to avoid gaps in protection of research participants.

b. Paragraph 5.3.2. of reference (e) provides guidance for studies involving more than one military department or agency (e.g., Army and Navy). A cooperative research plan or joint review agreement, signed by the heads of the activities, will state which activity has primary responsibility.

c. When more than one Navy activity is involved, primary responsibility for protection of research participants depends upon whether the research participants are patients of a Navy medical treatment facility (MTF) or dental treatment facility (DTF) as indicated below. A cooperative research plan, signed by the heads of the activities, will state which activity has primary responsibility.

(1) When the research, regardless of in-house or contract status, involves participation of patients of a naval MTF or DTF, the MTF or DTF has primary responsibility, except as provided by reference (e).

(2) For research not involving patients at a naval MTF or DTF, primary responsibility will be assigned by agreement of the heads of the activities involved.

d. The approving authority may agree to accept responsibility for issues related to protection of research participants from another activity.

e. Any responsibilities assigned to another activity must meet all requirements of this instruction and higher authority.

f. Signature of the investigator assurance agreement by each investigator is required. Documentation of individual institutional review and approval of the research is required for each institution unless an exemption or a joint review or other review arrangement applies. A given investigator may be exempt from these requirements if the work performed by that investigator is exempt from compliance with regulations for protection of research participants.

g. Concurrent or sequential review by multiple approving authorities may sometimes be required. In such cases, no changes to an approved research protocol are permitted without

concurrence by all parties. If changes in an approved research protocol are required by another reviewing authority, the changes must be sanctioned by resubmission of the modified protocol through the approval process.

h. The primary naval IRB must verify that the final protocol approved is the same protocol reviewed and approved by all approving authority(s). A specific statement to this effect shall be incorporated into the minutes of the IRB meeting reviewing the protocol.

i. In the case of nonnaval personnel conducting research under the auspices of naval activities, e.g., university personnel assigned under the Intergovernmental Personnel Act or other agreements, the naval activity will be the activity primarily responsible for protection of research participants. Formal agreements to minimize duplication of review efforts are encouraged. These matters should be a matter of concern in developing agreements for such personnel arrangements.

13. Selection of Research Participants

a. Exclusion of individuals as research participants because of age, sex, race, ethnicity, or socioeconomic or military grouping, must be based upon a sound scientific or operational rationale. In cases of exclusion of a specific group, the following information is required as a part of the research protocol:

(1) Exact criteria for the exclusion of individuals as research participants.

(2) Scientific or operational requirements that necessitate the exclusion.

(3) Potential effect on the individual member of an excluded group if the individual intended to be excluded is inadvertently enrolled and participates in the study.

(4) Potential effect on the research if the exclusion is not allowed.

b. The IRB and convening and approving authorities will review each research protocol for appropriateness of restrictions based upon the information provided.

c. Pregnant women may not be involved as research participants in research covered by this instruction unless:

(1) The purpose of the research is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs.

(2) The risk to the fetus is negligible, e.g., administration of questionnaires to pregnant women.

d. Non-pregnant women may participate as research participants in the following circumstances:

(1) If there is no known, expected, or potential risk to a pregnant woman, embryo, or fetus should the woman be unknowingly pregnant or become pregnant during the course of the study, full participation as a research participant is allowed. The informed consent document will include a statement that there is no known risk to a pregnant woman, embryo, or fetus if the research participant is unknowingly pregnant or becomes pregnant during the course of the study. The consent document will also outline any risks or concerns, real or potential, to a female participating in the study.

(2) If there is a risk to either a potentially pregnant female research participant, embryo, or fetus, the consent document will include a statement describing in detail the risks to a pregnant research participant, embryo, or fetus if the research participant is unknowingly pregnant or becomes pregnant during the course of the study. Prior to participation in the study, a clinical history must be obtained which indicates the participant is unlikely to be pregnant. In addition, investigators must objectively demonstrate that the participant is not likely to be pregnant as described below:

(a) A negative urine human chorionic gonadotrophin pregnancy test is required prior to participation of the research participant in any potentially hazardous activity, or whenever the research participant, embryo, or fetus is at risk due to an intervention based on participation in the study. The minimum requirements for the test are:

1. The test must be sensitive enough to detect 25 milli-International Units per milliliter (mIU/ml) of human chorionic gonadotrophin (hCG), or less.

2. The test must be performed on the first voided urine sample collected on the day of the experimental exposure.

3. The test sample must be run with a positive and negative control.

(b) In cases where the adverse effects of experimental exposure in pregnancy warrant a higher degree of certainty that the female research participant is not pregnant, a negative serum Beta human chorionic gonadotrophin (Beta-hCG) pregnancy test sensitive enough to detect 5 mIU/ml, performed in an appropriate laboratory, is required within 24 hours or less of participation of the research participant in any potentially hazardous activity, or whenever the research participant, embryo, or fetus is at risk due to an intervention based on participation in the study. This test may detect pregnancy 1 to 2 days before the urine test described above.

(c) In cases where the adverse effects of experimental exposure in pregnancy warrant the highest degree of certainty that the female research participant is not pregnant, the experimental exposure should occur during the first 10 days after the onset of menses (during the

proliferative phase of the menstrual cycle). In such cases, consultation with a qualified obstetrician must be sought to determine the optimal laboratory studies available to confirm this phase of the menstrual cycle. A negative serum Beta-hCG pregnancy test is also required.

(d) The time interval between collection of a specimen for use in determination of pregnancy and the experimental exposure risk will be included in the permanent research records of the individual participant tested.

(e) Historical reports of sexual abstinence and use of contraception will not generally be considered acceptable substitutes for a documented negative pregnancy test in female research participants of childbearing potential.

(f) The research participant will be advised of risks associated with becoming pregnant during the course of the study. If she thinks she may have become pregnant during the course of the study, she must be advised to report this to the medical monitor immediately. Statements to this effect will be included in the consent document.

(3) Requests for waiver of these requirements should be submitted following paragraph 23 of this instruction. Waiver may be granted in situations where the potential risk to the participant and her embryo or fetus is clearly outweighed by the expected benefit.

e. In research involving greater-than-minimal risk:

(1) The potential research participant must be either:

(a) An individual eligible for care at a military MTF, e.g., active duty member, retired member, family member of an active duty or retired member, or Secretary of the Navy designee for health care benefits.

(b) A civilian employee of the United States (U.S.) Government for whom it has been determined that the Federal Employees Workers' Compensation Program will be adequate to cover any injury or disability resulting from the employee's participation as a research participant.

(c) An individual who will be afforded medical or health care benefits applicable to any potential injury or disability resulting from participation in the research protocol.

(2) Additional considerations may apply in cases where the potential research participant is a foreign national or a member of a foreign military organization. In such cases, however, the minimum requirements of paragraph 13e above must be met.

(3) The adequacy of the proposed health care benefits coverage for the potential research risks is an element for review by the IRB. If coverage is not adequate, participation of the potential research participant in the research is not authorized.

(4) The reviewing IRB will ensure the informed consent document provides the research participant with complete information regarding any potential additional costs to the research participant that may result from participation in the research, e.g., insurance deductible or co-payment, administration costs, etc..

f. Research done under contract will follow the same guidelines described in paragraph 13e above.

g. U.S. military personnel may participate as research participants. Consideration should be given to how participation affects readiness and availability to perform military duties. Additional reimbursement of the research participant for participation, monetary or otherwise, is prohibited except as specifically authorized by law or regulation. Special attention should be given to avoid any real or apparent coercion to participate as a research participant, especially in training contexts, or other situations associated with major career branch points.

h. Persons receiving medical care at military MTFs, such as active duty and retired military personnel and family members, may participate as research participants in research related to their health care. Such persons may be compensated for these services when authorized by applicable directives.

i. No research involving prisoners or institutionalized mentally disabled persons serving as research participants will be permitted.

14. Research Conducted Outside the United States. Research protocols conducted outside the jurisdiction of the U.S. require approval by the appropriate authorized official(s) of the host country government. The following comments pertain:

a. It is recognized that the process of obtaining host government approval may be time consuming. The IRB and approving authority may, but are not required to, consider a protocol without host government approval.

b. Participants may not be allowed to participate in research without the required host government approval. Documentation of host government approval must be completed by the appropriate authorized officials of the host government and must state that:

(1) The host government is aware of the specific details of the research proposed.

(2) The host government concurs that it is appropriate research to be done in the host country.

(3) Approval for involvement of host country national research participants is granted.

(4) The host government understands the research will meet at least the minimum standards for the protection of research participants required by this instruction.

(5) The host government understands it will receive a timely copy of all reports related to protection of human research participants, including continuing reviews and reports of any unanticipated problems involving risks to research participants; any serious or continuing noncompliance with requirements for protection of human research participants; or any suspension or termination of IRB recommendation for approval of research.

(6) The host government understands it has the right to require additional restrictions to ensure the protection of research participants.

c. It is the responsibility of the IRB chair to ensure that host government approval is obtained from the appropriate level and branch of the host government, following the host country law and practice. If no policies exist for obtaining such approvals, involved activities must actively seek to have the host government establish such policies.

15. Maintenance of Records. All records associated with a protocol involving human research participants will be maintained as directed in references (b) and (f), and remain permanently retrievable by the performing activity, or by the funding activity in the case of contract work.

a. It is the responsibility of the approving authority to ensure that records are maintained following reference (f).

b. If cooperative research is conducted in conjunction with a nonnaval activity, the agreement between the activities (cooperative research plan) will specify that copies of all documents normally required by these regulations will be filed at the naval activity site. This provision is needed to ensure the requirements in paragraph 14 reference (b) for permanent storage of records will be met.

c. Microfiche copies are acceptable for permanent storage of all records.

d. Electronic media storage of experimental data initially recorded electronically is acceptable. Electronic media storage of original documents such as signed informed consent documents or records of IRB action, however, is not currently acceptable. This restriction will remain in force until such time as documents stored by these methods may be admitted as evidence in legal proceedings. The research protocol should clearly state how electronically stored data would be validated and protected.

e. A copy of each research participant's signed informed consent document will be filed in the research participant's medical or dental records following reference (b). The research

participant's medical records will also include sufficient documentation to substantiate what was done to the research participant during the research; clearly identify, by name or code, any drugs administered, and whether these drugs were investigational; identify investigational procedures performed; and identify significant observations, including any adverse effects. A specific notation of the existence and location of the experimental protocol and associated documents will be entered into the research participant's personal medical record. Entries into U.S. military medical and dental records are to be boldly labeled:

DO NOT REMOVE -
THIS DOCUMENT REQUIRED TO BE PERMANENTLY FILED IN MEDICAL/DENTAL RECORD FOLLOWING SECNAVINST 3900.39B

f. If the research participant does not have a formal medical or dental record, the research records will be provided to the participant or the participant's health care provider for retention.

g. The IRB recommendation with original signatures of the voting members, any endorsements, and the action of the approving authority will be returned to the performing site after action is taken by the approving authority. These documents will be permanently retained.

h. Each research activity will maintain a centralized system to record participation of all research participants in research protocols. This system will include:

(1) A computer database in which will be recorded:

(a) Identification of research protocol by name, unique research protocol number, work unit number (if applicable), status of protocol (pending, active, or complete), and a list of all investigators.

(b) Standardized identification of the research participants participating in the protocol (for example, full name and social security number).

(c) Inclusive dates of participation of the research participant in the protocol.

(2) A centralized repository in which, at the completion of the research, will be stored:

(a) The original approved protocol with all approved modifications.

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

(c) All original signed informed consent documents.

(d) Other relevant documents bearing original signatures.

(e) A 2- to 5-page executive summary of the research protocol including the research objectives, what was done, and the scientific results that were obtained.

(f) For each individual participant, a brief summary of the experimental exposure, the results obtained, and a complete description of all untoward events, including all diagnoses, treatments, and final outcomes.

(3) An individual research participant file may be maintained for each participant during the time of participation in the protocol. The contents of this file are to be determined by the principal investigator. Disposition of the documents will be described in the protocol and be considered by the IRB during the processes of initial and continuing review. If desired, a permanent individual file may be established and maintained. Such permanent individual files may include reports of research-related physical, laboratory, and other medical examinations and a chronological history of participation in studies.

i. The IRB will review these record maintenance elements of the research protocol with great care and thoroughness. The maintenance of such records will be a matter of primary concern during program review or inspection.

j. Approving authorities are required to keep a log of research protocols they have approved. This log and the approval process will be subject to inspection by MED-26H and higher authorities.

16. Continuing Review of Research by the IRB

a. The IRB will review work conducted under previously approved research protocols at least annually as required by paragraph 10d of reference (b). This review will take place more frequently if the IRB believes more frequent review is indicated.

b. The IRB review will monitor and evaluate the following items: untoward events, complications, or injury to research participants; adequacy of medical care rendered; adequacy of the consent document and procedures for obtaining informed voluntary consent; the number of research participants studied; adherence to protocol and provisions of the approval; information developed during the research; faithfulness of research and safety procedures to the information upon which the IRB's approval recommendation was based; qualifications of personnel; noncompliance with this instruction, related references, or other direction; completion of all required documents; maintenance of records and any other relevant information required by the IRB. In documentation of IRB review, a statement concerning the method of verification of information will be included.

c. If an investigator is added to the research effort after submission of the initial research protocol and initial investigator assurance agreement, a supplemental investigator assurance agreement will be prepared and signed. A copy of the supplemental investigator assurance

agreement with the signature of the new investigator will be submitted in a timely manner to the IRB and forwarded to approving authority. The original will be incorporated into the research protocol. The IRB will apprise the approving authority of all changes in investigators and collaborating institutions.

(1) Inclusion of an individual's name as an author on a formal report, manuscript, or other document for publication or presentation indicates investigator status for that individual. If an investigator assurance agreement signature has not been obtained for that investigator, the principal investigator is required to provide written explanation to the IRB why the investigator assurance agreement has not been completed, and the reason(s) for approval of the inclusion of the individual investigator as an author.

(2) The IRB may recommend, and the convening or approving authority may require, removal of an investigator's name as an author on any presentation, report, or publication if it is determined:

(a) The principal investigator was negligent in obtaining and submitting a completed investigator assurance agreement from the investigator in a timely manner.

(b) If the investigator participated in research utilizing research participants, identifiable participant data or identifiable specimens from participants prior to completing the investigator assurance agreement.

d. Whenever a protocol involving a collaborating institution is reviewed by that institution, the result of the review will be forwarded to the cognizant naval IRB. The IRB of the collaborating institution will perform such reviews at least annually. More frequent review may be required by the IRB as appropriate. Review by collaborating institutions will include, at least, the elements required in paragraph 15b above.

e. The IRB will not allow any significant deviations from the approved research protocol unless the change is reviewed by the IRB and approved in advance by the same authority who approved the original research protocol. The IRB will report unauthorized deviations to the convening and approving authority, and make recommendations regarding whether or not it is necessary for the convening or approving authority to direct cessation of the research activity, initiate investigation into the infraction, or take other action.

f. In the course of continuing review of a research protocol, the IRB may withdraw or modify its recommendation for approval. The IRB may recommend temporary suspension or permanent termination of the research protocol if the current balance of risk to research participants versus benefit from the study is judged sufficiently unfavorable or uncertain, or if investigators do not comply with requirements for protection of research participants. In such cases, this change in recommendation with justification will be forwarded to the approving authority for action.

(1) Recommendation for temporary suspension or permanent termination, and the rationale, will be reported to the principal investigator, the head of the activity, the approving authority, MED-26H and all other addressees in the approval chain.

(2) The IRB may recommend removing the suspension once all deficiencies have been resolved.

(3) A termination can be reversed only by treating the study as a new research protocol submitted for complete review and approval.

17. Reporting Complications. Performing activities must notify MED-26H and the research approving authority by message or facsimile within 24 hours of any incident, accident, untoward drug reaction, appearance of disease or injury which may have occurred, or which could reasonably have occurred, as a result of using research participants in research. Telephone communication should also be used in addition to the above if the responsible individual believes faster notification is indicated.

a. Any complication or problem, including adverse reactions to biologics, drugs, radioisotopes, medical devices, or procedures, must be reported without delay to the principal investigator, the medical monitor, or to the cognizant head of the activity by any individual who detects the problem.

b. Unless outlined differently in the research protocol, the most senior military member and civilian staff member present will take whatever immediate action they consider necessary to protect research participants. Their actions, and the medical or dental treatment provided to the research participant, will be reported directly to the head of the activity responsible for the study, who will then notify the IRB and all addressees in the approval chain of the research protocol.

c. As soon as possible, the IRB will convene to consider the report and to advise the approving authority regarding whether the study should be continued, temporarily suspended, or permanently terminated. The recommendations of the IRB will be forwarded to the approving authority and MED-26H without delay.

18. Other Reporting Requirements

a. The Director, Defense Research and Engineering requires prompt reports, via MED-26H, of the following:

(1) Any unanticipated problems involving significant risks to research participants.

(2) Any serious or continuing noncompliance with requirements for protection of human research participants.

(3) Any suspension or termination of IRB recommendation for approval of research.

b. Heads of activities are required to inform MED-26H of the approval of any research protocol for which they hold local approval authority. A copy of the protocol, all supporting documents, and the IRB minutes shall be forwarded to MED-26H at the time of approval for second level review.

c. Compliance with reference (g) is required if investigators propose to administer questionnaire surveys. Information is required for all proposals that involve the administration of a paper-and-pencil questionnaire that asks the respondent for any biographical, health, occupational, attitudinal, or similar information that is not part of an official service record. Compliance with this instruction does not pertain to questionnaire surveys involving Marine Corps personnel, but is applicable to work in which surveys are administered to Navy personnel, family members (either Navy or Marine Corps), civil servants, or any other civilian personnel. A copy of a completed report form (OPNAV 5214/10) should be included in the protocol. Special care should be taken in the proposal to demonstrate the questionnaire survey will provide worth-while data, and the survey has not been administered previously by other investigators under these same circumstances. Approval following reference (g) is required for a questionnaire survey to be administered.

19. Privacy Act Statements. All research participants who are either citizens of the U.S. or legally admitted aliens must be provided with a privacy act statement following reference (h). The privacy act statement information may be provided in the text of the consent document, or as a separate statement attached to the consent document. Research participants are not required to sign a specific privacy act statement. The privacy act does not apply to foreign national research participants unless they are legally admitted to the U.S. If a privacy act statement is not used in obtaining voluntary informed consent because the research participant is an alien not legally admitted to the U.S., it is recommended the concepts included in the privacy act statement be incorporated into the text of the consent document.

20. Additional Study Standards. Additional requirements for specific types of research are attached as enclosures (1) through (4) to this instruction.

21. Investigators Acting as Consultants. It is recognized that personnel have scientific expertise that may lead them to be sought as consultants. The policy for personnel participating as a consultant for research involving research participants and conducted by another agency or institution is as follows:

a. Participation in the scientific community as a consultant is encouraged.

b. In cases where naval personnel act as consultants, they are required to assess the scientific, ethical, and moral issues and conduct of the study for which they are consulted, and ensure the study is scientifically sound, complies with all applicable regulations, and the protection afforded research participants follows Navy policy.

c. Personnel acting as consultants will not have substantial participation in the research in question. Substantial participation is demonstrated if the degree of involvement in the design, conduct, analysis, or reporting of the study will lead to co-authorship. This degree of participation indicates co-investigator status and requires full compliance with all regulations pertaining to the protection of research participants, and review of the research protocol following this instruction.

d. Use of naval resources to support research, including the use of funds, technical personnel, laboratory facilities, equipment, supplies, or capabilities, is considered investigator participation in the research. Such research requires review and approval following this instruction.

e. Participation of naval personnel as consultants on research protocols involving human research participants requires the approval of the head of the parent activity of the consultant.

f. These policies also apply to the case where personnel from other institutions participate as consultants to naval projects. In all nonexempt research, if there is substantial participation in the research on the part of the nonnaval consultant (as noted in paragraph 21c), co-investigator status exists and completion of the individual assurance agreement and documentation of institutional review is required.

22. Restriction on Expenditure of Funds for Unapproved Research Involving Human Research Participants. Without the required approval for a research protocol involving research participants, heads of activities are directed that:

a. Funds may not be obligated or expended to:

(1) Enroll research participants in a study, acquire data, analyze data, or test specimens from research participants.

(2) Present research information by publication, submission for publication, presentation at meetings, or other means.

(3) Fund travel for conducting the research protocol or for activities directly related to the participation of research participants.

(4) Fund any other activities for which approval of the research protocol for participation of research participants is required.

b. Preliminary activities normally required for the planning and implementation of a study, prior to active participation or enrollment of research participants in a specific protocol, are permissible.

c. A research protocol involving research participants that is administratively suspended upon the recommendation of the IRB for failure to meet the requirements of this instruction will be considered to be unapproved.

d. The restriction on use of funds does not apply to meeting existing payrolls for employees or contractors who have been hired under previously existing approved research protocols. Under these circumstances, no new employees may be hired, or contractual obligations made, without the approval of MED-26H.

e. Purchase of general-purpose equipment and supplies (not related to a specific unapproved research protocol) and travel for administrative support of ongoing research activities (not specifically related to an unapproved protocol requirement) is permitted.

f. Investigators are not authorized to present research information either by publication, submission for publication, or presentation at meetings, unless the research protocol under which the information was collected or analyzed has specific approval.

g. Requests for waiver of this requirement, that are based on unusual extenuating circumstances are clearly demonstrated to meet the needs of the Navy and do not place research participants at risk, shall be forwarded to MED-26H for review.

h. It is expected that, due to the potentially significant adverse consequences of suspension of funding authority, all involved will act to resolve deficiencies in an expedient and professional manner, so that this restriction will be pertinent only in extreme circumstances.

23. Waiver of Requirements. Although it will be the rare exception, circumstances may exist wherein the best interest of the research participant is served by waiver of one or more of the requirements of this or other regulations. Requests for waiver should be submitted via MED-26H, using the chain of command, to the authority establishing the requirement or to the authority specifically authorized to waive the requirement. A recommendation for approval of the request for waiver by the IRB, and by each echelon in the chain of command is required. Failure to obtain these recommendations for approval will result in disapproval and return of the request to the originator.

24. Authorization to Initiate Research Involving Human Research Participants. Research involving human research participants requires compliance with this instruction and higher guidance. Investigators may enroll participants only after receipt of both the final approval of the research protocol and the local authorization to initiate the research granted by the head of the performing activity.

25. Action. This instruction is effective immediately. Heads of activities involved with or supporting naval research or any research involving naval personnel as volunteer human research

participants shall comply with the provisions contained herein. Heads of activities shall ensure that provisions are made for sufficient administrative support to meet the requirements of this instruction.

26. Form. Paragraph 18c requires a copy of a completed report form (OPNAV 5214/10) be included in the protocol. OPNAV 5214/10 (Rev. SEP 1981), Report Analysis Data is available at: http://neds.nebt.daps.mil/Directives/forms/5214_10.pdf.

27. Reporting Requirement. Report control symbol MED 3900-3 has been assigned to the Complication in Study Using Human Subjects report required by paragraph 17 of this instruction. This report has been approved by the Chief of Naval Operations for a period of 3 years from the date of this instruction.

D. C. ARTHUR
Deputy

Available at: http://navymedicine.med.navy.mil/instructions/external/external.htm

RESEARCH INVOLVING INVESTIGATIONAL DRUGS, BIOLOGICS, OR DEVICES

Use of investigational drugs, biologics, or devices requires compliance with applicable U.S. Food and Drug Administration (FDA) regulations. In addition:

1. If a research protocol involves the use of investigational drugs, biologics, or devices, approval by MED-26H and Naval School of Health Sciences, Bethesda is required, regardless of whether or not the protocol is reviewed by another body normally having authority to grant approval for such protocols. If the study is conducted outside the U.S., approval of the host country government is also required.

2. If an agreement exists for review and approval of research by a collaborating institution, the agreement is considered void for the purpose of this class of investigation, unless the agreement specifically pertains to the exact investigational product and exact research protocol under review.

3. If a research protocol involves the testing or use of a drug, biologic, or device in human participant research that either: (1) is not commercially available in the U.S., or (2) is produced or manufactured in a foreign (non-U.S.) facility, the product must be specifically described in the protocol.

a. Commercially available laboratory diagnostic equipment and devices are excluded from description provided the purpose of the research does not include testing of the equipment or device itself.

b. Drugs, biologics, and devices that are produced or manufactured in foreign facilities, but are also approved or licensed by the FDA for sale in the U.S. must be identified in the research protocol.

c. Drugs, biologics, and devices that are produced or manufactured in foreign facilities, but are not approved or licensed by the FDA for sale in the U.S. are considered investigational and will require compliance with applicable FDA regulations. This applies whether or not the product is used for an indication and in a dosage regimen that is accepted for the same generic compound produced in an FDA approved process.

4. Supplementation of an existing investigational new drug (IND) application or an investigational device exemption (IDE) with a new research protocol is desirable. This requires concurrence of the current responsible holder of the IND or IDE and approval by the FDA.

RESEARCH INVOLVING THE UNLABELED USE OF DRUGS AND BIOLOGICS

Any deviation from the indications, dose, route of administration, dosage form or treatment population of a drug, biologic, or device approved or licensed by FDA is considered an unlabeled use. The following comments pertain:

1. Provided that the route of administration and the dosage form are not changed, a physician may modify an approved dosage regimen of an approved drug for treatment of individual patients. In cases where treatment of a disease or malady is the purpose of the modification, this unlabeled use is considered the "practice of medicine" and is not regulated by the FDA. The physician treating the patient bears the increased liability for the consequences of any deviation from accepted therapy.

2. If the purpose is not treatment of an individual patient, but rather a scientific study using human research participants, this is considered research and not the "practice of medicine". Such activities are regulated by the FDA and usually require filing of an IND and compliance with applicable regulations.

a. Unlabeled use of approved drugs or licensed biologics will require either an IND or documentation issued by the FDA of exemption from requirements for an IND. Similar requirements apply to devices.

b. If the research involves study of an approved drug or licensed biologic purchased or provided from an approved source with only a minor modification in dosage or indication, the primary issue in review by the FDA will be safety. In such cases, expedited processing and waiver of the usual 30-day review period at the FDA may be requested.

c. By meeting appropriate published criteria, the proposed use may be exempt from the requirement for an IND. The criteria used by the FDA in determining eligibility for an exemption are:

(1) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.

(2) If the drug undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.

(3) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risk (or decreases the acceptability of the risks) associated with the use of the drug product.

(4) The investigation is conducted in compliance with the requirements for institutional review and voluntary informed consent.

(5) The investigation is conducted in compliance with the restrictions on promotional sale of an investigational drug.

3. In all cases involving the use of an approved drug or licensed biologic for an unlabeled indication, the research will be considered greater than minimal risk and:

a. The principal investigator will request from the FDA and provide to the IRB a document indicating exemption from the requirement for IND.

b. The consent document will clearly state:

(1) An approved drug or licensed biologic is being used for an unlabeled indication.

(2) What is the variance from the labeled indications and proposed usage.

(3) An explanation of reason for the unlabeled use.

RESEARCH INVOLVING TESTING OF RESEARCH PARTICIPANTS SUSPECTED TO BE INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS (HIV)

The following comments pertain to research protocols involving testing of research participants for infection with HIV, and whose test results can be associated with personal identifiers, i.e., are not anonymous:

1. Research participants must be told in advance they will be tested for infection with HIV, and that this information will be reported to them and to the appropriate military or civilian authorities if required by law or regulation. These statements are to be incorporated into the informed consent process.

2. Research participants must be told the investigators are obligated to make test results available to the individual research participant. If a research participant does not want to know his or her result, his or her only recourse is not to participate in the study.

3. If a research participant is informed that he or she has tested positive for infection with the HIV, the investigators are obligated to ensure the research participant is provided with the opportunity for appropriate counseling about the disease and infectivity.

4. If the human research participants are foreign nationals and research is conducted under the auspices of a host government, it remains the responsibility of naval investigators to ensure the research participants are informed of their positive test result and provided the opportunity to receive appropriate counseling. Delegation of either of these responsibilities to host country officials is prohibited without such participation by naval investigators that they could verify that the ethical and legal responsibilities have been properly executed. This policy does not require naval investigators to personally and exclusively inform and counsel research participants, nor does it preclude appropriate delegation of these responsibilities. This policy does require the naval investigators participate in the process to the extent that they can verify their research participants are being appropriately informed and counseled.

5. One of the greatest potentials for harm to a research participant involves disclosure of the confidential information regarding the research participant's HIV positive status. Considerations for protection of data and confidentiality are of particular importance in research involving research participants with HIV infection. These considerations and safeguards must be fully disclosed in the research protocol and consent document.

RESEARCH INVOLVING PHYSIOLOGICAL STRESS

The following comments pertain to studies conducted at, by, or in collaboration with naval activities or by contractors funded by naval activities or their subordinate activities.

1. Studies are considered greater than minimal risk if they are designed to either increase heart rate to more than 70 percent of predicted maximal heart rate or oxygen consumption to more than 70 percent of predicted maximal oxygen consumption. These studies require:

a. A completely equipped "emergency cart" be immediately available at the site where the research participant undergoes the experimental stress. This "emergency cart" is to be properly stocked and maintained as directed by the commanding officer, officer in charge, or cognizant officer of the performing activity, and is to include equipment and drugs necessary to provide advanced cardiac life support. At a minimum there will be: capability to intravenously administer emergency cardiac drugs; equipment for endotracheal intubation and controlled ventilation with 100 percent oxygen; equipment to monitor and record cardiac rhythm; and equipment to electrically convert abnormal cardiac rhythms.

b. A qualified medical officer (or civilian physician), currently certified in advanced cardiac life support, must be readily available during the entire study. The criteria that constitute reasonable proximity to the site of the experimental exposure are to be specified in the research protocol and approved by the reviewing IRB.

c. At the beginning of the study, the medical officer (or civilian physician) will approve initiation of the study for each research participant. At the conclusion of the study, the medical officer (or civilian physician) will clear each research participant for release and resumption of normal activities.

d. At least one member of the research team will be continuously with the research participant from the beginning of the study until a medical officer (or civilian physician) releases the research participant. This research team member is required to have, at least, current "basic life support" certification. Appropriate advanced medical training is strongly encouraged.

2. In all research involving significant physiological stress to research participants, specific criteria for termination of an individual research participant's participation in the experiment will be stated in the protocol and reviewed by the IRB. Criteria for cessation of experimental exposure and an emergency treatment plan for any reasonably expected untoward event will be fully described in the protocol and readily available at the site of the experimental exposure.