



DEPARTMENT OF THE NAVY
NAVAL MEDICAL RESEARCH CENTER DETACHMENT

LIMA, PERU
UNIT NUMBER 3800
APO AA 34031 - 3800

IN REPLY REFER TO

NMRCINST 3900.6E
03 May 04

NMRCD INSTRUCTION 3900.6E

From: Officer-in-Charge
To: Distribution List No.3

Subj: PROTECTION OF HUMAN SUBJECTS IN MEDICAL RESEARCH

Ref: (a) NAVMEDRSCHCEN Instruction 3900.6A

Encl: (1) Protocol Assessment Form
(2) Continuing review format
(3) Final review format
(4) Assurance agreement format

1. Purpose. To provide guidance and establish procedures relating to the use of human subjects in medical research, which entails possible risks to the subjects as a result of their participation.

2. Cancellation. NMRCD INSTRUCTION 3900.6D

3. Scope. It applies to all research utilizing human subjects when conducted under the authority of or in collaboration with NMRC, whether conducted in government facilities or in collaboration with contractors when NMRC personnel are participating as key individuals, especially on the investigator level; regardless of the source of funding. Its provisions encompass all biomedical and behavioral research when human subjects are involved.

The determination of whether a research protocol involves more than minimal risk shall be made by the Naval Medical Research Center Institutional Review Board (IRB).

Submissions of new protocols for IRB review, as well as Responses to IRB comments, Continuing and Final Reviews, shall be sent to the Research Services Department and the package will be reviewed by the Ethics Specialist for the command. Upon his approval, a cover letter will be prepared by the Research Services Department to be signed by the Officer-in-Charge. The package will be sent via e-mail and simultaneously via regular mail to the NMRC IRB offices in Silver Spring, MD.

The submission package must include the protocol in English, translation of the consent forms into Spanish and a back translation of them into English, properly signed signature pages and assurance agreements, and the host country approval if

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available. Back translations are not needed when the original consent form was drafted in Spanish. In this case, only a translation into English is needed.

4. Action.

a. All investigators shall become familiar with the provisions of references (a) and (b) and enclosures (1) through (5).

b. This policy is effective immediately. Pursuant to the issuance of this instruction, NMRCD is to establish or amend and reissue local instructions implementing enclosure (1) and likewise to establish and maintain separate manuals of standard operating procedures for the implementation of the same. All NMRCD personnel conducting research involving human research volunteers will comply with the provisions contained in this instruction and enclosure (1).



G. J. MARTIN

NAVAL MEDICAL RESEARCH CENTER
INSTITUTIONAL REVIEW BOARD
PROTOCOL ASSESSMENT FORM

(The following assessment guide questions are designed for the use of those assigned to lead the IRB deliberations for new protocols or major modifications/amendments to protocols already approved. Reviewers are to provide a verbal assessment of a given protocol's or amendment's ethical quality concerning the protection of human subjects from research risks. The reviewers' assessment explicitly is not a scientific review or judgment of research efforts. Those assigned should make every effort to direct their critique toward ethical and not scientific or laboratory review.)

Ethics Review provided for

New Protocol

Modification to Existing Protocol

Reviewer's Name:

Assessment Date:

DoD Protocol Number:

Protocol Title

NMRC Principal Investigator (or related NMRC Collaborators)

I. PROTOCOL GENERAL TEXT:

- 1 The protocol materials provide for all requirements regarding the ethical protection of human subjects from research risks.

Yes

No

If No, briefly comment and indicate which parts are in need of completion and/or revision.

- 2 The protocol materials are consistent on ethical issues relating to the protection of human subjects.

Yes

No

If No, briefly comment

II. RISK LEVEL:

This protocol represents research involving human subjects that would be classified as:

Exempted Research

Minimal risk

Greater than minimal risk

Briefly comment on whether the research risks to human subjects found in this protocol are reasonable in relation to the anticipated benefits.

If applicable, provide comments concerning justification for this protocol to be classified as exempted research.

III. RESEARCH POPULATION:

4. The protocol addresses appropriately and consistently the anticipated number of human subjects to be enrolled.

Yes

No

- 5 Does the anticipated number of subjects meet the research need without exposing undue numbers of enrollees to research risks?

Yes

No

If No, briefly comment.

IV. COLLABORATIVE RESEARCH REQUIREMENTS:

6. Are there any collaborating institutions involved that require submission of their IRB/IRB review and institutional approval?

Yes

No

If Yes, what institutions?

- 7 Are there any potential institutional conflicts between the various participating agencies?

Yes

No

If Yes, identify potential conflicts and propose solutions.

8. Is a Department of the Navy medical or dental treatment facility one of the collaborative agencies?

Yes

No

If Yes, which institution?

9. If this protocol represents a collaborative effort, does the protocol present a clear research plan delineating the ethical and administrative responsibilities of each party?

No

If No, briefly comment

V. SUBJECT POPULATION:

Are any groups excluded from research?

Yes

No

If Yes, identify which specific groups.

11. If any groups are excluded, is there sound scientific and ethical reasoning included in the protocol which justifies the exclusion?

Yes

No

If No, briefly comment.

12 Does this protocol involve any special or vulnerable subjects in the study population (e.g. minors, potentially pregnant women*, fetuses)?

Yes

No

If Yes, is the protocol consistent with agency policy for this special group? If No, briefly comment.

Note: If a potentially pregnant female research volunteer is to be enrolled, a negative pregnancy test is required immediately prior to participation. This matter must be explicitly stated in the protocol.

Does the population include active duty service personnel?

Yes

No

14 If the population includes active duty service personnel, has adequate consideration of potential for coercion, operational commitments and interference with duty responsibilities been given in the protocol?

Yes

No

If No, briefly comment

15 The protocol includes optimum procedures for safeguarding confidentiality.

Yes

No

If No, briefly comment

VI. VARIA

16 The protocol lists a qualified medical monitor and procedure for monitoring.

Yes

No

If No, briefly comment

17. Does the protocol involve the administration or use of any drugs/agents or devices?

Yes

No

If yes, comment if use is investigational (IND status), off-label indication versus approved FDA method.

18 The protocol includes detailed procedures for maintenance of records including original signed consent forms and materials related to the same.

If No, briefly comment

19. Is the investigator involved in clinical decision making?

Yes

No

If Yes, is the role appropriately defined?

20. Are there any unique circumstances or problems of any ethical nature related to the research (e.g. host government laws, different cultural customs or prohibitions)?

Yes

No

If Yes, specify.

If Yes, does the protocol address adequate provisions to meet the unique problems or circumstances cited?

VII. SUBJECT CONSENT AND INFORMED CONSENT CHECKLIST

(The following question is designed to assess the protocol's overall and specific provisions for informed consent. The assessment is to provide a specific critical review of the form-materials to be used for informed consent by research subjects. Assessment must include answers to the checklist.)

21. The protocol completely meets all requirements for informed consent provisions including a mechanism for witnessed documentation and an appropriate method for the subject to contact the Principal Investigator, the medical monitor, and/or a member of the NMRC IRB or the IRB of one of the collaborating agencies.

Yes

No

If No, briefly comment and list specific revisions required.

A. General Considerations:

Item	Yes	No	Are the following applicable to the submitted consent form?
1.			Is the consent form complete, accurate and clear?
2.			Is the consent form in layperson/non-technical language?
3.			If applicable, are foreign language translations included? As best as can be determined, are foreign translations linguistically accurate, culturally appropriate for the indigenous region? Has certification of translation (or at least translator contact info) been included with the foreign translation?
4.			If applicable and regardless of language, does the consent form address cultural or other particularities which may affect the subject's ability to render truly "informed and free" consent?

B. Specific Consent Form Items:

Item	Yes	No	Are the following found on the submitted consent form?
5.			Statement that the proposal involves research.
6.			Explanation of the purpose of the research.
7.			Expected duration of the subject's participation.
8.			Simple but accurate identification of research procedures.
9.			Approximate total number of subjects to be involved in the study.
10.			Clear description of any reasonably foreseen risks/discomforts

			to the subject.
11.			Description of subject benefits/compensations which may reasonably be expected.
12.			Disclosure of appropriate alternative procedures/courses of treatment, if any, that may be advantageous to the subject.
13.			Statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
14.			Statement noting possible FDA inspection of related records.
15.			Explanation as to whether any medical treatments are available if injury were to occur; and, if so, what such medical treatments would consist of or where related further information can be obtained.
16.			Clear contact information and contact procedures for answers to questions regarding the research, the research subject's rights, and whom to contact in the event of research-related injury to the subject.
17.			Statement that participation is voluntary, that refusal to participate will involve no penalties or less of benefits to which the subject is otherwise entitled.
18.			Statement that the subject may discontinue participation at anytime without penalties or loss of benefits to which the subject is otherwise entitled.
19.			If applicable, provision to meet the ethical requirement for justified third party consent procedures.

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Item	Yes	No	When appropriate, one or more of the following elements shall also be provided to each subject.
20.			Statement that the particular treatment or procedures may involve risks to the Subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable.
21.			Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
22.			Additional costs to the subject that may result from participation in the research.
23.			Consequences of a subject's decision to withdraw from the research; procedures for orderly termination of participation by the subject.
24.			Statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

GENERAL OR MISCELLANEOUS COMMENT

IX. FINAL REVIEWER RECOMMENDATION:

Approve protocol as submitted.

Defer action:

- a. Conditional approval contingent on the following minor revisions (specify):

- b. Require significant modification of the protocol before approval (specify):
(Modification must be reviewed and approved by the full committee)

- c. Request investigator to discuss problems with committee.

Reject the protocol: (Detailed explanation required)

*Signature of Reviewer

Date

**Signature and date are required only for hard*

Institutional Review Board

Naval Medical Research Center

Continuing Review Report for Protocols Involving the Participation of Human Subjects

General Directions:

1. As mandated by the Code of Federal Regulations, all protocols involving the use of human subjects must be reviewed at least annually by the Institutional Review Board (IRB). The Code requires more frequent continuing reviews for particularly important factors such as greater levels of risk etc. The purpose of continuing review is to assess a protocol's progress and direction, to determine its adherence to ethical norms and original approvals, to direct new ethical needs in the light of new requirements, and to reauthorize the research effort for its next period of performance. A research effort becomes unauthorized and thereby falls into non-compliance when its continuing review deadline is not met. In the case of such non-compliance, as directed by higher authorities the IRB Chair or Command officials take immediate action with the investigator and related staff to suspend the research effort until compliance is re-established.
2. To meet the important task of continuing review, an IRB revisits each protocol under the same categories under which it first gave approval. Part of the continuing review process includes a review and re-approval of informed consent procedures and processes. Concerning the informed consent document, the document itself must be re-approved and reissued at the time of continuing review. Reissuance is certified by an authoritative stamp that indicates the performance period in which the informed consent may be used with permission of the IRB.
3. The minimally required annual review must coincide with the anniversary date of the protocol's original IRB review. Even in the case of protocols not implemented for various reasons after initial review, an annual continuing review is required so as to assess the need for modifications that may be necessary in the light of new requirements due to scientific advancement, ethical insights and norms, or other regulations. The Office of Research Administration (ORA) or other IRB Office in the local activity must notify the Principal Investigator or other relevant individual at least 60 days prior to the scheduled date that the required review is imminent. More frequent reminders should be arranged to ensure absolute compliance and to reduce at all costs any instances of non-compliance. However, it is ultimately the responsibility of the submitting investigator to ensure that a protocol meets continuing review requirements. Investigators are not to rely on executive staff solely for continuing review notifications.
4. . The Principal or other relevant investigator is to complete the form below as completely as possible. Once completed, the continuing review report must be routed

through relevant program, department and directorate Chief Scientists for review and validation before submission to ORA or the local IRB office. For reports submitted from the NMRC-DET in Lima, Peru, reports should be reviewed, validated and submitted through the Officer in Charge or his/her delegate.

5. After review and validation, continuing review reports must be received in the most timely manner possible. For NMRC and NMRC-DET, continuing review materials must be received in ORA NLT the last day of the month prior to the month of the protocol's anniversary date.

6. The IRB may require additional information from investigators to be appended to submitted reports.

7. The IRB may recommend to the Commanding Officer additional continuing reviews of research during the year. Additional reviews, however, do not substitute for the yearly required review at the protocol's anniversary date.

8. Questions or need for clarification should be addressed to:

Executive Administrator
Institutional Review Board
Office of Research Administration
Naval Medical Research Center
Tel: (301) 319-7276
Fax: (301) 319-7277
E mail: ora@nmrc.navy.mil

Continuing Review Report for Protocols Involving the Participation of Human Subjects

1. Dates of Present Reporting Period:

2. DoD Assurance Number:

3. IRB Protocol Title:

4. Risk level (Exempt, Minimal, or Greater than minimal):

5. Performing Laboratory Designation:

(Command, Program, Department, Directorate etc)

6. Applicable Work Unit Number(s):

(List full work unit numbers for all applicable work units. Please note that the work unit number is not the financial Job Order Number information.)

7. Principal Investigator:

8. NMRC Investigator: (If the PI is not an NMRC-related scientist)

9. Original Start Date of Research:

10. Summary and schedule for research remaining::

11. Number of Volunteers authorized for enrollment:

12. Number of Volunteers Enrolled in Reporting Period (Attach a list of subjects enrolled in reporting period identified by study number and initials):

13. Total Number of Volunteers Enrolled to date with a summary of and/or breakdown by demographics (e.g. breakdown by gender, ethnic/racial group and other subdivisions as may be applicable and essential to continuing review purposes etc):

(If the total number of volunteers exceeds the number of volunteers approved in the original protocol, provide narrative and/or justification explaining the enrollment increase.)

14. Number of subjects that withdrew with reason for withdrawal:

15. Is the study still actively enrolling volunteers? Y/N

16. Summary of Research Efforts Performed in Reporting Period:

17. Summary of Scientific/Medical Results Obtained:

(Please attach copies of any published abstracts or papers that have been generated from this study)

18. List and describe all Expected Adverse Events or Medical Complications:

(Investigators should provide a tabular summary of adverse events)

19. List and Describe any Serious and/or Unexpected Adverse Events or Medical Complications: (if applicable): (Please comment if these events alter the risk to volunteers)

20. Summary of any information that has appeared in the literature or evolved from this or similar research that might affect the IRB's assessment of the risk/benefit ratio of this study:

21. Investigator's Analysis of the Informed Consent Processes and Informed Consent Materials Used (Attach a clean copy of the Informed Consent Form formatted for IRB approval):

(Investigators are to provide an assessment of the adequacy of the informed consent processes which have occurred between volunteers and staff members. Investigators are to provide an assessment of the informed consent materials used. Changes to approved informed consent procedures and materials are to be summarized and justified. Additional assistance for informed consent processes and materials should be requested in this narrative.)

22. Location of Study Records to Date. How is confidentiality being protected?

23. Revisions to or Issues Concerning Research and Safety Procedures: (if applicable)

24. Changes in Investigator Staff or medical monitor:

(List all new investigators or note investigators who have left the protocol. For additions to investigator staff, signature pages and signed investigator assurance agreements must be submitted if not done previously. Changes in investigator staff may require changes in the consent form point of contacts. Changes in investigator staff includes additional authors on papers utilizing data from the protocol.)

25. Changes in Collaborating Institutions:

(List any additions or deletions of institutions collaborating on the protocol. In the case of issues relative to foreign countries, specify any relevant issues. Please attach copies of approval documentation and other correspondence from collaborating institutions.)

26. Protocol deviations and Non-Compliance Issues including but not limited to the following:

Description and explanation of all deviations or variances from the approved protocol (e.g. If the total number of volunteers exceeds the number of volunteers

approved in the original protocol, provide narrative and/or justification explaining the enrollment increase)

Description and explanation of subjects who either did not meet inclusion criteria or who met exclusion criteria but were enrolled regardless

Summary of all complaints relating to the research from any subject, investigator or other person and the action taken to address them.

Please attach a copy of the approved consent form currently in-use. If revisions are necessary to reflect changes in study procedures, investigators, or potential risks, etc., a revised consent must be included.

**Institutional Review Board
Naval Medical Research Center**

**Protocols Involving the Participation of Human Subjects
Executive Summary/Final Report**

General Directions:

1. As required, final executive summaries (2-5 pages maximum) must be submitted for all protocols involving the use of human subjects that have been completed. Final reports must be submitted NLT ninety (90) days after the completion of research.
2. The Principal or other relevant investigator is to complete the form below as completely as possible. Once completed, the final report must be routed through relevant program, department and directorate Chief Scientists for review and acceptance before submission to ORA. For reports submitted from the NMRC-DET in Lima, Peru, reports should be reviewed, validated and submitted through the Officer in Charge.
3. The IRB may require additional information from investigators to be appended to submitted reports.
4. Questions or need for clarification should be addressed to:

**Executive Administrator
Institutional Review Board
Office of Research Administration
Naval Medical Research Center
Attn: IRB
Tel: (301) 319-7276
Fax: (301)319-7277
E mail: ORA@nmrc.navy.mil**

Protocols Involving the Participation of Human Subjects Final Report/Executive Summary

1. Dates of Research Performance:

2. DoD Assurance Number:

3 Title of IRB Protocol:

4. Principal Investigator/NMRC Investigator(s):

5. Applicable Work Unit Number(s):

6. Total Number of Enrollees:

7. Summary of Research Objectives:

8. Summary Narrative of Research Performed:

(Include in this section a portrait of the enrollee population. If applicable, include in this section a summary of any adverse events or medical complications that may have occurred. How were these expedited?)

9. Summary of Scientific Results Obtained:

10. Statement of Benefits of Research to the Accomplishment of Military Medical Requirements:

INVESTIGATOR ASSURANCE AGREEMENT

I, a research investigator, promise to protect the ethical rights and welfare of human participants enrolled in a research protocol entitled, "(Insert Name of Protocol)." I understand and accept my responsibility for the protection of human research subjects as found in The Belmont Report and the provisions of Title 32 Code of Federal Regulations Part 219 (Protection of Human Subjects), Department of Defense (DoD) Directive 3216.2 (Protection of Human Subjects in DoD-Supported Research), Secretary of the Navy Instruction (SECNAVINST) 3900.39C (Protection of Human Subjects), Bureau of Medicine and Surgery Instruction (BUMEDINST) 3900.6B (Protection of Human Subjects), Naval Medical Research Center Instruction (NAVMEDRSCHCENINST) 3900.6A (The Protection of Human Subjects In Medical Research), and all other relevant regulations concerning standards of conduct for the Department of Defense and the Department of the Navy. I will abide by all applicable laws and regulations relevant to the ethical protection of the rights and welfare of human research subjects; and I guarantee that I will follow the most restrictive regulation in all cases and without exception. In the event any question regarding my obligations arises during the conduct of this project, I will consult with the Institutional Review Board Chair and any other human research authorities in my chain of command.

Signatures and dates:

(DD/MM/YY)

(Typed Name)

Principal Investigator

___/___/___

(Typed Name)

Co-Investigator

___/___/___

(Continue to include all investigators.)