



DEPARTMENT OF THE NAVY
NAVAL MEDICAL RESEARCH CENTER
503 ROBERT GRANT AVENUE
SILVER SPRING, MARYLAND 20910-7500

IN REPLY REFER TO:

NAVMEDRSCHCENINST 3900.6A

00R/ 8094

MAR 26 2002

NAVMEDRSCHCEN INSTRUCTION 3900.6A

From: Commanding Officer, Naval Medical Research Center

Subj: THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH

Ref: (a) 10 USC 980
(b) 32 CFR 219
(c) DoD Directive 3216.2
(d) OSD Guidance for Assurance of Compliance with
The Federal Policy for the Protection of Human
Subjects of 10 June 1993
(e) Office of Human Research Protections Procedures
for Registering Institutional Review Boards and
Filing Federal Assurance of Protection for Human
Subjects of December 2000
(f) OPNAV 5300.8B
(g) SECNAVINST 3900.39C
(h) SECNAVINST 5212.5D
(i) SECNAVINST 5215.1C
(j) BUMEDINST 3900.6b with Interim Policies Supplement

Encl: (1) Protecting Human Subjects: Principles and
Policies for the Ethical Protection of Human
Subjects from Research Risks

1. Purpose. To establish Institutional Review Boards (IRB), IRB oversight Systems, the Human Subjects Protections Program (HSPP) system, and their responsibilities for protecting the rights and welfare of human subjects participating in research studies conducted by the Naval Medical Research Center (NMRC) and all of its subordinate activities.

2. Cancellation. NAVMEDRSCHCENINST 3900.6 and NAVMEDRSCHCENINST 3902a.

3. Scope. This instruction 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 funding source. Its provisions encompass all biomedical and behavioral research when human subjects are involved. Nothing in this instruction shall supersede requirements for health hazard or other safety reviews required by other regulations. Specific provisions are found in enclosure (1) for those activities described as exempt by paragraph 101 of reference (b).

4. Policy. Enclosure (1) establishes mandatory minimum policies for all NMRC Echelon 3 and 4 activities for the ethical protection of the rights and welfare of human participants from research risks. Enclosure (1) implements all requirements as found in references (a) through (j). All modifications to enclosure (1) must be approved by the NMRC Commanding Officer.

5. Administration. Within and under the Office of Research Administration (ORA), NMRC has established the Human Subjects Protections Program (HSPP) for all Echelon 3 and 4 activities. Authority is delegated to ORA-HSPP for the oversight, administration of and assistance with the development of policy, procedures, Department of the Navy and Federal Wide Assurance requirements, and all extramural agency relations relative to federal and local agency requirements for the ethical protection of human subjects from research risks. ORA-HSPP is assigned the responsibility for the ongoing implementation of enclosure (1) and its related materials.

6. Action. This policy is effective immediately. Pursuant to the issuance of this instruction, all Echelon 4 activities are directed 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 NMRC personnel conducting research involving human research volunteers will comply with the provisions contained in this instruction and enclosure (1).



R. B. OBERST

Distribution:
List(s)
A, B, C and D

**Protecting Human Subjects:
Principles and Policies for the Ethical
Protection of Human
Subjects from Research Risks.**

**Naval Medical Research Center
Silver Spring Maryland**

Chapter	Title	Page
1.	Scope	1
2.	Background	2
3.	Delegation of Authority.	3
4.	Definitions.	4
5.	Organization and Structures for IRB Policy, Procedures, Oversight and Administration	6
6.	Institutional Review Board (IRB) and Office of Research Administration (ORA) Organization, Duties ,and Responsibilities	10
7.	IRB Education, Training and Certification.	14
8.	Basic Submission, Review and Approval Norms.	19
9.	Authorization to Initiate Research Involving Research Subjects.	26
10.	Exempted Research Activities	27
11.	Expedited Review	31
12.	Responsibility for Protection of Research Volunteers in Research Involving More than One Activity	38
13.	IRB Continuing Review of Research.	43
14.	Reporting Complications.	51
15.	Other Reporting Requirements	57
16.	Research Conducted Outside the United States	58
17.	Research Protocols	60
18.	Selection of Research Volunteers	64
19.	Voluntary Informed Consent	67
20.	Privacy Act Statements	70
21.	Additional Study Requirements and Safeguards	71
22.	Maintenance of Records	72

23.	Investigators Acting as Consultants.	75
24.	Restrictions on Expenditure of Funds for Human Subjects Research.	77
25.	Conflicting Regulations.	78
26.	Waiver of Requirements	79

Appendices

(1)	Sample Format for Research Protocols
(2)	Sample Consent Form
(3)	Sample Privacy Act Statement
(4)	Investigator Assurance Agreement Form
(5)	Protocol Recommendation Forms
(6)	Continuing Review Recommendation Form
(7)	Definitions of Categories of Research Authorized for Expedited Review
(8)	Continuing Review Report Form
(9)	Final Report/Executive Summary Form
(10)	Format for Institutional Review Board Protocol Assessment Form
(11)	Format for Institutional Review Board New Proposal or Modification Administrative Review
(12)	Informed Consent Principles and Critical Elements
(13)	Research Involving Investigational Drugs, Biologics or Devices.
(14)	Research Involving the Unlabeled Use of Drugs or Biologics.
(15)	Research Involving Testing of Research Volunteers Suspected to be Infected with the Human Immunodeficiency Virus.
(16)	Research Involving Physiological Stress.
(17)	Safety Provisions for the Enrollment of Non-Pregnant Women
(18)	Program 7.2 Review Criteria: Protection of Human Subjects
(19)	A Historical, Ethical and Regulatory Overview

Special Supplement: Special Supplemental Policies to BUMEDINST
3900.6b

CHAPTER 1**SCOPE**

1. This instruction applies to all research utilizing human subjects regardless of funding source conducted at, or under the authority of, or performed in collaboration with NMRC; to all research utilizing human subjects in NMRC-supported studies conducted by either other government facilities or contractors and to all research involving the participation of NMRC personnel at other institutions as an investigator, regardless of funding source. Its provisions encompass all biomedical and behavioral research of any risk level that requires the use of human subjects. Nothing in this instruction shall supersede requirements for health hazard or other safety reviews required by other regulations. Its provisions do not apply to those activities described as exempt by paragraph 101 of reference (b).

CHAPTER 2**Background**

1. For all federally sponsored research and all research conducted in federal facilities, the United States government has enacted laws, regulations and directives for the ethical protection of the rights and welfare of human subjects from research risks. A brief overview of the historical, ethical and regulatory parameters relevant to human subjects protections is found in Appendix (19) of this manual.
2. The requirements of the federal government have been further specified and implemented by the Department of Defense (DoD) and the Department of the Navy (DoN) for research activities on the local agency and subordinate activity levels.
3. The provisions of this instruction are in conformity with all laws, regulations, directives and requirements of the federal government, the DoD, the DoN and the Bureau of Medicine and Surgery (BUMED) as found in references (a) through (j).
4. In any multi-agency or cross-agency human research efforts where conflict of requirements may occur due to circumstances, the stricter interpretation is always to be in force per federal regulations.
5. Since the ethical, regulatory and legal requirements incumbent upon human research activities by their nature evolve over time in concert with scientific and social discoveries, it is incumbent upon all activities and human research personnel to know, implement and abide by new standards as they emerge.

CHAPTER 3**Delegation of Authority**

1. Reference (g) assigns the Surgeon General of the Navy (SG) approval authority for all Navy studies using research volunteers that do not require approval by the Assistant Secretary of the Navy (Research, Development and Acquisition) [ASN(RD&A)] or higher authority. Per paragraph 12.a.1 of reference (g), the categories of research reserved for higher authority approval include all studies involving nuclear weapons effects and chemical warfare agents, classified research, projects involving severe and unusual intrusions either physical or psychological on the person of the human subject, research involving potential political or public embarrassment to the DoN, and such other projects as may be designated by the Assistant Secretary of the Navy.
2. The SG has delegated approval authority to a medical or dental officer for studies involving research volunteers that are supported by the Navy Clinical Investigation Program (CIP) and do not require ASN(RD&A) approval.
3. The SG has delegated approval authority to another medical or dental officer assigned to BUMED involving research volunteers that are supported by BUMED ASN(RD&A) approval, and which are not part of the CIP.
4. The SG has delegated to Commanding Officers of BUMED approval authority for studies involving research volunteers conducted by their respective Commands and Detachments within particular limits and subject to higher authority.
5. In all cooperative and contract research, the cooperative research plan or contract, as appropriate, will clearly define the responsibility and authority of all parties such that the requirements for the protection of research volunteers will not be diminished.

CHAPTER 4**Definitions**

1. Human Subject. A living person from whom a researcher obtains data through interaction with the individual, or the individual's records, including both physical procedures and manipulations of the subject or the subject's environment.
2. Non-U.S. Citizens. Foreign nationals, excluding for the purposes of this instruction, personnel on active duty as members of the U.S. military services.
3. Research. A systematic investigation designed to develop or contribute to generalizable knowledge, to include any project, task, test, experiment, evaluation, or similar undertaking in humans concerned with health care of members of the military community, including active duty, retired and dependents. The term does not include individual or group training of military personnel in areas such as combat readiness, effectiveness, proficiency, or physical fitness.
4. Risk. The possibility of harm - physical, psychological, sociological, or other - as a consequence of any act or omission that goes beyond the application of established and accepted methods or procedures which are in an individual's best interests, or increase the possibility of harm inherent in his/her daily life or in his/her occupation or field of service. Determination of the nature and degree of risk is a matter of common sense and sound professional judgement.
5. Minimal Risk. As defined in references (a) and (d), minimal risk is an anticipated risk of harm no greater in probability and magnitude than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
6. Study. A general term for research.
7. Expedited Review Procedure. Expedited review is a procedure for minimal risk categories of research specifically delineated by higher authority where ethical review can be given by an IRB Chair or a subset of IRB members. In Naval medical research and development activities, expedited review must be applied for and authorized by the Bureau of Medicine and Surgery before implementation.

8. Prisoner. Any person who is involuntarily confined in a penal or correctional institution, whether such institution is for the confinement or rehabilitation of juvenile offenders, for persons charged with or convicted of criminal offenses, or for other purposes.

CHAPTER 5**Organization and Structures for IRB Policy, Procedures, Oversight and Administration.**

1. Under the authority and assurance system of the Office of the Surgeon General of the Navy, Bureau of Medicine and Surgery, NMRC has established a comprehensive organization for the development of ethics policy, a system of ethical reviews and approvals, standard operating procedures, executive oversight and administration, education, training and certification among all of its Echelon 3 and subordinate Echelon 4 activities so as to provide for the ethical protection of the rights and welfare of human subjects from research risks. This comprehensive organization is directed by the NMRC Commanding Officer, administered by the Human Subjects Protections Program (HSPP), NMRC Office of Research Administration (ORA) and executed by the review and approval authorities and structures in the various activities. These structures are organized under the chain of command between research activities and higher authorities.

2. In addition to the DoN's assurance system under the Office of the Surgeon General of the Navy, NMRC Echelon 3 and 4 activities cooperate with the Federal Wide Assurance (FWA) system of the Office for Human Research Protections (OHRP) insofar as NMRC Echelon 3 and 4 activities collaborate with or assign personnel to participate on human subjects research efforts involving DHHS sponsorship, personnel, resources etc.

3. As required under reference (b) and in compliance with reference (d), NMRC and its Echelon 3 and 4 subordinate activities will submit to higher Navy authorities application materials for the granting of human subject research assurance and human use approval authority on termed bases. Length of assurance term bases is determined by higher authority. Unless directed otherwise, applications for Navy human use assurances and approval authority submitted through the chain of command must include the following from each activity:

a. Cover Letter: An official letter from the Commanding Officer (convening authority/institutional official) indicating clearly the firm intention of the activity to abide by all federal agency and local regulations for the ethical protection of the rights and welfare of human subjects. The official letter is to make a formal request for human use assurance for the institution and a formal request for human use approval

authority for the Commanding Officer. Both elements are required.

b. Command Instruction: An official copy of the local ethical policy that enacts this document and all laws and higher agency regulations.

c. Standard Operating Procedures: Current manual for IRB operations on the local level.

d. IRB Roster: A complete roster of all voting and non-voting members including their affiliation, IRB role as to whether one is a scientist or non-scientist, specified roles for non-scientists where applicable (e.g. ethicist, chaplain etc), degrees etc. For OCONUS activities, to certify local community involvement the roster is to list those members who are representatives of the local Ministry of Health.

e. IRB Protocol Inventory: A complete listing of all active protocols with DoD Assurance Number. The listing must include all protocols regardless of risk level including those that have exempt status.

f. IRB Agreements: Copies of all inter-agency agreements that provide for concurrent IRB review and approval or provisions for regular lead IRB status for multi-center efforts.

g. Self-Assessment (optional unless directed otherwise): The local activity may perform a self-assessment of IRB ethical procedures and programs and submit evaluative documentation of the same at the time of assurance and approval authority renewal. Such self-assessment may be required by higher authority.

4. Under the chain of command, the NMRC Commanding Officer will hold the approval authority for NMRC Echelon 3 activities. Limitations on approval authority are determined by higher authority. Approval authority is distinct from recommendation authority that must be vested in an institutional review board (IRB) duly and validly constituted for the protection of the rights and welfare of human subjects from research risks as outlined in federal, DoD, DoN, agency and local laws, regulations and directives.

5. NMRC will establish for its Echelon 3 activities an IRB duly and validly constituted according to all federal, DoD, DoN and local regulations. The NMRC IRB will provide requisite

recommendations to the NMRC Commanding Officer who is the approval authority concerning the ethical protection of the rights and welfare of human subjects from any and all research risks. As in all other IRB structures under federal assurance, the IRB must determine its recommendations prior to any approval or disapproval action and the initiation of research.

6. NMRC will oversee the human subjects assurance systems and procedures of each of its Echelon 4 activities after such assurances have been granted by higher authority. NMRC Echelon 4 activities will apply for and receive Navy human use assurances from higher authority in accordance with all directives and regulations. Applications for assurances will be prepared and processed through the NMRC chain of command. Each subordinate Echelon 4 activity holding a human subjects assurance will be granted approval authority for human use research in the person of the Commanding Officer. Limitations on approval authority under the principles of tiered review are determined by higher authority.

7. To provide for approval requirements, each activity holding a human use assurance must obtain the ethical review and recommendation of an IRB duly and validly constituted, organized and recognized under reference (b). To meet this requirement, each activity holding an assurance may establish its own IRB. Where numbers of personnel or other factors may preclude the ability to establish its own IRB, an activity may make written request of NMRC to utilize the NMRC IRB or another NMRC Echelon 4 IRB for ethical review requirements. Alternatively, an activity may elect to utilize any other non-NMRC DoD IRB validly constituted under reference (b) provided that all DoN standards are strictly upheld and that requisite memoranda of agreement of are developed and approved for the purposes of this service from one activity to another. If so directed, such agreements may require approval by higher authority.

8. To serve the executive administration needs of all Echelon 3 and 4 activities, NMRC has established HSPP as a subordinate activity of ORA. ORA-HSPP is directed by the ORA Director who in this capacity serves as Command Research Ethics Counselor, a Special Assistant to the NMRC Commanding Officer (00R). ORA-HSPP will be responsible for the overall development of policy, administration, education, training and certification resources for human subject protections at NMRC and its subordinate activities. Furthermore, ORA is responsible to the Commanding Officer for the executive administration of all assurance requirements as pertinent to higher authority and FWA

processes and regulations. Detail regarding ORA duties is found in paragraphs to follow in this instruction.

9. To assist Echelon 4 activities with on-going continuing audit, oversight, education, training and certification needs, at the direction of the NMRC Command, ORA-HSPP participates in required site assist visits and inspections. For human research review and inspection purposes, ORA-HSPP maintains, develops and provides to all activities official oversight, review, inspection and audit resources that assist local activities with continual improvements. The official site assist and inspection checklist is found in Appendix (18).

CHAPTER 6**Institutional Review Board (IRB) and Office of Research Administration (ORA) Organization, Duties and Responsibilities**

1. For all Echelon 3 and 4 activities, proposed studies involving research volunteers covered by this instruction will come under the authority of and be reviewed by a duly and validly constituted Institutional Review Board (IRB). Executive research administration programs related to the mission, policy and functions of IRB's will be directed by the executive responsibility of ORA-HSPP.

2. Members of the IRB will be appointed in writing by the Commanding Officer, with appointments made by name, not by position. The terms of IRB members will be staggered to ensure that continuity in IRB actions will not be effected by the normal expiration of terms. Terms of appointment will be made for a minimum of two years. Members may be reappointed for consecutive terms at the discretion of the Commanding Officer.

3. The IRB must be sufficiently qualified to provide initial and continuing review of each proposed study and to ensure respect for its advice and counsel for safeguarding the rights and welfare of human subjects. Members will be chosen from various IRB-related professions and groups of personnel to meet the requirements of reference (b).

4. Five voting members of an IRB will constitute a quorum for the valid conduct of IRB affairs. With members being able to fulfill functions simultaneously, the quorum for each meeting must include the following:

a. At least one member whose primary expertise is in scientific areas.

b. At least one member who is a physician or a medical practitioner when protocols are of a biomedical nature.

c. At least one member whose primary expertise or professional service is in nonscientific areas.

d. 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. In accordance with paragraph 6.b.(4) of reference (g), unaffiliated members must be federal employees or federal appointment

equivalents such as appointments via Intergovernmental Personnel Act (IPA) agreements or special government consultancies as permissible under 5 USC 3109. In the latter case regarding special government consultants, individuals may be appointed either as contributed service or compensated experts. For contributed service consultants, requirements for volunteers under the American Red Cross or other equivalent organizations are to met as required and as applicable depending on diverse circumstances. For compensated consultants, standard personnel action requirements are to be made in accordance with regulations and internal procedures. Per 5 USC 3109, annual appointment renewals and reporting of such appointments to higher authorities are to be made as required.

5. For OCONUS activities, the Commanding Officer will appoint at least one host country national member (e.g. Ministry of Health) who will serve as a special liaison member for the IRB. The appointee (or appointees) may be named to non-voting status with voice or may be named to special government consultant status with voice and deliberative vote. However, as in the case of all other IRB members, such members must avoid any semblance of conflict of interest.

6. The Chair will be a member of the professional staff; will be appointed by the Commanding Officer by name, not position; will have completed all required IRB ethics and administration training in conformity with all regulations and the terms of all assurances; and shall have the following responsibilities:

a. Conduct IRB meetings in accordance with this instruction and all references and shall collaborate with Command offices for the initiation and on-going development of a IRB manual of standard operating procedures.

b. Report IRB recommendations to the Commanding Officer.

c. Prepare a statement of assurance when required by regulations.

d. Will support and assist ORA-HSPP in its direction of IRB orientation and continuing education programs to IRB members to include information concerning:

(1) the basic principles governing the use of human subjects in research,

(2). regulations and instructions governing the IRB's function, and

(3). current literature with information relative to the IRB's function.

(4). review and grant acceptance of revisions that were required by the IRB. This authority extends only to those projects which were approved pending the submission of identified modifications.

7. In addition to the Chair, the Commanding Officer will appoint either one or more Vice Chairs or alternate Chairs as may be needed.

8. Depending upon need, the Commanding Officer will appoint additional staff to direct or assist IRB administration. At NMRC, the Commanding Officer will appoint an Executive Administrator who will direct IRB policy implementation and operations and an Executive Secretary who will assist the Executive Administrator with operational items such as meeting agendas, recording of minutes, IRB rosters and attendance records, documents and other matters as may be needed. At other activities, the Commanding Officer will appoint staff members to similar positions given availability of personnel and need. In all activities, such executive responsibilities may be undertaken by the same person provided that there is not an excessive workload burden to any individual.

9. ORA-HSPP is established to serve all Echelon 3 and 4 activities regarding the oversight of all IRB procedures and the establishment of programs and resources supportive of the IRB mission with special attention being given to policy development, programmatic development and education and training programs.

10. For those activities where applicable, ORA-HSPP will provide professional direction and oversight for local Echelon 4 IRB Offices to assist them in meeting their own mission on the local level.

11. For all activities, ORA-HSPP will coordinate all matters for assurances and assurance updates/renewals for Navy higher authority requirements and also for the OHRP FWA system.

12. Regarding the NMRC IRB, to ensure that there is no conflict of interest the Director, ORA-HSPP, is given responsibility for

the nomination of new NMRC IRB members and NMRC IRB officials such as the Chair, Vice Chair, Executive Administrator, Executive Secretary etc. Regarding these nominations, however, the Director, ORA-HSPP, will seek counsel, advice and opinion from a variety of staff members. For Echelon 4 activities, nominations of IRB members, Chairpersons and the appointment of administrators or support personnel are to be made such that there is no appearance or substance of conflict of interest. Due to the serious nature of the IRB ethical oversight mission, only the most qualified personnel are to be considered especially in light of the nature of the research to be undertaken, higher authority assurance requirements, the ethical focus of IRB service, and the needs of the wider local community.

13. For all activities, ORA will provide leadership and oversight for all educational, training, certification and accreditation requirements as may be required.

14. 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.

15. The Commanding Officer may appoint permanent, non-voting consultants to the IRB to provide technical expertise required in a field that is not adequately represented by the IRB members present. These consultants may be excluded from IRB deliberations at the discretion of the IRB Chair, and are neither eligible to vote nor to be considered in determining the presence of a quorum. In addition, on a case by case basis, the IRB Chair may request the presence of subject area experts to provide special expertise for particular protocols at given IRB meetings. These occasional adjunct experts are invited for open discussion but cannot exercise deliberative voice and vote.

CHAPTER 7**IRB Education, Training and Certification**

1. The ethical protection of the rights and welfare of human subjects from research risks is a total Command responsibility that involves all hands. This fundamental responsibility requires education and training of investigators, associate investigators and other key personnel. ORA-HSPP is directed with responsibility for the design, development, and oversight for all human use ethics educational resources and programs for all activities.

2. To maintain the highest level of awareness of issues, requirements and ramifications surrounding the ethical protection of human subjects from research risks, initial and continuing education opportunities are required to be developed in broad and diverse ways. All activities are to collect and make available for all personnel substantive educational resource texts or other educational items and the sponsorship of educational forums of information and formation.

3. Each activity is to plan in yearly budgets for appropriate human use ethical education program needs especially for those in IRB board or administration leadership. IRB leadership must always comply with continuing educational requirements and plan accordingly for conferences, accreditation modules and other items as directed or as deemed appropriate.

4. In all Echelon 3 and 4 activities, all key personnel on human use protocols must complete requirements for education, training and certification registry prior to involvement on human use protocols even at the exempt level. Key personnel include those listed as principal or associate investigators and senior leadership in roles related to data management, patient/enrollee consent personnel, data analysts, technicians handling sensitive specimens or data, and other personnel who may in any way become connected to issues surrounding the welfare and rights of human subjects.

5. Under ORA-HSPP leadership, required personnel will complete educational programs for certification. Completion of certification will be indicated by ORA-HSPP issuance of an IRB certification number to each individual. This number, signifying valid certification for three year periods, is required to be used on all protocols and other correspondences. Recertification is required every three years. Educational requirements for

recertification are the responsibility of ORA-HSPP and will be designed under that office's direction. All certification and recertification processes are under the direction of the Director, ORA-HSPP, for all Echelon 3 and 4 activities.

6. The Director, ORA-HSPP, is given oversight responsibility for investigator education compliance for all Echelon 3 and 4 activities. Evidence of non-compliance will be remanded by the Director, ORA-HSPP to the NMRC Executive Officer and Commanding Officer for amelioration or corrective action.

7. The Director, ORA-HSPP, is directed with responsibility for developing and maintaining all human use ethics educational programs, resources and lectures as may be available for all NMRC members and for assisting Echelon 4 activities to develop the same for their own constituents.

8. To meet the requirements listed in the preceding paragraphs, ORA-HSPP will establish and direct the NMRC IRB Ethics Education (IRBEE) Program Curriculum. Cooperatively with the NMRC Federal Wide Assurance (FWA) initiative, this curriculum will meet the standards for human research ethics education detailed during the 2001 Educational Summit of the Office for Human Research Protections, Department of Health and Human Services, namely that all such curricula must be substantive, ongoing, and contain measures of accountability. To clarify:

a. By substantive is meant that a human research ethics curriculum must include general ethical theory and comprehensive content as well as materials regarding legal, regulatory, administrative and practical requirements.

b. By ongoing is meant that the program will require initial certification, certification renewal and continuing education enrichment.

c. By measures of accountability is meant that the curriculum will include various educational strategies (e.g. tests and measurements or various other techniques) that give participants the opportunity to explore or demonstrate the implications of theory for field utility.

9. The IRBEE Curriculum will be divided into three areas: initial education/certification, education/certification renewal, and continuing education resources and opportunities. The following pertain:

a. Initial Education/Certification: ORA-HSPP will design and develop a comprehensive initial curriculum with measures of accountability (tests) for relevant personnel. ORA-HSPP will establish the standard success rate scores for testing materials. The curriculum and its tests will be made available for personnel and activities in diverse formats for user-ease (e.g. web base, CD, hard copy etc). Responsibility that personnel complete the initial curriculum and its tests lies with the local IRB Chair/Policy Officer and local command authorities. After completion, personnel will complete a standard registration form and submit the same with copies of all completed and scored tests to ORA-HSPP by email or other means. Upon receipt and approval, ORA-HSPP will issue to the individual the IRBEE certification number valid for three years. The certification number will be sent to the individual as soon as possible and will be followed with official correspondence the individual may use for personnel records as desired. Per reference (a), registration and certification are required prior to involvement in human research efforts. The initial curriculum will be the baseline required of all personnel. However the following adaptations are authorized:

(1). For personnel who have completed human research ethics educational programs at other institutions prior to NMRC laboratory service (e.g. other federal programs, university on-line programs etc), the local IRB Chair/Policy Officer will dispense for that person those parts of the IRBEE initial curriculum that would be duplicative. However, such prior education must meet the substance of the IRBEE curriculum. It is assumed that the only aspects that would not be met by prior extramural education would be those that are NMRC and/or Navy specific which would then require completion. After completing these parts and any others the IRB Chair/Policy Officer directs, the individual will submit the registration form as usual with accompanying test materials as required. The IRB Chair/Policy Officer will notify ORA-HSPP of the circumstances and needed adaptation; and, will certify that the intention of the full curriculum has been met. If the individual has documentation from prior educational programs, copies of such documents are to accompany the registration form.

(2). For OCONUS activities, the local IRB Chair/Policy Officer is given wide latitude to adapt and refine the standard baseline IRBEE initial curriculum and tests for those members for whom English is not the primary language or for whom the materials and tests are culturally or educationally challenging or inappropriate. In these instances, the IRB

Chair/Policy Officer can register individuals for certification provided that circumstances are specified, that alternative educational strategies are explained, and that the IRB Chair/Policy Officer will certify that the individuals have met the spirit and intent of the IRBEE educational curriculum. It is the responsibility of the IRB Chair/Policy Officer and the local command authority to ensure that personnel for whom these adaptations are necessary are properly prepared for human research involvement and are fully aware of and committed to their ethical, legal, regulatory and administrative responsibilities.

(3) All activities are strongly encouraged to explore with ORA-HSPP other adaptations as may be needed to meet the spirit and intention of the IRBEE curriculum. However, unless emergency circumstances dictate otherwise, exceptional adaptations require ORA-HSPP concurrence and approval.

b. Education and Certification Renewal: Initial IRBEE certification is valid for three years. At the start of either the fiscal or calendar year, ORA-HSPP will notify local activities of those members whose certifications will expire in the following year. To ensure local records are current, the local IRB Chair/Policy Officer may request a registration list at any time from ORA-HSPP. Prior to the expiration of current certification, personnel must be re-certified. When recertification is accepted by ORA-HSPP, a new IRBEE certification number is issued. The following is the overall plan for education and certification renewal.

(1). Broad recertification parameters are outlined in the following paragraph. However, precise strategies are left to the local activity to implement and oversee under the leadership of the IRB Chair/Policy Officer making use of local resources as applicable.

(2). To be re-certified, each member must complete six (6) hours of human research ethics continuing education during the three year period prior to recertification. Continuing education may include experiences such as completion of local lectures/seminars; on-line educational programs; special programs such as IRB 101/102 or RCR 101; a re-review of and re-testing for the initial IRBEE curriculum; participation at professional meetings such as PRIM&R, ARENA, SRA International, NCURA, ASBH; CME continuing education experiences related to human research ethics; etc.

(3). To assist activities in amassing resources to offer individuals for recertification needs, ORA-HSPP will provide materials and program announcements to local activities as in paragraphs 3.b.(2) above and 3.c below. In addition, ORA-HSPP will provide seminars and lectures for local activities as requested and/or directed by the NMRC Commanding Officer.

(4). Individuals registering for recertification will complete a standard form that will include space where continuing education experiences will be listed and summarized. The local IRB Chair/Policy Officer will certify that the information listed is accurate. With IRB Chair/Policy Officer concurrence for accuracy, the individual will forward materials to ORA-HSPP for review and approval. Submitted materials will include certificates of completion from various programs if applicable. Upon review and approval, ORA-HSPP will issue the new IRBEE certification number as usual.

c. Continuing Education Resources and Opportunities: ORA-HSPP will provide educational resources, videotapes, web-based curriculum information, relevant literature and other materials to build local collections and assets for human research ethics resources and libraries. ORA-HSPP will be available as requested and as directed by the NMRC Commanding Officer for on-site educational teaching. ORA-HSPP will explore potential human research ethics seminars as may be possible with extramural collaborators. As needed and as practicable, ORA-HSPP will assist local activity leaders and IRB Chairs/Policy Officers with all other matters that may enrich local programs of continuing education enrichment in human research ethics.

CHAPTER 8**Basic Submission, Review and Approval Norms.**

1. All activities are required to develop in manuals separate from local instructions the basic standard operating procedures for the development, review and approval of human research protocols. Such manuals are to be maintained and updated regularly. These manuals comprise part of the requirements for the submission of requests for the renewal of human use assurances. For NMRC, the basic procedures for review and approval of human research protocols will be delineated, maintained and developed in its own manual of standard operating procedures (SOP). The NMRC IRB SOP may be adapted by subordinate Echelon 4 activities. For all activities, the general norms found in the following paragraphs must be maintained in IRB standard operating procedures. To assist all activities, examples of forms for the submission of Continuing Review, Final Reports, New Proposals and Reviewer Protocol Assessment Forms are attached as appendices (8-11).

2. All investigators are encouraged to work with the IRB Chair and IRB administrators to develop protocols that meet all required elements and thereby avoid preventable delays in IRB assessment. Research protocols must be developed such that all critical elements are included for all submissions. Key among these critical elements are the delineation of risks/benefits, informed consent processes/procedures and documents, and all other matters critical to the ethical review and approval process.

3. Scientific review per se is not the purview of IRB ethical assessment. To obtain the most objective assessment possible, scientific review is to be performed by a professional body apart from the IRB and the review of this body must be completed prior to submission to the IRB. However, though scientific review is not actually part of the IRB ethical assessment, adherence to the principles of sound scientific theory and practice is critical to any final assessment of sound ethical safeguards. In this light, ethical review and scientific assessment support and complement each other for the sake of the final good of the proposed research effort. To ensure complementarity of review and assessment, investigators must comply with all scientific review and IRB requirements.

4. In the first instance, determination must be made as to whether the developed protocol meets the definition of research as applicable to human subjects ethics regulations. Responsibility for this determination rests with the IRB Chair in consultation with others whose expertise would assist in this determination. It is the prerogative of the IRB Chair to request the further discernment of the IRB in the matter. If determination is made that the effort does not qualify as research per se, then an official memorandum for the record is attached to the original protocol submission and sent back to the investigator for further processing. A copy of all materials is kept with the IRB Office as a record of a consultation provided. However, a DoD Assurance Number is not assigned and the protocol record is not recorded in any IRB information database resources.

5. It is the responsibility of the Commanding Officer, the IRB Chair, and the Director, ORA-HSPP to ensure that research protocols are expeditiously reviewed, and evaluated in strict compliance with all elements of pertinent laws, regulations, and instructions. There is to be no delay in the processing, review and action upon any and all submissions.

6. Maximum time is to be afforded for mature consideration of materials submitted. Each activity is to establish clear timelines for the submission of materials to the IRB after scientific review. For serious reasons, exceptions to timeline requirements can be made. A written request with justification must be submitted by the investigator to the IRB Chair and endorsed by the investigator's chain of command. Final decisions in this regard rest with the IRB Chair. However, submission within timeframes is not a guarantee of placement on the IRB agenda. All administrative, ethical and scientific requirements must be met before an IRB can consider any item. The following pertain to acceptance for the agenda:

a. Upon receipt of all submissions, materials will be given an administrative and ethical pre-review.

b. Protocols that lack substantive elements, lack complete scientific review or raise questions that must be resolved before IRB consideration will be returned.

c. The decision to return submissions will be made by the IRB Chair or other senior staff as may be applicable.

7. Expedited review: Unless prohibited by higher authority, expedited review will be used for all applicable protocols as determined by federal authorities in such official forms of communication as The Federal Register etc. See relevant sections of this instruction regarding expedited review and its implementation where authorized.

8. Exemption from IRB Regulations: Paragraph 101 of reference (b) details particular research activities that are exempt from human subjects regulations. For these activities and all other activities that may be determined by federal authorities to qualify under this same initiative, each activity is to develop standard operating procedures and detail such procedures in local IRB manuals. Procedures must include specifications for initial review by the Chair or Chair-delegate, annual status reports, final reports and announcements of the same to the IRB.

9. No research protocol involving children or fetal related research may be determined to be exempt from full IRB review.

10. Research involving prisoners or the mentally disabled is not authorized.

11. Review and approval of any protocol must be completed prior to either enrollment of any research volunteers, or collection or use of any data or specimens derived from research volunteers.

12. No member of the IRB may vote upon 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 Commanding Officer or approving authority.

13. If the Commanding Officer 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.

14. Investigator Assurance Agreements as found in appendix (4) are required to be signed by all Navy and Navy-supported

investigators who are not otherwise under another human use assurance from another United States federal agency. This applies uniformly to all those named as principal or associate investigators. Failure to have assurance agreement requirements met necessitates suspension of a protocol's approval until all assurances have been received and accepted. For the sake of expediency especially in the light of distances and other circumstances, the Chair may accept finalization of assurance requirements in the name of the IRB after review but before final action of the approval authority. However, it must be clear that no investigator may participate in any way in nonexempt research involving human volunteers, or in the collection or use of data or specimens derived from such research volunteers, prior to completion of the Investigator Assurance Agreement requirement.

15. In all cases where there are multiple collaborative efforts on protocols, but especially in instances where collaborating institutions are not Navy activities, the IRB and its leadership must assist investigators with the development of cooperative research plans. In all cases and wherever possible, arrangements should be made to avoid duplication of effort in the review process. However, even in cases where another agency assumes lead review responsibility, such lead responsibility never dispenses with Navy approval authority for any applicable effort. Consultation with higher authorities is always suggested to assist with any need for clarification etc.

16. The IRB is required to review all aspects of the welfare of the research volunteers related to their participation in the study. Of special IRB concern must be the role of NMRC investigators, qualifications of research and clinical/medical staff, assessment of measures and resources for providing for subjects in the light of need for medical care, assessment of informed consent processes and procedures, and any other matters that are pertinent to the ethical protection of the rights and welfare of human subjects. In all cases the protection of the rights and welfare of human subjects is pre-eminent.

17. Pursuant to standard operating procedures for ethical review, the IRB may recommend approval of the protocol; recommend approval with minor revisions; return the protocol directly to the submitting investigator for substantive modifications; or return the protocol as disapproved until the investigator resubmits the protocol with major revisions.

18 If a protocol is returned for any reason whatsoever, the minutes of the IRB will so state, and the protocol will be returned to the investigator with comments from the Chair. The minutes of the IRB will describe all requirements in exact and complete detail.

19. If a protocol is recommended for minor revisions the IRB can delegate the Chair to accept the revisions in its name (with written certification for files/records) and without further review. However particular circumstances or the substance of revisions may necessitate an additional full review. This would be the case in the light of disapproval. However, in all cases the Chair may elect to submit any revised protocol for an additional full review.

20. If an investigator wishes to modify a protocol in a way that exceeds the parameters of the original approval (e.g. increase of numbers of enrollees, change in consent form, change in investigator staff etc.), modifications must be submitted and approved prior to implementation. As determined by the Chair in each case and noted in IRB minutes, non-substantive or truly minor modifications can be approved by the Chair. Substantive modifications must be reviewed and recommended the IRB itself with approval of the approval authority. If an investigator desires to modify an already approved protocol such that the changes are within the parameters of the original approval (e.g. withdraw a 5 cc blood specimen volume instead of the approved 10 cc specimen volume, exercise a volunteer for 10 minutes at the approved exercise intensity instead of 15 minutes at that intensity, etc.), these changes may be made by the investigator without submission to the IRB for additional review. These changes are to be made as notifications in the next continuing review. In each activity, manuals of standard operating procedures are to include clear directions by which all protocol modifications or amendment needs are met.

21. When considering a new protocol, the IRB must assign the required DoD Assurance Number. Intrinsic to the review of a new protocol, the IRB will determine a level of risk to research volunteers and make a formal recommendation to the Commanding Officer and the approving authority whether a specific research protocol should be approved or disapproved. 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. Standard operating procedures should contain clear norms outlining the review, recommending and approval processes.

22. A copy of the minutes of the IRB meeting will be forwarded to the approving authority, along with the recommendation for action by the Commanding officer. 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(s) for each vote to disapprove or abstain from voting. A copy of the minutes must be retained permanently with each relevant research protocol.

23. Final approval of protocols involving research volunteers will be based upon the tiered review process:

a. Studies involving no more than minimal risk will be reviewed by IRB and will be approved by the Commanding Officer.

b. Studies involving greater than minimal risk will be reviewed by IRB and will be forwarded through the chain of command to the respective approval authority along with the recommendation of the IRB and the Commanding Officer.

c. Research protocols which require ASN(RD&A) approval will be submitted via the chain of command to the Chief of Naval Operations (NO93 and NO91) for forwarding to the ASN(RD&A). Correspondence must also be forwarded via the Chief of Naval Personnel if Navy personnel will be subjects, or by the Commandant of the Marine Corps (ATTN: Chief of Staff for Manpower) if Marine Corps personnel will be subjects.

d. Care must be taken that original documentation is maintained and that original signatures are obtained as required. Of particular importance is the maintenance of originals of consent forms and original signatures on Investigator Assurance Agreements.

e. The addition of a new investigator to the research effort after submission and approval of the initial research protocol is considered a modification to the protocol and must be reviewed and approved accordingly. A Supplemental Investigator Assurance Agreement will be prepared, signed, and submitted to the IRB by memorandum from the principal

investigator for review and approval. A copy of the supplemental Investigator Assurance Agreement with the signature of the new investigator will be forwarded to the approving authority, and the original will be filed with the research protocol.

f. It is to be noted by all that the requirements for protection of research volunteers 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, however, is never authorized. An assessment of risk, any requirement for the protection of research volunteers, or the disapproval of a protocol may not be downgraded, superseded, or overturned in the chain of command review. In no case may the approving authority approve research without the positive recommendation for approval of the reviewing IRB and of its convening authority. In the event of a dispute, all relevant information is to be forwarded through the chain of command to higher authority for review and resolution.

g. Upon receipt of a research protocol forwarded 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 protection afforded research volunteers.
- (3). Assign either a greater level of risk, protection from risk, or requirement for review to a protocol than has 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.

CHAPTER 9**Authorization to Initiate Research Involving Research Subjects**

1. For all activities, research involving human subjects requires compliance with this instruction and higher guidance and the receipt of specific approval before any measures can be undertaken for the enrollment of human subjects. Approval for all protocols must be validly rendered by the signature of the approval authority upon the official recommendation form or by another form of authorizing correspondence. For administrative expediency, if official approval is rendered by signature of the approval authority upon the official recommendation form, a by direction letter may be issued by the IRB Chair, an IRB Executive (e.g. For NMRC, ORA-HSPP Director) or other senior staff member certifying that approval has been given by the appropriate authority.

CHAPTER 10

Exempt Research

1. Federal regulations provide that certain categories of innocuous research may be exempted from formal IRB review in order to lessen the regulatory burden without compromising the protections afforded to potential human research participants. This chapter details policies and procedures related to research efforts categorized as exempt.

2. The policies and procedures that follow are to be implemented by all NMRC Echelon 3 and 4 activities on the local level.

3. Exempt research is not subject to full IRB review because of the inherent low risk associated with the research; however, a determination of exemption does not mitigate the obligation to meet the requirements of human research policy nor does it release the investigator from ethical responsibilities to protect a human subject's rights.

4. For the sake of clarification, if a specific project does not meet the federal definitions of both "research" and "human subjects," the effort is not human subjects research and is not covered by these regulations. However, if an effort is human use research, the effort may be eligible for exemption from full IRB review. Finally, if the effort does not qualify as exempt, it may still be eligible for expedited review. It is to be noted that determination of exemption is unrelated to expedited review per se, and the eligibility categories for each are different as found in Chapter 11 of this document.

5. A research effort is defined as exempt if the specific project is both minimal risk and meets the eligibility criteria for exemption established by higher authority. The categories for exempt research in this chapter are defined by reference (b) and the Office of the Surgeon General of the Navy.

6. Exempt research must meet all applicable requirements for the protection of human subjects, and investigators are specifically responsible for complying with applicable regulations. By Navy policy, a protocol found to be exempt must be assigned a standard DoD assurance number, subjected to annual continuing reviews or status reports, and tracked to completion to ensure that the effort continues to be eligible for exemption. Initial determination of exemption is subject to

revision and change dependent upon the review of the IRB Chair and the IRB.

7. The IRB is charged with making the determination of the level of risk involved in a research proposal and its eligibility for exemption. The investigator must submit in the standard fashion a human use research protocol that contains sufficient detail to facilitate the determination of exemption. The protocol must include all information relative to determining risk and issues of privacy. The submitting investigator is to cite the specific exemption category that may apply. All submissions must include signed Investigator's Assurance Statements from all investigators involved in the research.

8. No research can be classified as exempt that involves information obtained or recorded in such a manner that participants could reasonably be identified either directly or indirectly through one or more identifiers linked to the participants. Likewise, no research can be classified as exempt that involves information which, even if unintentionally disclosed, could place the participant at risk of criminal or civil liability, or which could be damaging to the participant's financial standing, employability or reputation.

9. Investigators are not required to obtain advance informed consent when conducting exempt research as it is not considered research per reference (b) for purposes of compliance with reference (a). However, potential participants must still be provided information explaining the purpose of the research, how privacy will be protected, and making it clear that participation is voluntary.

10. Classified research or research involving prisoners, fetuses, pregnant women or human *in vitro* fertilization cannot be considered for exempt status.

11. Research involving children shall not be found to be exempt if the research involves surveys, interviews, or observations of public behavior if the investigator(s) participate in the activities being observed.

12. The Principal Investigator (PI) remains responsible for protection of human subjects when conducting exempt research. Special emphasis should be placed on mitigating psychological, social and economic harms and in protecting the subject's privacy.

13. All serious adverse events related to the exempt research must be reported in a timely manner following current policy and Chapter 14 of this document.

14. Exempt projects must receive annual continuing review and re-approval based upon the submission of status reports per Chapter 13 of this document. The PI must submit a summary to the IRB in such time as to allow for the proper review and re-approval of the project prior to the end of the approval period. This summary must include all pertinent data required for continuing review including summary of progress to date, descriptions of all significant changes made in the research and any factors that may affect either the risk-benefit ratio or exempt status of the project.

15. The PI shall submit a notification of completion to the IRB at the end of the project.

16. All actions relating to exempt research are subject to subsequent review by the IRB, approval of the Commanding Officer, and second level review of higher authority.

17. Research Categories Eligible for Exemption: The following are the categories of research specified by federal regulations and higher Navy authorities as eligible for determination of exempt status. To be exempt, a proposal must both involve no more than minimal risk and belong to one of the following categories:

a. Exempt Category 1: Human use research focused on and conducted in established or commonly accepted educational settings involving normal educational practices.

b. Exempt Category 2: Human use research involving the use of educational tests, survey procedures, epidemiologic practices, interview procedures or observation of public behavior, as long as

(1). Information obtained is recorded in such a manner that participants can not be identified either directly or indirectly through one or more identifiers linked to the subject; and

(2). The participant would not be placed at risk

of embarrassment, criminal or civil liability or damage to their financial standing, employability or reputation if their responses were inadvertently disclosed.

c. Exempt Category 3: Human use research involving the collection or study of data, documents, records, or pathological or diagnostic specimens that already exist at the time the research was proposed, if

(1). These sources are publicly available, or

(2). The information is recorded in such a manner that participants cannot be identified either directly or indirectly through one or more identifiers linked to the subject.

d. Exempt Category 4: Human use research involving excreta or any specimen collected during the normal management of a patient as long as the sample cannot be identified.

Chapter 11

Expedited Review

1. Expedited review is the review of proposed research by either the IRB Chair or by one or more designated voting members of the IRB (rather than by the full IRB) to facilitate approval prior to the next regularly scheduled IRB meeting without sacrificing the protection of human subjects.

2. Expedited review authority is not an assumed authority given at the time of human use assurance or of local approval authorizations. Expedited review requires specific written delegation by the BUMED Institutional Assurance Issuing Authority. Expedited review authority may not be further subdelegated or assigned by NMRC to any of its subordinate Echelon 4 activities; however, the NMRC Commanding Officer as approving official may specifically subdelegate expedited review approval authority to the NMRC IRB Chair for matters relative to NMRC Echelon 3 and NMRC-Detachment human use protocol efforts. NMRC Echelon 4 activities will implement expedited review applications, approvals and processes as directed by higher authority and within standard chain of command procedures for submissions. ORA-HSPP will assist NMRC Echelon 4 activities with expedited review applications, procedures and oversight as applicable.

a. Once authorized, the expedited review process may be used to:

(1). Review and approve minimal risk research protocols that fall within one of the categories included in paragraph 4 below and in Appendix (7).

(2). Review and approve minor changes to previously approved research protocols.

(3). Conduct expedited continuing review and re-approval when the:

(a). Initial protocol was reviewed using expedited review procedures; or

(b). Protocol meets the criteria of either paragraph 4.H. or 4.I. below.

b. Expedited review procedure will not be used:

(1). For any classified research projects involving human subjects;

(2). For any greater than minimal risk research;

(3). For any research involving vulnerable classes of persons such as pregnant women, children or prisoners; or

(4). When even inadvertent or unintended identification of the subjects and/or their responses could place them at risk of criminal or civil liability, or could be stigmatizing or damaging to their financial standing, employability, insurability or reputation.

3. Procedures for Expedited Review

a. After investigators have routed relevant submissions through their regular chain of command and after having received scientific reviews as applicable, human research protocols and related materials are to be submitted to ORA-HSPP in the usual manner.

b. ORA-HSPP staff will review materials and, with the NMRC IRB Chair, will determine if submissions qualify for expedited review. If materials so qualify, expedited review will be conducted by the IRB Chair. Alternatively, the expedited review may be carried out by one or more experienced reviewers specifically designated by the IRB Chair from among the voting members of the IRB. Reviewer(s) delegated by the IRB Chair will not be part of the research effort nor have any semblance of conflict of interest in the project.

c. In conducting expedited review, the expedited reviewer(s):

(1). Have the same responsibilities and may exercise all of the authorities of the NMRC IRB, except that they may not disapprove the research. Disapproval requires action by the full IRB.

(2). Must determine that there is no more than minimal risk involved and that the proposed activity is eligible for expedited review, citing the specific expedited review

eligibility that applies as found in paragraph 4 below and in Appendix (7).

(3). May request reasonable changes in the protocol designed to gain approval. They are not, however, obligated to recommend approval, and may refer the protocol to the full IRB at any time for any reason.

(4). Must ensure that all requirements are met for obtaining advance informed consent.

(5). Must ensure that adequate safeguards are in place to protect the subjects and that appropriate precautions are taken to minimize risks related to invasion of privacy and breach of confidentiality.

(6). Must assign a date for continuing review that shall not be more than one year from the date of the expedited review.

(7). Shall forward their recommendations to the NMRC IRB Chair, who may then approve the research if so authorized in writing to grant such approvals by the Commanding Officer. Research activities may then begin without awaiting for review by the full IRB.

d. All actions taken under expedited review authority shall be reviewed by the full IRB at the next regular meeting. The full IRB must specifically confirm each action or take appropriate corrective action. Details of this IRB review and votes on recommendations shall be included in the minutes and forwarded to the Commanding Officer for action. In addition, all actions related to expedited review will be forwarded and subject to higher BUMED oversight authority as usual. Following oversight review, higher authority may make further determinations or direct additional requirements.

4. Research Categories Eligible for Expedited Review. The following categories of research may be eligible for expedited review. This list derives from categories published in the Federal Register but takes precedence over it as it is more restrictive per direction from higher BUMED authorities. These categories apply regardless of the age of the subjects, except as noted.

a. Expedited Review Category 1. Clinical studies of drugs and medical devices when either condition (1) or (2) is met.

(1). Research on drugs for which an investigational new drug application is not required. (Note: Research on marketed drugs in which the research exposure would significantly increase the risks or decrease the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(2). Research on medical devices for which either:

(a). An investigational new device exemption application is not required; or

(b). The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/ approved labeling.

b. Expedited Review Category 2. Collection of blood samples by finger stick, heel stick, ear stick or venipuncture according to the restrictions in the applicable category:

(1). Healthy nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period, and the collection may not occur more frequently than 2 times per week.

(2). Other adults and all children. Considering the age, weight, and health of the subjects, the collection procedure, the amount of blood collected, the frequency with which it will be collected, the amount drawn may not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period, and collection may not occur more frequently than 2 times per week.

c. Expedited Review Category 3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

(1). Hair and nail clippings collected in a non disfiguring manner;

(2). Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

(3). Permanent teeth if routine care indicates a need for extraction;

(4). Excreta and external secretions (including sweat);

(5). Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;

(6). Placenta removed at delivery;

(7). Amniotic fluid obtained at the time of rupture of the membrane prior to or during delivery;

(8). Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

(9). Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

(10). Sputum collected after saline mist nebulization.

c. Expedited Review Category 4. Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays, microwaves, or potentially injurious directed energy such as lasers. When medical devices are employed, they must be cleared or approved for marketing. (Note: Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples of activities that may be eligible for expedited review include:

(1). Physical sensors that are applied either to the surface of the body or at a distant and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

(2). Weighing, and testing sensory acuity;

(3). Magnetic resonance imaging;

(4). Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;

(5). Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

d. Expedited Review Category 5. Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes, such as medical treatment or diagnosis.

e. Expedited Review Category 6. Collection of data from voice, video, digital, or image recordings made for research purposes.

f. Expedited Review Category 7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus groups, program evaluation, human factors evaluation, or quality assurance methodologies.

g. Expedited Review Category 8. Continuing review of greater-than-minimal risk research that was previously approved by the full IRB may be conducted using expedited review procedures if it falls into any one of the following categories:

(1). Where all three of the following conditions are met:

(a). The research is permanently closed to the enrollment of new subjects; and

(b). All subjects have completed all research-related interventions; and

(c). The research remains active only for long-term follow-up of subjects.

(2). Where no subjects have yet been enrolled and no additional risks have been identified since IRB review; or

(3). Where all remaining research activities are limited to data analysis.

h. Expedited Review Category 9. Continuing review of approved minimal risk research may be conducted using expedited review procedures when the research was originally reviewed by

the full IRB only because it did not fit into Categories 2 through 7, as long as:

(1). The research was not conducted under an investigational new drug application or investigational device exemption, and

(2). No additional risks have been identified since the full IRB review.

5. Transitional Direction for Implementation of Expedited Review Processes

a. Federal regulations require the full IRB to perform continuing reviews of all IRB protocol submissions if the original protocol was reviewed by the full IRB. However, higher authority has authorized a reasonable modification to this matter since expedited review is only recently authorized for Naval medical research and development activities in calendar year 2002. Subsequent to the approval of expedited review for NMRC, the following is permissible:

b. If a given protocol would have initially been eligible for expedited review, then the continuing review for this effort may be conducted using expedited review procedures. This special exception must be clearly annotated for every case in IRB minutes for the benefit of future auditors.

c. This transitional guidance will expire and shall not be used after 31 December 2003.

CHAPTER 12**Responsibility for Protection of Research Volunteers in Research Involving More than One Activity.**

1. For efforts involving more than one agency or research activity, every possible provision should be made by all NMRC Echelon 3 and 4 activities to avoid all duplication of review effort by assigning through clear organization plans and other standard interagency agreements that one activity will have primary review responsibility for the protection of research volunteers. The activity with primary responsibility must exercise that responsibility even during phases of the research carried out by other activities. Continuity of primary responsibility is necessary to avoid lapses in upholding the highest standards for the protection of the rights and welfare of human subjects from research risks. It is to be noted, however, that determination of lead review responsibility does not abrogate nor dispense from Navy approval requirements, standards and authority. In all cases, Navy standards for protection of research volunteers and requirements for compliance must be maintained. However, investigators are advised that in current practice non-Navy activities are not bound to accept by administrative concurrence Navy review but may elect under their own standards to insist upon separate review under their own authority.

a. In the first instance, already approved research efforts that involve only investigators from agencies that have Federal Wide Assurances or assurances from other signatories of the Common Rule, may be reviewed by the IRB Chair and forwarded for approval under ethical/administrative concurrence as follows:

(1) For research protocols already reviewed and approved by other agencies having duly constituted review boards under a federal assurance system and to whom it is appropriate to have lead IRB status with lead IRB responsibility, the IRB Chair may provide concurrence-review of these protocols with follow-on approvals from the appropriate level of authority in the standard fashion.

(2) Concurrence-review is not to be construed as an administrative procedure. Its intention is to streamline review procedures where multiple agencies under authoritative assurance systems are participants. However, concurrence-review, even after its being granted, may always be superceded because of

circumstances. In such extraordinary cases, full IRB review would be required.

(3) The decision to employ concurrence-review rests with the IRB Chair. If applicable, the Chair must hear the recommendation of subject area experts on the matter. The following are the standard operating procedures for concurrence-review.

(a) When a protocol is submitted that has already received full review and approval by agencies under an existing federal assurance system, subject area experts or the IRB Chair him/herself assess(es) the protocol for qualification for concurrence review. Qualification for concurrence-review is not dependent on level of risk.

(b) After having heard the recommendation of subject area experts or after having completed the initial assessment, the IRB Chair makes the decision for or against concurrence-review. When a decision is made against employing concurrence-review, standard procedures are followed for full IRB review. When a decision is made to employ concurrence-review, the IRB Chair may perform the review him/herself or may delegate the review to one or more of the regular voting members of the board.

(c) When concurrence-review is performed, investigators are to work with the IRB Chair or other reviewers for the completion of required items. Once all requirements have been met and if a positive recommendation is given, the IRB Chair sends the protocol to the approval authority with a written memorandum recommending approval. The IRB Chair's recommendation will note that the protocol was already reviewed and approved by a collaborating agency that has a duly constituted review board under a federal assurance system. The recommendation will further note that the protocol has received concurrence-review.

(d) Approval of concurrence-review, like all others, will be given in writing. The approval letter, however, will also inform the investigator that at any time during the life of the protocol circumstances may require full board review. While anticipated as unusual, investigators further must be aware from the very beginning of the process that extreme circumstances could require abeyance of research activities until full IRB review and subsequent action were taken.

(e) Those providing concurrence-review cannot "disapprove" a protocol. Therefore, if a positive recommendation cannot be given subsequent to concurrence-review, the protocol must then be submitted for full IRB review unless the investigator rescinds the original submission.

(f) When concurrence-review has been completed, the action is announced by the IRB Chair at the IRB meeting immediately following the review action. A brief summary of the action is given to the IRB during the information or announcements period of the meeting and the IRB Chair's summary is made part of the official minutes. A continuing review date is established accordingly, the protocol is entered into official databases and treated in exactly the same fashion as other protocols that receive full IRB review.

(g) During the announcement of concurrence-review activities, it is the prerogative of any voting member of the IRB to open discussion regarding the matter. If prudence dictates and if a simple majority of the voting members present concur, the protocol may be required to be submitted for full IRB review. Such a requirement may involve abeyance of previously approved research. To avoid any and all complications or issues regarding non-compliance it is the responsibility of the IRB Chair to contact the relevant investigator regarding such actions or requirements.

(h) Unless the IRB Chair determines otherwise for specific reasons or in the light of circumstances, continuing reviews of and final reports for concurrence-review protocols are treated the same as the original submission.

2. Reference (c) provides general guidance for studies involving more than one military Department or Agency (e.g., Army and Navy). For military efforts involving more than Navy researchers, Navy investigators should work as best as possible with non-Navy military researchers to implement the reasonable standards for determination of primary review responsibility among in-house DoD participants. This should be done as may be required through memoranda of agreement etc. Such multiple agency provisions, however, must be accomplished without abrogating Navy ethical standards or the responsibility of the Navy's chain of command for approval and assurance under the Office of the Surgeon General or the Secretary of the Navy.

3. When more than one Navy activity is involved, primary responsibility for protection of research volunteers depends upon whether the research volunteers are patients of a Navy Medical Treatment Facility (MTF) or Dental Treatment Facility (DTF) as indicated below.

a. When the research, regardless of in-house or contract status, involves participation of patients of a Naval MTF/DTF, the MTF/DTF has primary responsibility unless the MTF/DTF itself approves of an alternative plan.

b. For research being conducted by Navy researchers at more than one Navy activity but not involving patients at a Naval MTF/DTF, primary responsibility will be assigned and explained in the protocol itself. The IRB will recommend and determination of lead IRB status will be specifically detailed in the letter of approval of the Commanding Officer or the letter of recommendations for protocols needing to be reviewed at higher levels for approval.

c. Among the NMRC Echelon 3 and 4 activities, automatic acceptance of each other's review authority will be granted reciprocally by each activity for all collaborative efforts. Determination of lead IRB status among the NMRC Echelon 3 and 4 activities should be based upon place of research execution or other factors on a case by case basis. For all collaborative efforts, individual Commanding Officers, however, must give approvals/permissions as relevant to those billeted to their activity. In the event there is need for clarification or modifications, these are to be secured where applicable by the IRB Chairs and/or the Commanding Officers.

4. For all multiple agency efforts involving non-military federal, private sector and international researchers, a clear and detailed organizational plan must assign lead IRB roles and responsibilities. The IRB and the Navy approving authority must review and approve the organizational plan such that the protection of human subjects and all Navy responsibilities are met without compromise.

5. Non-Navy agencies participating in any way with Navy-involved research efforts must ensure that all requirements of this instruction and the provisions of all pertinent laws, regulations and standards of the DoN are maintained.

6. Signature of the Investigator Assurance Agreement is required by all Navy affiliated investigators and all investigators who are not under another federal government assurance. If other investigators are under another federal assurance, this must be indicated and known to the IRB.

7. Until other federal provisions are made, concurrent or sequential review by multiple approving authorities may sometimes be inescapably required. In such cases, no changes to a Navy higher authority approved research protocol are permitted without the concurrence of that higher authority office. If changes in a higher authority approved research protocol are required by another reviewing authority, the changes must be sanctioned by resubmission of the modified protocol through the Navy higher authority approval process. The IRB must verify that the final protocol approved by all the activities is the same. A specific statement to this effect must be noted in the minutes of the IRB meeting reviewing the final completion of the protocols processing.

8. In the case of non-NMRC personnel conducting Command research (e.g. personnel assigned to NMRC under Intergovernmental Personnel Act or other, contracts, or agreements), the Command itself will be the activity primarily responsible for protection of research volunteers. Formal agreements to minimize duplication of review efforts should be included in agreements for such personnel arrangements.

CHAPTER 13**IRB Continuing Review of Research**

1. Each Echelon 3 and 4 activity is required to ensure with the utmost care that efforts conducted under approved research protocols are given continuing review and approved by the approval authority at least annually as required by references (b) and (j). Continuing review may take place more frequently if the IRB believes that more frequent review is indicated especially in consideration of matters related to risk level or other circumstances. Continuing review by its very nature includes the re-authorization for the continuation of the research effort into subsequent periods of performance. For each protocol, activities are to assign a permanent "due date" by which continuing review must be provided and approved at least annually. The due date is to be the date on which the protocol was first reviewed by the IRB. Failure to meet the continuing review requirement by the annual due date results in a lapse of authorization. All activities are to institute careful and comprehensive administrative systems that will preclude any possibility that research protocols will lapse into non-compliance. For all activities, it is the responsibility of the IRB and the approval authority to adopt methods and procedures by which non-compliance can be reported, met, and ameliorated without delay.

2. Reference (j) defines continuing review as a periodic administrative reevaluation of a human use research project based on requirements found in paragraph 109(e) of reference (b). Continuing review policies and procedures below are authorized per reference (j) and in accordance with reference (b).

3. In accordance with required timelines, continuing review must be performed on all ongoing human subject research regardless of the level of risk involved. This specifically includes research found to be exempt. Continuing review involves a complete reevaluation of the risk-benefit ratio based on the actual experience with the conduct of the research and considering recent experience with related work done elsewhere. As experience is gained during the actual conduct of a project, the IRB shall require revision of the Informed Consent Document (ICD) as necessary to reflect the new understanding of the risks. To demonstrate ICD reauthorization resulting from continuing review, activities are to use approval stamps. Only

copies of the ICD showing the "Approved" stamp and expiration date shall be used.

4. Monitoring of the actual conduct of the research or the adequacy of the informed consent process is part of the ongoing responsibility of the IRB to ensure the safety of the subjects. The IRB may at any time observe or have a third party observe any part of the consent process or of the research itself.

5. The paragraphs to follow contain the general requirements for continuing review. All NMRC activities are to include specific directions for meeting these requirements in standard operating procedure manuals separate from local IRB policy instructions.

6. All NMRC Echelon 3 and 4 activities with IRB's must have IRB standard operating procedures that detail clearly written local policies fully explaining continuing review procedures and specifying the required contents of the principal investigator's summary report.

7. Each human research PI is responsible for submitting a continuing review summary report and supporting documents to the IRB in sufficient time to allow for appropriate continuing review and approval before the end of the current approval period.

8. Human subject research is never to be conducted outside of the approval period. If the approval period expires, federal law requires that the IRB temporarily suspend the project and that work involving human subjects temporarily cease. Administrative extension of the approval period is prohibited. Continuing review must be properly completed and re-approval granted before the end of the approval period in order to avoid interruption of the research.

9. Prolonged suspension due to failure of the PI to provide required documentation is to result in permanent termination of the research. If a project is terminated, a complete initial submission, scientific peer review, IRB review and formal approval (as for a new project) will be required before the work can be resumed.

10. The IRB Chair must temporarily suspend any research in which there is a substantial concern for the safety of subjects, significant deviation from approved procedures, or in which the balance of the risk-benefit ratio appears to have

become unfavorable, pending a thorough review of all material information.

11. Approval letters and ICD's must clearly state the date of the end of the approval period. This expiration date shall not be more than one year from the date of the convened meeting at which the IRB voted to recommend approval, regardless of when the project was actually approved or started.

12. The duration of the approval period should be based on the level of risk and the specifics of the research; the approval period should not always be a full year but shortened as necessary to help ensure the safety of the subjects. In determining the date of the next continuing review, consideration must be given to the experience with the research to date, the number of human subjects involved and the level of confidence in the safety of the procedures used in the research as well as the nature of the adverse effects that may be anticipated.

13. In any multi-agency or multi-site human research effort, it must be clear which IRB holds primary responsibility for ongoing monitoring of research and the conduct of continuing reviews. Collaborative or cooperative research efforts necessarily require consideration of joint review agreements that will eliminate unnecessary duplication of review effort, however, without abrogating Navy approval responsibility and authority. Joint agreements that allow for reciprocal acceptance of IRB ethical review with extramural collaborators may require approval of higher Navy authority and individual activities are required to determine applicability of this requirement in each case.

a. Regarding in-house joint Navy efforts among the NMRC Echelon 3 and 4 laboratories, reciprocal acceptance of each other's continuing review is permissible and authorized but subject at all times to the review and concurrence of each affected IRB Chair and local approval authority. In various circumstances, either the IRB Chair or the local approval authority may remand specific continuing reviews to full local IRB consideration before acceptance. This same permissibility may be applied to all human research efforts being performed jointly by any and all activities under BUMED jurisdiction.

b. When the continuing review is performed by a primary IRB which is outside BUMED jurisdiction, the responsible Navy IRB must still perform continuing review and make a

recommendation regarding re-approval. In conducting their review, the local Navy IRB is strongly encouraged to consider the continuing review report from the primary IRB.

c. Whenever a protocol involving a collaborating institution is reviewed by that institution, a copy of the continuing review summary and IRB actions is to be obtained for NMRC and submitted to the NMRC IRB by the principal investigator. The IRB of the collaborating institution is to perform such reviews at least annually, and include, at least, the elements required in paragraph 14 of this chapter. For these collaborative inter-agency efforts, the continuing review of the non-Navy IRB may suffice for the materials to be submitted for the Navy IRB continuing review. In this case, the non-Navy continuing review is to be submitted with the approval or action correspondences from that agency. Any Navy required element for continuing review not found in the non-Navy agency's documentation must be supplied by the investigator to the Navy IRB.

14. The PI shall submit a summary report to the IRB for its CR. A sample format for continuing review report submission is found in appendix (8). In all activities, per reference (j) continuing review forms must require at least the following information:

a. A summary of progress to date, significant events, and problems encountered; an explanation for unplanned delays; and a description of all significant changes made in the protocol.

b. A summary of demographics, to include:

(1). The total number of subjects who signed a consent form, regardless of whether they actually completed the research,

(2). The number of males and of females, and

(3). The number of each racial group (Caucasian, African American, Hispanic, Other). This requirement is waived if the original protocol was approved without a specific requirement that this information be obtained from subjects.

c. A description and explanation of all deviations or variances from the approved protocol since the last CR.

d. A description and explanation of any subjects who were inappropriately enrolled in the research; that is, those who either did not meet selection criteria or who met exclusion criteria but were enrolled anyway.

e. A summary of any recent literature or professional knowledge as well as any special circumstances or considerations that may affect the perception of the risk-benefit analysis.

f. A description of and schedule for work remaining to be done.

g. An accounting of all subjects who signed an ICD, identifying factors that affected their participation in the research.

h. Number of subjects who completed the project as expected without problems, complications, or complaints.

i. Number of subjects who did not complete the project and the reason(s) for their failure to finish. This specifically includes accounting for voluntary withdrawals, "no shows" and those lost to follow-up as well as medical disqualifications, deaths, or injuries, even if previously reported.

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

k. A cumulative summary of all adverse events experienced in the research at all sites since the initiation of the project, with an indication of the importance of any trends or unexpected findings.

l. The PI's analysis of and comments on the project, explaining and providing perspective as appropriate to assist the IRB in understanding and appreciating implications.

m. Documentation of all changes in investigator personnel; attach signed Investigator Assurance statements for new researcher if not previously submitted.

n. An updated version of the ICD reflecting any new information, and including an updated revision number and date in the footer even if there are no changes.

o. Appointment and approval letters for the current medical monitor if a change has occurred.

15. In conducting the continuing review, the IRB shall:

a. Review all the information submitted by the PI.

b. Determine that the risk-benefit ratio has not changed unfavorably.

c. Consider whether subjects have been able to complete the protocol as planned, and whether the actual risks are as originally anticipated.

d. Determine if the study requires verification from sources other than the PI that no new material changes have occurred.

e. Determine if the informed consent process has been both adequate and appropriately documented and that only approved ICD's are being used, and make recommendations to correct any deficiencies.

f. Revise the ICD to reflect new findings, knowledge, or adverse effects, and determine what specific information must be communicated to past subjects who have not previously been given this new information.

g. Verify that subjects enrolled fit selection and exclusion criteria, and review subject demographics to ensure compliance with federal gender and diversity requirements.

h. Consider whether there has been adequate protection of the subjects' privacy and of the confidentiality of the data, including storage and handling of previously collected personally identifiable data.

i. Review and consider carefully the addition of new investigators even as authors on publications who are required to sign the standard Investigator Assurance Agreement. Consider matters relative to the addition of new collaborating agencies and requirements thereof. In the case of non-reporting of these issues, consider regarding these same matters reasons and make recommendations to the approving authority regarding pertinent requirements and/or sanctions.

j. Specifically approve a new updated ICD and authorize its reissuance for use.

16. The IRB must document its discussions, recommendations, and votes on each CR separately in the minutes, including individual reviews of exempt projects. Separate packages for approving official action are required for each minimal risk or greater than minimal risk protocol, but administrative actions related to re-approval of exempt protocols may handled collectively.

17. For each NMRC IRB, a primary reviewer system is to be used to facilitate review by the full IRB. Another analogous system may also be employed. The primary reviewer should provide a summary to the full IRB, directing the IRB's attention to specific items or considerations of importance. When using a primary reviewer system, each IRB member must receive the complete continuing review package for each protocol sufficiently in advance to allow for evaluation before the IRB meeting.

18. Continuing review may be conducted using expedited review procedures provided that the activity holds specifically delegated local expedited review authority AND either:

a. the protocol was initially reviewed using an expedited review procedure, or

b. the only activities remaining in the study are eligible for expedited review.

19. Continuing review using expedited review procedures is not required at any time. Special circumstances may suggest a continuing review by the full IRB even if the protocol was originally reviewed using an expedited process.

20. All administrative actions, reports, and documents relating to Continuing review must be submitted to higher authority for second level oversight review.

21. Transitional Guidance Due to Recent Implementation of Expedited Review Authority

a. Current federal regulations require the full IRB to perform a CR if the original protocol was reviewed by the full IRB. However, reasonable consideration would suggest a modification to that rule since expedited review has only been recently authorized in the Navy.

b. If an NMRC Echelon 3 or 4 activity is granted expedited review authority, and if a protocol would have initially been eligible for expedited review, then the continuing review for that effort may be conducted using expedited review procedures. This special exception must be clearly annotated for every case in the minutes for the benefit of future auditors.

c. This special variance will expire and shall not be used after 31 December 2003.

CHAPTER 14**Reporting Complications**

1. Requirements for the reporting of various research complications are set for all NMRC activities by higher authority. The requirements below are directed for NMRC and NMRC-Detachment efforts. NMRC Echelon 4 activities are directed to make similar provisions based upon the same direction from higher authority as found in reference (j).

2. The requirements in the following paragraphs do not supercede those directed by research sponsors or the requirements of the Food and Drug Administration (FDA) for relevant FDA studies. Copies of all reports made to the FDA or to other research sponsors must be integrated for submission with the following requirements, may supplant reporting requirements below where applicable and reasonable, or will be submitted in addition to the following directed actions.

3. Definitions:

a. Adverse Event (AE) means any untoward sign, result, event, misadventure, injury, dysfunction, adverse drug reaction or other undesirable happening that involves any volunteer human subject regardless of whether it was listed on the ICD as an expected risk.

(1). The adverse event could have occurred during any interaction with the subject including solicitation, screening, selection, training of volunteers, as well as during the actual experimental procedure or subsequent follow-ups.

(2). Adverse events specifically include, but are not limited to, accidents, injuries, exacerbations of preexisting conditions and non-physical harms such as personal or socio-cultural embarrassment, financial hardship, and adverse administrative actions or career influences.

(3). In the special case of surveillance or longitudinal epidemiologic studies, determination of what constitutes an adverse event requires consideration of the specific interventions of the research and not the characteristics of the underlying disease(s).

b. Serious Adverse Event (SAE) means any adverse event that has grave potential or effect. SAEs include, but are not limited to, occurrences that are fatal, life threatening, permanently disabling, require hospitalization, or are iatrogenic (such as administration of the wrong drug or of an excessive dose.)

(1). An SAE is considered expected if it was listed as an anticipated risk in the approved ICD. An SAE is unexpected if it was not included in the ICD.

(2). Different authorities overseeing research may have different definitions for what constitutes a SAE. For example, the "serious adverse drug experience" defined by the US Food and Drug Administration (FDA) is one type of SAE. When more than one authority has responsibility for a specific research protocol, the broader, more inclusive definition shall apply.

c. Other Events:

(1). Occurrences, such as significant deviations from the protocol, enrollment of a subject who did not meet selection criteria, or failure to document an individual's informed consent are not considered as adverse events for these purposes. They are, however, breeches in the protocol or procedure that require review and corrective action.

(2). Reports of damage to property, personnel injuries and deaths, and significant public relation issues may require separate reporting within the chain-of-command to BUMED, Naval Safety Center, CNO, etc., in accordance with other regulations.

3. Policy: Responsibility for the timely detection, reporting, and correction of adverse and serious adverse events rests with the Principal Investigator (PI), the IRB chair and the research activity's approving official. The research activity will make every effort to:

a. Ensure the research protocol and the informed consent documents fully describe all foreseeable or anticipated risks or potential complications.

b. Document, investigate, and review occurrences of adverse events and SAE, even though they may not initially appear to have a causal relationship to the research project.

c. Ensure proper care is rendered to subjects harmed by participation in the research project and to take appropriate actions to avoid imposing harm on subsequent research participants.

d. Collate the adverse event experience from all participating sites in multi-site studies, unless some central organization, such as a Data Safety Monitoring Board, exists to perform this function.

4. Responsibilities

a. The Institutional Review Board (IRB) shall:

(1). Ensure the timely review of adverse and SAEs reports at their regularly scheduled meeting. They may accept the PI's report and recommendations, request additional information, or impose additional requirements to minimize the risk to future subjects and maintain a favorable risk-benefit ratio for the research.

(2). Specifically determine if any unexpected SAE requires revision of the ICD to reflect a new risk and if previous subjects should be notified of the new information.

(3). Consider the adverse event experience as part of their continuing or completion reviews in perspective with other information relating to the study. Based on the overall experience with the research they may require modifications to the protocol or ICD, or may revise the time of the next continuing review.

(4). Specifically recommend re-approval of the research after required changes have been implemented if the research had been temporarily suspended.

(5). Retain records pertaining to adverse events as permanent records

b. Reporting of Adverse Events

(1). The PI shall cumulate data concerning adverse events throughout the study at all sites, and provide a written summary to the IRB as part of each continuing review and as part of the project's completion report.

(2). This summary report shall include all adverse and SAEs to date, even if previously reported, and should clearly indicate any significant findings, trends or patterns in the adverse event experience.

(a). Adverse events may be logically grouped for convenience of analysis and reporting, but unforeseen or unexpected events should be clearly identified and discussed separately.

(b). If an adverse event report is required by another agency (such as the FDA) that report may be submitted in lieu of writing a new report as long as it contains similar information and any additional information required herein is appended.

(c). Private personal identifying data should be not be included in adverse event reports, although when necessary anonymous codes may be used for clarification.

(d). The IRB should review the adverse event summary report as part of their continuing review or end-of-project review in perspective with other information relating to the performance of the study.

c. Reporting of Serious Adverse Events (SAE)

(1). The PI shall:

(a). Ensure necessary care is provided to the subject, and that appropriate actions are taken to avoid harm to other subjects and to prevent recurrences.

(b). By electronic, telephone or other appropriate means, inform the medical monitor and the IRB Chair of the SAE within twenty-four hours of discovery, detailing its gravity and potential impact on other subjects.

(c). Conduct a timely investigation into the SAE and provide a written report to the IRB Chair. The timeframe for the submission of the report will be determined by the IRB Chair on a case by case basis after a review of the facts in consultation with the PI and the local approving official. The report must include at a minimum:

(i). A clear summary description of the SAE that places events in perspective so that its significance and import are understandable to non-medical and non-scientific personnel who may be within the chain of command.

(ii). A statement whether the SAE was expected or unexpected. Expected SAE's are those discussed in the protocol itself and information about which has been included to subjects in the informed consent processes and approved documents.

(iii). The investigator's opinion as to the causal relationship, if any, between the research and the SAE; and how this SAE affects the overall risk-benefit ratio of the research when considered in perspective with all previous adverse and serious adverse events;

(iv). Specific recommendations as appropriate for changes to the protocol, policies or operating procedures to minimize the risks of recurrence.

(v). Specific recommendations for modification of the ICD to ensure the fully informed consent of future subjects if the risk could reasonably be expected to recur;

(2). Expected SAE reports should be reviewed at the next regular IRB meeting, filed with the IRB minutes and endorsed, approved and submitted via the chain of command in a routine manner for oversight review by higher authority.

(3). Unexpected SAEs:

(a). Upon discovery of an unexpected SAE, investigators must notify the IRB Chair within twenty-four hours of the event and its circumstances. Notification must include detailing of all circumstances. Such notification can happen electronically, by telephone or by any other means possible. In the event of the absence of the IRB Chair, a Vice-Chair, another member of the IRB or the approval official suffice for immediate notification. The IRB Chair or other official will discuss the facts surrounding the event and make determinations for the appropriate course of action as follows. Discussions concerning the SAE will be particularly attentive as to whether the SAE is or is not reasonably associated with the research itself.

(b). After receiving notification from an investigator concerning an unexpected SAE, the IRB Chair shall notify appropriate levels within the chain of command within twenty-four hours of the unexpected SAE occurrence, its circumstances and the immediate corrective actions taken. Specifics regarding unexpected SAE initial notifications will depend on such factors as the gravity of the unexpected SAE and the likelihood of its affecting other subjects.

(c). The PI and medical monitor must implement appropriate action(s) in a timely manner to protect subjects and to minimize the chance of reoccurrence. The IRB Chair must either concur with the adequacy of these actions by specifically endorsing them or require additional safeguards.

(d). The IRB Chair should temporarily suspend the research pending implementation of corrective actions if appropriate to protect other subjects. The approving official may re-approve the suspended research protocol only upon receipt of a favorable recommendation by the IRB following their review.

(e). Each unexpected SAE shall be reviewed by the full IRB and the unexpected SAE report with endorsements shall be forwarded as a separate administrative action via the chain of command to higher authority for second level review within 30 days. Electronic transmission is acceptable.

5. Other Matters: While the primary focus of the reporting of serious adverse events, adverse events and other complications is clearly upon the protection of the rights and welfare of human subjects, the same situations are of importance to the Office of the Surgeon General of the Navy. Therefore, investigators, IRB Chairs, IRB Executives, Command personnel and approval authorities are to make strict use of the chain of command for the reporting of any and all incidents that may, in addition to ethical protection of human subjects, have meaning and concern for Navy public affairs.

CHAPTER 15

Other Reporting Requirements

1. For those human research protocols in which the sole research procedure is the administration of a survey, the requirements of reference (f) must be met. In these instances such surveys must receive approval from the requisite higher authority. Requirements for survey approval are found in paragraph 9 of reference (f). Approval for surveys must be granted prior to IRB consideration. Survey documents submitted for IRB review must include official approval documentation.

2. Applicable reports arising from human research matters in this instruction are exempt from reports control by SECNAVINST 5214.2B

CHAPTER 16**Research Conducted Outside the United States**

1. For all Echelon 3 and 4 activities, research protocols that are conducted outside the jurisdiction of the United States require approval by the appropriate authorized officials of the host country government (Ministry of Health). All activities must institute clear standards, procedures and methods for international research efforts involving the enrollment of human subjects. Such efforts must take into account ethical matters of international importance and of importance to the indigenous culture involved.

2. It is recognized that the process of obtaining host government approval may be time consuming. Therefore, for the sake of expediency, the IRB and approval authorities should begin to consider a protocol prior to the granting of host country approval especially if that is the only outstanding item.

3. However, volunteers are not to be allowed to participate in research before required host government approval is granted. Documentation of host government approval must be completed by the appropriate authorized officials of the host government and must state that:

a. The host government is aware of the specific details of the research proposed.

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

c. Approval for involvement of host country national research volunteers is granted.

d. The host government understands that the research will meet at least the minimum standards for the protection of research volunteers required by the U.S. Navy.

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

approval of research; and the host government understands that it has the right to require any additional restrictions desired to ensure the protection of research volunteers.

4. It is the responsibility of the IRB Chair and the convening authority to ensure that host government approval is obtained from the appropriate level and branch of the host government, in accordance with host country law and practice. However, standards of conduct for international studies must likewise conform with all federal and Department of Defense regulations. In the case of conflicting standards, stricter interpretations must always apply.

CHAPTER 17**Research Protocols**

1. Each Echelon 3 and 4 activity must design and institute application materials and procedures for the submission of research protocols involving the enrollment of human subjects. Submission forms are to be based upon the protocol application form found in appendix (1). Since oftentimes protocols are conducted in collaboration with extramural agencies that have already established forms and procedures, it is recommended that activities separate out experimental design sections or sections that elucidate the scientific effort with greater complexity from sections that would summarize with precision all matters directly related to ethical concerns. Appendix (1) makes this distinction and may serve as an example for all activities. The following also pertain for protocol forms, content and submission procedures:

2. For each study involving research volunteers, a research protocol will be prepared that fully describes the proposed study. The basic elements required for human use protocols are found in appendix (1). Alternate formats are acceptable as long these contain the basic elements found in appendix (1).

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

4. 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. The safeguards in place to minimize risk and deal with emergencies.
- d. The total number of volunteers to be enrolled in the entire study and in any specific groups included within the study, whether they are military or civilian, male or female, and the age range of volunteers; precise listing of any populations to be excluded with precise justification for such exclusions.
- e. A justification to show that studies in animals or *in vitro* systems could not address the hypothesis(es) under test.

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

6. The 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 IRB for the appropriateness of exposing research volunteers to research risks relative to the likelihood that the research results will adequately address the hypotheses under test. In the event that sample size calculations are not warranted, explanation for omitting this aspect of the research protocol will be stated for review and consideration by the IRB.

7. Procedures that will be performed by other than NMRC 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.

8. Per reference (j), for each research protocol assessed as greater than minimal risk, a single appropriately qualified medical monitor (i.e. a credentialed physician or dentist, military or civilian) will be designated by name. This individual must be someone other than the principal investigator. The medical monitor may be an appropriately credentialed individual from a collaborating institution or, in the OCONUS context, a member of the Ministry of Health medical or dental staff. An IRB itself or higher authority may determine that a medical monitor may be required for other reasons for protocols that are not greater than minimal risk.

9. The medical monitor is to be the individual responsible for the overall medical control of the study with the authority and responsibility to terminate any exposure of volunteer(s) to research related risks whenever it is medically indicated. The medical monitor is principally responsible for the safe and ethical treatment of a research volunteer during a study, and is not to be confused with a medical watch officer who may be present to respond to emergencies during a protocol. Although a medical monitor may serve as a medical watch officer, these roles are not to be considered synonymous.

10. The primary qualifications and experience of the medical monitor must be determined to be sufficient to meet all requirements for the safe conduct of the study.

11. The principal investigator will ensure that any change of the designated medical monitor for an approved study will be reported to, and approved by, the IRB. A request for a change in the medical monitor will be submitted in memorandum form by the principal investigator to IRB Chair. The request will include the qualifications (e. g., a current CV) of the replacement medical monitor for IRB review and approval.

12. 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 which will be filed in Appendix D of the protocol file.

13. In the event that a greater than minimal risk study does not warrant a medical monitor, a request for waiver of this requirement is to be forwarded to the appropriate authority in accordance with chapter 26 of this instruction.

14. For studies that involve minors or third party permission, and are conducted outside the legal jurisdiction of the United States, 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. For studies involving minors where childhood assent is required by the IRB per 45 CFR 46 Subpart D, specific procedures with separate assent forms must be provided.

15. For each protocol, the principal investigator will include 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. Letters requesting modifications to an approved protocol will include the location (page and paragraph numbers) of the elements to be added or changed in the protocol.

16. All IRB Protocols are required to be assigned a DoD Assurance Number as received from higher authorities as certification of DoD/DoN assurance under the Office of the Surgeon General of the Navy. It is to be noted that, despite its administrative usages, the DoD Assurance Number is not a

tracking number. The DoD Assurance Number is to be used as a formal identification number indicating that a protocol and its conduct are under Navy authority. The DoD Assurance Number is permanently assigned to the specific research protocol and to its modifications, amendments and all documentation of any kind.

CHAPTER 18**Selection of Research Volunteers**

1. All Echelon 3 and 4 activities must review with particular care and ethical regard standards and methods for the enrollment and selection of human subjects including any and all advertisements concerning the same. In accordance with the principle of justice found in The Belmont Report of 1979, the exclusion of individuals as research volunteers because of age, sex, race, ethnicity, or socioeconomic, military grouping, or other factors is prohibited unless based upon a sound scientific or operational rationale.
2. In cases of exclusion of a specific group, the following information is required as a part of the research protocol:
 - a. Exact criteria for the exclusion of individuals as research volunteers.
 - b. Complete justification for exclusion including any scientific or operational requirements that necessitate the exclusion.
 - c. 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.
 - d. Potential effect on the research if the exclusion is not allowed.
3. The IRB, the Commanding Officer, and the approving authority will review each research protocol for appropriateness of restrictions based upon the information provided.
4. Pregnant women may be enrolled as participants in research covered by this instruction provided that risks to the mother and fetus are negligible and, furthermore, that the requirements of 45 CFR 46 Subpart B are met as directed by reference (d).
5. Non-pregnant women may participate as research volunteers provided that appropriate safety precautions are maintained. The specific provisions required in this regard are found in appendix (17).

6. In research involving greater than minimal risk, the potential research volunteer must be either:

a. An individual eligible for care at a military medical treatment facility (e.g. active duty member, retired member, dependent of an active duty or retired member, Secretary of the Navy designee for health care benefits);

b. A civilian employee of the 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 volunteer;

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.

7. Additional considerations may apply in cases where the potential research volunteer is a foreign national or a member of a foreign military organization.

8. 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 volunteer in the research cannot be authorized.

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

10. Research done under contract will follow the same guidelines described in paragraph 12.e.

11. U.S. military personnel may participate as research subjects. Consideration should be given to how participation affects readiness and availability to perform military duties. Additional reimbursement of the research volunteer for participation, monetary or otherwise, is prohibited except as specifically authorized by law or regulation.

12. Regarding the enrollment of military personnel special attention must be given to avoid any real or apparent coercion to participate as a research volunteer, especially in training contexts, or other situations associated with major career branch points. The enrollment of military personnel as research subjects must clearly avoid any and all elements that would bring into question the ability of the individual or group to make a free decision for enrollment. Military subjects must clearly understand that enrollment will not benefit their service status and a decision against enrolling will not bring retribution or question of one's loyalty to service. If researchers or any other staff members encounter any elements that could give rise to even the perception of coercion of military personnel to enrollee, the individuals involved may not be enrolled and the matter is to be reported immediately to the senior researcher present and to the IRB Chair.

13. Persons receiving medical care at military treatment facilities, such as active duty and retired military personnel and dependents, may participate as research volunteers in research related to their health care. Such persons may be compensated for these services when authorized by applicable directives. Retired officers of a regular component are subject to limitations of 5 U.S.C. 5532.

14. Research involving prisoners or institutionalized mentally disabled persons serving as research volunteers is prohibited per reference (g).

CHAPTER 19**Voluntary Informed Consent**

1. All activities are mandated to adopt the most comprehensive and stringent oversight and review measures for informed consent processes and procedures because informed consent is at the very center of the protection of the rights and welfare of human subjects. Per reference (a), for Department of Defense activities the obtaining of voluntary informed consent is mandated. Therefore, voluntary informed consent must be obtained for all research within the scope of this instruction. References (b) and (g) detail the basic elements for ICD's. These critical elements, in accordance with references (b) and (g) and shaped for NMRC local usage are provided in Appendix (12). It is further to be noted that informed consent is both a process and a procedure. It is a process in that it occurs in the relationship between investigator-staff and participants. It is a procedure in that the free granting of informed consent must be certified by record. The process and procedures of informed consent must clearly give testimony that participants freely volunteer to participate in a study, have been given requisite information to make the decision for participation, and have an accurate comprehension of the procedures, risks, benefits, consequences and other factors related to study-participation. Therefore, informed consent processes and procedures must be performed and shaped (written) in the language of the subject and on the level of the subject's comprehension. Informed consent processes and procedures are for the benefit of the subject and not the scientist or medical practitioner.

2. Whenever possible, written informed consent (as demonstrated by a signed consent form) will be obtained. If it is not possible to obtain written informed consent, a waiver of this requirement may be requested in accordance with chapter 26 of this instruction. This request for waiver must be clearly documented and justified in the protocol. Provided that the described voluntary informed consent process meets the requirements of applicable guidance and the research exposure involves no more than minimal risk to the volunteer, waiver of the requirement for obtaining a signed consent form (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 form has been waived, investigators will document the consent process in writing in accordance with the requirements of reference (g), paragraphs 7.d through 7.g.

Waiver of the requirement to obtain a signed consent form in research involving human volunteers is not meant to be a routine procedure.

3. Except as noted below, individual voluntary informed consent of each research volunteer is required. While it also may be necessary to 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.

4. 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.

5. In the case of third party consent, 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 by the investigator in the protocol concerning the intent of the investigator to provide information to the individual participant for whom third party permission is obtained.

6. Under the direction of the IRB Chair and the IRB itself, investigators will make all provisions for the assent of children where they are of sufficient age. Careful documentation of childhood assent is critical in ICD's. Since children are a particularly vulnerable population, the approval of measures for childhood assent is to be reflected in the minutes of the IRB meeting with great care.

7. 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, all of the following conditions must be met:

a. the prospective participant in the research must be legally incapable of giving informed consent.

b. the measures to be used in the research must be intended to be beneficial to the participant.

c. investigators must demonstrate that the individual providing permission is legally authorized to do so.

d. the permission is legally effective in the locale where it is obtained and the research exposure of the participant takes place.

8. The consent form will provide names and telephone numbers or other appropriate means of contact for the principal investigator, the medical monitor, review authority, and the approval authority in the event that the research volunteer has a question that arises during or after the course of the study.

9. Foreign national volunteers and volunteers who are not fluent in the English language must be provided the informed consent process and procedures in their native language. All consent forms used must have an accurate and complete translation of the English version into the appropriate foreign language and shaped according to the comprehension of participants. Individual IRB's may also require back-translations. All translations will be an integral part of the protocol and will be submitted with the original protocol for review. All translations must be certified and signed by those making the translation. Willful failure to provide and use an accurate and complete translation will result in disapproval or termination of the research.

10. Only the approved version of consent forms can be used. Certification of this matter is to be part of the continuing review of research. Activities are to institute means by which this certification can be annotated administratively for the maintenance of records (e.g. the use of approval stamps etc.).

11. A sample consent form is provided as appendix (2).

CHAPTER 20**Privacy Act Statements**

1. All research volunteers who are either citizens of the United States or foreign nationals legally admitted to the United States must be provided with a Privacy Act statement. The Privacy Act statement information may be provided in the text of the consent form, or as a separate statement attached to the consent form. Research volunteers are not required to sign a specific Privacy Act statement. The Privacy Act does not apply to foreign national research volunteers unless they are legally admitted to the United States. If a Privacy Act statement is not used in obtaining voluntary informed consent because the research volunteer is an alien not legally admitted to the United States, it is recommended that the concepts included in the Privacy Act statement be incorporated into the text of the consent form. A sample Privacy Act Statement is provided as appendix (3). This may be modified as appropriate.

CHAPTER 21**Additional Study Requirements and Safeguards**

1. In all research, particular safeguards shall be required as added protection for subjects. In addition, investigators are to refer to appendices (13) through (16) as listed below for special study requirements.
2. For biomedical or biodental studies of greater than minimal risk, a physician or dentist, military or civilian, shall be responsible as the medical monitor for the medical or dental welfare, respectively, of all subjects. This person shall be someone other than the principal investigator.
3. During or after any study, medical or dental treatment, including hospitalization if necessary, will be provided to any subject who requires such treatment or hospitalization as a result of his or her participation in the study, as soon as such need is recognized.
4. Where appropriate, provisions shall be made in advance for rapid medical evacuation of subjects to an adequate hospital facility, military or otherwise, in case of emergency.
5. In addition, Navy requirements include other Special Study Standards that must be maintained.
 - a. See Appendix (13): Research Involving Investigational Drugs, Biologics or Devices.
 - b. See Appendix (14): Research Involving the Unlabeled Use of Drugs or Biologics.
 - c. See Appendix (15): Research Involving Testing of Research Volunteers Suspected to be Infected with the Human Immunodeficiency Virus.
 - d. See Appendix (16): Research Involving Physiological Stress.
 - e. See Appendix (17): Safety Provisions for the Enrollment of Non-Pregnant Women.

CHAPTER 22**Maintenance of Records**

1. For all Echelon 3 and 4 activities, all records associated with a research protocol involving human volunteers will be maintained with due care for their sensitivity and importance in accordance with all regulations related to research, ethics, law and matters that may be related to intellectual property and technology transfer as applicable. Records will contain all applicable elements and will remain permanently retrievable by their respective activities. For NMRC the official records of active protocols will be maintained in ORA-HSPP. ORA-HSPP will likewise maintain protocol files for a minimum of three years beyond the close of a research protocol before transfer to the NMRC Research Archives. However, all protocol files will remain within the Command. It will be the responsibility of Echelon 4 activities to adopt similar practices for their own efforts but also to send information copies of all protocol files to NMRC in care of ORA-HSPP for headquarters' purposes. The following paragraphs give greater detail regarding official files and archival requirements.

2. It is the responsibility of the Commanding Officer to delegate responsibility for a centralized system to record participation of all human volunteers in research protocols. This system will include:

a. A centralized computer database or databases in which will be recorded:

(1) Identification of research protocol by name, unique research protocol number, Work Unit number or other assignment identifying the human use protocol as consistent with an activity's military medical research mission, status of protocol (pending, active or complete) and list of all investigators.

(2) Standardized identification of the research volunteers participating in the protocol (e.g. Social Security Number, if available).

(3) Inclusive dates of participation of the research volunteer in the protocol.

b. A centralized archives in which, at the completion of the research, will be stored:

(1) The original approved protocol with all approved modifications including continuing and final reports.

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

(3) All original signed consent forms.

(4) Other documents bearing original signatures.

(5) A volunteer registry database.

(6) For each individual volunteer, 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. It is suggested that space for such entries be allocated at the end of the Consent Form to record this data. Since this material may be identical to the medical record entry (see below), a single document may provide a record of the consent process and the experimental results in both individual and Command records.

(7) Documentation when a local program, department or other activity division is given permission by ORA-HSPP or other activity authority to maintain records and/or consent forms in another approved location after the conclusion of study. In this case, the designation of document location and approval of the same is to be indicated clearly in protocol database records.

3. If cooperative research is conducted in conjunction with a non-U.S. Navy activity which holds the primary responsibility for the protection of the research volunteers, the agreement between the activities (cooperative research plan) will specify that copies of all documents required by this instruction will be made available for files at NMRC.

4. A temporary or permanent individual research volunteer file may be created and maintained within the laboratory for each volunteer during the time of his/her participation in the protocol. The contents of this file are at the discretion of the principal investigator, and may include reports of research related physical, laboratory, or other medical examinations and a chronologic history of participation in studies. Such files may be useful when individuals are assigned to commands as research subjects. Disposition of the documents collected will

be described in the protocol and be considered by the IRB during the processes of initial and continuing review.

5. Microfiche copies are acceptable for permanent storage of all records. Electronic media storage of experimental data initially recorded electronically is acceptable. Electronic media storage of original documents such as signed consent forms and 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 will be validated and protected.

6. A copy of each research volunteer's consent form will be filed in the volunteer's medical or dental records as directed by regulations. The volunteer's medical records will also include sufficient documentation to substantiate what was done to the research volunteer 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 also be entered into the volunteer'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 IN ACCORDANCE WITH SECNAVINST 3900.39B**

7. In the event the research volunteer does not have a formal medical or dental record, the research records will be provided to the volunteer or the volunteer's health care provider for retention.

8. 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.

CHAPTER 23**Investigators Acting as Consultants.**

1. It is recognized that NMRC Echelon 3 and 4 personnel have scientific expertise which may lead to these personnel being sought out as consultants. The policy for all personnel participating as consultants for research involving human volunteers 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 NMRC-related 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 that the study is scientifically sound, complies with all applicable regulations, and that the protection afforded research volunteers is in accordance with Navy policy.

c. To be considered as only a consultant, NMRC-related personnel must not have substantial participation in the research in question. Substantive participation is specified in paragraph (d) below. In addition, substantive participation also includes interactions with research enrollees or other matters that could raise the issue of Navy involvement in research. If participation is limited to that of a consultant, no review of the human use aspects of the research is required. If participation is substantive, full compliance with all regulations pertaining to the protection of research volunteers, and review of the research protocol in accordance with this instruction is required.

d. Use of Navy resources to support research, including the use of funds, technical personnel, laboratory facilities, equipment, supplies or capabilities, is considered substantive participation in the research. Such research requires full review and approval in accordance with references (a) and (e) and this instruction.

e. Participation of NMRC-related personnel as consultants on research protocols involving human volunteers requires the written approval of the Commanding Officer.

2. These policies also apply to the case where personnel from other institutions participate as consultants to NMRC projects. In all non-exempt research, if there is substantial participation in the (e.g. authorship) on the part of the non-NMRC individual, co-investigator status exists and completion of the Individual Assurance Agreement as applicable and documentation of institutional review by that individual's organization is required.

CHAPTER 24

Restrictions on Expenditure of Funds for Human Subjects Research

1. Without the required approval for a research protocol involving research volunteers, NMRC investigators are:

a. Permitted to engage in preliminary activities normally required for the planning and implementation of a study, prior to active participation or enrollment of research volunteers in a specific protocol.

b. Prohibited from obligating or expending funds to:

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

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

(3) Perform travel for the purpose of conducting the research protocol or for other activities directly related to the participation of research volunteers.

(4) Carry out any other activities for which approval of the research protocol for participation of research volunteers is required.

2. Per reference (a), non-DoD activities receiving DoD funding for research involving human subjects are required to obtain informed consent from enrollees.

CHAPTER 25

Conflicting Regulations

1. Issues pertaining to the protection of human volunteers participating in research are in a state of evolution. This may result in confusion and apparent conflict in the applicable regulations. NMRC personnel are instructed that:
2. References (a) and (b) carry the force of law and supersede administrative regulations and references (c) through (l).
3. In all cases, the regulation requiring the strictest or greater protection for research participants will prevail. This includes regulations cited in references (c) through (j); this instruction; institutional regulations; local, state and Federal laws and regulations; and, where applicable, foreign laws and regulations.
4. In the event of significant conflict or ambiguity between regulations, requests for guidance should be forwarded to the IRB and/or to higher authority through the chain of command.

CHAPTER 26**Waiver of Requirements**

1. Waiver of requirements may be granted if permissible under the law and all regulations and only if there is no danger, whether real or perceived, that the ethical protection of the rights and welfare of human subjects would be compromised in any way. Requests for waiver are to be submitted, 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, the Commanding officer and by each successive echelon in the chain of approval is required. Failure to obtain any of these recommendations for approval will result in disapproval and return of the request to the originator.

Appendix (1)

**APPLICATION FOR HUMAN SUBJECT RESEARCH
PROTOCOLS
NAVAL MEDICAL RESEARCH CENTER
ECHELON 3 AND 4 LABORATORIES**

GENERAL DIRECTIONS

The following pages comprise the standard application for protocols involving human subjects that must be assessed for ethical propriety and approval under federal and agency regulations.

This application format is to be considered as the standard to be implemented for local usage. While research experimental design appendices and other enclosures may be shaped in accordance with a variety of needs for a variety of reasons, the given formats for the application summary information and the investigator assurance agreement are mandatory. Investigators may add to the categories but may not delete items or areas listed.

Submitting investigators should collaborate and/or meet with IRB officials and executives to shape protocols from the concept stage onward. Such collaborative efforts are designed to explore key issues and needs that may be required for the successful, expeditious, and prudent assessment of protocols..

All protocols must receive full scientific review prior to submission to IRB Program Offices and/or IRB Chairs. Directorate Chiefs or other Command authorities are responsible for ensuring that scientific review has been accomplished by requisite bodies. Signature on the routing sheet or on other authoritative documents by Directorate Chiefs or other designated authorities is the certification that scientific review has been completed and that all related issues have been met.

All protocol packages must be routed through one's chain of command to IRB Program Offices where applicable and then to the IRB Chair for consideration for IRB review at a scheduled meeting. All submissions must be received by IRB Program Offices and/or IRB Chairs according to the announced timeline schedule. Investigators must obtain timeline schedules from IRB offices. . However, meeting application deadlines is not a guarantee that a particular protocol will be placed on the agenda for a given IRB meeting. No proposal can be placed on the IRB agenda until all prior items have been met. Failure to meet requirements prior to placement on the agenda will result in the return of the proposal application to the submitting investigator until all matters have been met.

PART I: COVER MEMORANDUM:

The Submitting Investigator is to complete a standard cover memorandum addressed to the IRB Chair of the respective Command via the IRB Office (where such an office exists).

Without any reference to suggested level of risk or other matters that may be perceived as directing the judgment of the IRB itself, the submitting investigator requests in the memorandum consideration of the protocol application.

Submitting investigators must include in the cover memorandum special circumstances that require attention. Such circumstances would include calling attention to the IRB and its officers whether the Command will serve as lead agency for full IRB ethical review responsibility or whether the Command is participating on an effort for which another federally assured agency will serve as lead.

Special circumstances also include such matters as requests for the rapid review of protocols and their approval. In this case when serious and unforeseen circumstances may suggest waiver of more rapid timelines for proposal consideration, submitting investigators must provide complete justification and the request itself must be endorsed by the submitting investigator's scientific leadership through the chain of command. Since ethical considerations regarding the protection of the rights and welfare of human subjects require a level of prudence that comes only with the maturity of time, requests for rapid timelines should be for exceptional circumstances only. Since ethical considerations supercede any and all other matters, rapid timelines cannot be granted for administrative expediency or institutional conveniences.

PART II: APPLICATION SUMMARY INFORMATION

- A. Protocol Number (DoD Assurance Number to be assigned IRB Program Officials)
- B. Protocol Title
- C. Relevant Work Unit Title and Work Unit Number (or other military relevance certification)
- D. Principal Investigator/IRB Certification Number
(IRB Certification Number only if NMRC affiliated)
- E. NMRC Submitting Investigator/IRB Certification Number
(If different than the Principal Investigator)
- F. Co-Investigator(s)
(Name, title, institutional affiliation, with all NMRC investigators listed with IRB certification number)
- G. Research Location(s)
- H. Lead Agency
(Agency with lead or primary IRB responsibility)
- I. Collaborating Domestic Institution(s)
- J. International Approval Agency
(If applicable)
- K. Proposed Start and End Dates
- L. Projected/Estimated Total Number of Enrollees
- M. Inclusions
(List all included populations as may be necessary to articulate)
- N. Exclusions
(List any excluded populations and provide *brief* bulletized justifications for each)
- O. Anticipated Risks:
(*Briefly* bulletize or list all estimated risks to enrollees: physical, psychological, socio-cultural etc)
- P. Proposed Risk Reduction Methodologies and Provisions:
(*Briefly* bulletize or list all proposed efforts by which risks will be ameliorated or eliminated)

Q. Protocol Abstract
(500 words maximum)

PART III: INVESTIGATOR ASSURANCE AGREEMENT

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 Research 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 (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 and other key personnel)

PART IV: PROTOCOL CRITICAL ELEMENTS

While research protocols may vary given circumstances and requirements, the following elements must be included in the experimental design section found in Part V Section A. If protocol formats used to satisfy collaborator requirements do not include any of the following, then these items where applicable must be included as appendices to the experimental design.

A. SCIENTIFIC BACKGROUND AND OBJECTIVES

1. Background
2. Objectives
 - (a) Hypothesis(es) to be tested
 - (b) Other objective(s)

B. EXPERIMENTAL METHODS (May be supplemented by appendices)

1. Experimental Procedures and Rationale including information to show that studies in animals or *in vitro* systems could not address the hypothesis(es) under test.
2. A sample Size Determination with Statistical Power Calculation (if indicated), including the total number of volunteers to be enrolled in the entire study and in any specific groups included within the study, whether they are military or civilian, male or female, and the age range of volunteers
3. Procedures that will be performed by other than NAVMEDRSCHCEN institutions (if any)
4. Detailed Inclusion and Exclusion Criteria. Exclusions must include justification.
5. Required Equipment and Supplies (as needed to ensure proper coordination of research effort)

C. ORGANIZATION OF RESEARCH EFFORT (RESEARCH PLAN)

1. Duties and Responsibilities of Investigators and other individuals involved in the protocol. Delineate responsibilities for ethical review, administrative oversight etc as needed.
2. Multicenter organizational plan with responsibilities for IRB review and approval.

D. RISKS AND DISCOMFORTS TO RESEARCH VOLUNTEERS

1. List of the significant risks to the Volunteer and the safeguards in place to minimize risk and deal with emergencies
2. A description of how appropriate anonymity will be maintained for any human samples or identifiable data collected or used
3. Special Risks to Pregnant or Potentially Pregnant Women Volunteers
4. Safety Precautions and Emergency Procedures

5. Assessment of Sufficiency of Plans to Deal With Untoward Events or Injuries
6. Qualification of Medical Monitor and Medical Support Personnel

E. DESCRIPTION OF THE SYSTEM FOR MAINTENANCE OF RECORDS

1. Experimental Data
2. Research Protocol, Consent Forms, and Related Documents for Protection of Human Research Volunteers
3. Individual Medical Records

PART V: REQUIRED ENCLOSURES

- A. Research Experimental Design (including all critical elements indicated in Part IV above)
- B. *Curriculum Vitae*: Principal Investigator and/or Submitting NMRC Investigator
- C. *Curriculum Vitae*: Medical Monitor (where applicable)
- D. Documentation of review and action taken by all collaborating institution(s) (for collaborative efforts)
 - 1. Acceptable results of review are approval, exemption from review, joint review or other formal review agreement
 - 2. Certification by the principal investigator that protocol submitted for review is the same final copy approved or under simultaneous review by collaborating institution(s)
- E. Federal Wide Assurance Information (where applicable and required)
- F. Ministry of Health Approval (for international efforts)
- G. Informed Consent Process Summary/Narrative
- H. Informed Consent Documents (including Privacy Act Statements where applicable/required)
- I. Informed Consent Translations (for international efforts and including certification of accuracy)
- J. Informed Consent Back Translations (where required for international efforts and including certification of accuracy)
- K. Record of changes to the protocol (where applicable)
- L. Other documentation (as required)
 - 1. Unlabeled use of approved drugs or licensed biologics
 - (a) Documentation from the Food and Drug Administration (FDA) authorizing exemption from the requirement for Investigational New Drug Application (IND)
 - 2. Experimental drugs, biologics or devices
 - (a) Documentation of an approved IND or Investigational Device Exemption (IDE) from the FDA
 - (b) Approval of the Naval Investigational Drug Review Board (NIDRB)
 - 3. OPNAV 5300.8B Permission (if required for questionnaire survey - include survey approval number or symbol)
 - 4. Request for waiver of requirement(s) for protection of human research volunteers. Requests must include justification.

Appendix (2)

SAMPLE CONSENT FORMS

CONSENT TO PARTICIPATE IN A MEDICAL RESEARCH STUDY TO STUDY THE EFFECTS OF ASPIRIN ON COMMON MUSCLE ACHE

You and about 200 of your neighbors are being invited to take part in a medical research project. The title of the project is "Evaluating the Effects of Acetaminophen on Common Myalgia." This study will test how helpful Aspirin is in getting reducing common muscle pain. As you may know, Motrin is usually used in your area to help reduce muscle pain; however, using Aspirin in this study will help us determine exactly how effective Aspirin is in reducing common muscle pain. The study will last eight (8) weeks. During this eight (8) week period, we will ask you to write down on a form we will give you the times you feel common muscle pain and a general description of that pain (i.e., whether it is severe, mild, moderate, etc.). Immediately after experiencing the pain and writing it down on the form we give you, you must take two (2) aspirin, which we will also give you, and, over the course of the next several hours, write down on our form how much, if any, your muscle pain has decreased. Also, once a week, you will meet with a doctor at the clinic who will examine you briefly and ask you some questions about how taking the Aspirin has affected you and your muscle pain. Most of you should experience no additional pain or discomfort from taking the aspirin. However, some of you may get a little upset stomach from taking the aspirin. Aspirin does have the effect of thinning the blood and therefore may make it difficult for your body to clot your blood (which is necessary for stopping bleeding). Although this probably will not pose a serious risk to most of you, you should be aware of this effect of Aspirin.

Your involvement in this study should not cost you or your family any money whatsoever. As stated above, a doctor at the clinic will be monitoring your health. If there is any evidence that the Aspirin is having or may have really bad effects on you, the doctor will remove you from the study and give you the appropriate medical treatment at no cost to you. The judgment of the doctor to remove you from the study, whether you want to be removed or not, will always be made with your best interests in mind.

The records you make and any records regarding your involvement in this study will be kept secret. While these records may be reviewed by authorized government agencies, your

identity will be kept secret and only a number will identify you

If you have any medical questions about this study or if you get sick at any time during this study, contact Dr. Bombay of the Naval Medical Research Center at the clinic, 123-4567. If you have any questions about the study in general or your rights as a participant in this study, contact Dr. Smith of the Naval Medical Research Center at 234-5678. You may also write the above individuals at the following address:

Aspirin-Muscle Ache Study
1313 Mockingbird lane
Bethesda, MD

We want to make it clear that YOU CANNOT AND WILL NOT BE FORCED TO JOIN THIS STUDY AGAINST YOUR WILL. YOU MAY JOIN THIS STUDY ONLY OF YOUR OWN FREE WILL. FURTHERMORE, YOU MAY QUIT THIS STUDY AT ANY TIME. IF YOU DECIDE TO QUIT THIS STUDY, NO ONE MAY PRESSURE YOU TO CHANGE YOUR MIND AND YOU WILL NOT BE PUNISHED OR LOSE ANY BENEFITS YOU MAY OTHERWISE BE ENTITLED TO.

I have read the paragraphs of this consent form and they are clear and understandable, or they have been read to me in a language that is clear and understandable. I have been given the opportunity to ask questions and to discuss any aspect of the research project with a member(s) of the research team. I understand the intent, risks, duration, and procedures of this study. By my signature below I agree that my involvement in this study is completely voluntary [for U.S. Nationals—"and I certify that I have been made aware of the provisions of the Privacy Act."]. A copy of this consent form has been given to me.

NAME: _____ AGE: _____ (yrs)

Signature of Volunteer/guardian Date

Signature & Name of witness Date

Investigator's signature Date

CONSENT TO PARTICIPATE
IN MEDICAL RESEARCH FOR EVALUATING
RESISTANCE TO CHLOROQUINE BY MALARIA

You and about 100 of your neighbors have been invited to participate in a project entitled, "Diagnosis of resistance to chloroquine in *Plasmodium vivax* and *Plasmodium falciparum*" which will evaluate how malaria in your area responds to chloroquine. This is the drug used in your area to treat vivax malaria. Falciparum malaria is usually treated with quinine because the Ministry of Health suspects it may work better than chloroquine. Treating you with chloroquine in this study is intended to see just how well that drug works. It is possible that chloroquine will not work against your infection. This is why we will be watching your progress very carefully. There is a risk that chloroquine will not work and your infection will return and make you ill. If it becomes clear that chloroquine is not working for you, treatment with quinine will be immediately given. Whether chloroquine works or not, during this 4 week study we will ask you to permit us to take a drop of blood from your finger each day this week, and once or twice a week for the remaining 3 weeks. Also, we will ask you to allow us to draw 15 milliliters of blood from your arm once today and, if your treatment with chloroquine fails to work, once more. Both of these procedures hurt a little, but only for an instant. If your child is being asked to participate, a special needle that does not hurt as much will be used. You will be asked to take chloroquine today, tomorrow, and the day after tomorrow. You will be offered this treatment whether you choose to participate in this study or not.

Your participation in this study should not cost you or your family any money for any reason whatsoever. By participating in this study the doctors will be watching whether chloroquine has cured your infection or not. If there is evidence that chloroquine did not work, the doctor is required to give you quinine, which is believed to usually work well.

The records of your examinations will be kept confidential. While they may be reviewed by government health agencies, you will be identified by a number only and it will not be possible for the reviewer to know specifically who did or did not participate in this study.

If you have any questions about this research, your rights, or wish to report any possible effects of the drugs, report to the doctor who gave you the medicine. Ask for Dr. Moti Ramgopal, Dr. Kevin Baird, Dr. Greg Martin, Dr. Alan Magill, Dr. Ellen Andersen, or Dr. Rita Guenther. These investigators can be reached directly in the clinic, or you can contact one of

them by phone by calling (phone# for malaria clinic) They can also be reached by telephoning the USA on 301-295-6991 (Dr. Baird) . You may also write a letter to them at this address (this is where this form will eventually be stored): Malaria Program, 12300 Washington Avenue, Rockville, Maryland 20852

IF YOU ARE SICK AND FEEL YOU NEED MEDICAL ATTENTION, THESE ARE THE PHYSICIANS YOU SHOULD CONTACT:

DR. MOTI RAMGOPAL

DR. GREG MARTIN

DR. ALAN MAGILL,

DR. RITA GUENTHER

You cannot and will not be forced to join this study against your will. You may join only of your own free will. At any point in the study, you have the right to refuse further participation without any explanation. If you decide to quit, no one may pressure you to change your mind. Once you have quit the study, no one may discriminate against you in any way.

The primary benefit to you of participation is the very high degree of medical attention you will receive during the month following treatment with a drug. We will be watching you very closely to be certain that you are not ill with a disease. Any illness you may be feeling will be examined by a doctor and, if possible, relieved. If you develop unexpected complications related to the conduct of this study, the doctors will provide treatment to you which represents the best they can provide without regard to cost. The cost of this treatment will be covered by the research team. If you suffer any permanent injury as a direct result of participation in this study, you have the right to seek compensation from the U.S. Navy by routine legal means. In the highly unlikely event of such an injury, the research team will instruct you on how to proceed with such a claim.

The doctors may decide you may no longer participate in this study, whether you wish to continue participation or not. This judgement will always be made with your best interests in mind. It is to protect you against possible bad effects of the drug, or to avoid giving you drugs you do not need.

I have read the above, or it has been read to me, and I have been given the opportunity to raise questions and to discuss the research project with members of the research team. I understand the intent, risks, duration, and procedures of this study. By my signature below I affirm my voluntary participation in this research project. A copy of this form has been given to me.

NAME: _____

AGE: _____ (yrs)

Signature of volunteer/guardian

Signature & Printed name of witness

Date: _____

Date: _____

Investigator's signature

Date: _____

Appendix (3)

SAMPLE PRIVACY ACT STATEMENT
(Format May Be Modified As Necessary)

1. Authority. 5 U.S.C. 301

2. Purpose. Medical research information will be collected in an experimental research project entitled "(State Name of Research Protocol)" to enhance basic medical knowledge, or to develop tests, procedures, and equipment to improve the diagnosis, treatment, or prevention of illness, injury, or performance impairment.

3. Routine Uses. Medical research information will be used for analysis and reports by the Departments of the Navy and Defense, and other U.S. Government agencies. Use of the information may be granted to non-Government agencies or individuals by the Navy Surgeon General following the provisions of the Freedom of Information Act or contracts and agreements. I voluntarily agree to its disclosure to agencies or individuals identified above and I have been informed that failure to agree to this disclosure may make the research less useful. The "Blanket Routine Uses" that appear at the beginning of the Department of the Navy's compilation of medical data bases also apply to this system.

4. Voluntary Disclosure. Provision of information is voluntary. Failure to provide the requested information may result in failure to be accepted as a research volunteer in an experiment or removal from the program.

Attached: Consent statement for this experiment, signed by the research volunteer.

Appendix (4)

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)

Appendix (5)

INSTITUTIONAL REVIEW BOARD RECOMMENDATION

For: NEW PROTOCOL

Date of Review:

DoD Number and Protocol Title:

Principal Investigator:

Participating NMRC Investigator:

Approximate Dates of the Research:

Work Unit Number:

Unless otherwise noted below, it is our opinion that the research and safeguards described in the reviewed research protocol meet the standards set forth in 32 CFR 219, DoD Directive 3216.2, SECNAVINST 3900.39C, BUMEDINST 3900.6B, and NAVMEDRSCHCENINST 3900.6A (and local instructions, as applicable) – namely, that the participation of humans as experimental research volunteers is limited to those situations in which voluntary informed consent is obtained; and that such participation is confined to research projects and clinical investigations which are necessary, scientifically sound, reasonably safe, and in which the benefit to be derived clearly justifies the risk incurred by the research volunteer. Minutes of our deliberations concerning the review of this research protocol are attached, including anonymous statements giving reason(s) for nonconcurrence or abstention (if the recommendation of the committee is not unanimous).

By vote of ___ for, ___ against, ___ abstaining, with ___ members disqualified from review and ___ members absent, we recommend to:

Approve*, as research of no more than minimal risk. See attached minutes for detailed minor modifications needed.

Approve*, as research of more than minimal risk but not requiring ASN (RD&A) approval. See attached minutes for detailed minor modifications needed.

Approve*, as research requiring ASN (RD&A) approval. See attached minutes for detailed minor modifications needed.

Return to principal investigator for specific revision before resubmission. See attached minutes for requirements.

Disapprove. * See attached minutes for reason(s).

**Depending on the protocol reviewed, “recommended approval/disapproval” is either for the research protocol if the IRB is the lead for ethical review OR participation of NMRC (or NMRC-Det) investigators if another agency is lead.*

The Committee recommends the first scheduled review on

Completed signature pages are attached.

RECOMMENDATION OF COMMANDING OFFICER

1. I concur with the recommendation of the Institutional Review Board (IRB).
2. I concur with the recommendation of the IRB, but recommend additional modifications or restrictions (See attached)
3. I disagree with the recommendation of the IRB and recommend the following. (See attached)

First Name, Middle Initial, Last Name
Rank, Corps
United States Navy
Commanding Officer

DATE:

APPROVAL AUTHORITY OF COMMANDING OFFICER

1. I concur with the recommendation of the Institutional Review Board Subjects (IRB).
2. I concur with the recommendation of the IRB, but recommend additional modifications or restrictions. (See attached)
3. I disagree with the recommendation of the IRB and recommend the following. (See attached)

First Name, Middle Initial, Last Name
Rank, Corps
United States Navy
Commanding Officer

DATE:

INSTITUTIONAL REVIEW BOARD RECOMMENDATION

For: PROTOCOL AMENDMENT Date of Review:
Risk Level of Current Approved Protocol:

DoD Number and Protocol Title:

Principal Investigator:
Participating NMRC Investigator:
Approximate Dates of the Research:
Work Unit Number:

Unless otherwise noted below, it is our opinion that the research and safeguards described in the reviewed protocol amendment meet the standards set forth in 32 CFR 219, DoD Directive 3216.2, SECNAVINST 3900.39C, BUMEDINST 3900.6B, and NAVMEDRSCHCENINST 3900.6A (and local instructions, as applicable) – namely, that the participation of humans as experimental research volunteers is limited to those situations in which voluntary informed consent is obtained; and that such participation is confined to research projects and clinical investigations which are necessary, scientifically sound, reasonably safe, and in which the benefit to be derived clearly justifies the risk incurred by the research volunteer. Minutes of our deliberations concerning the review of this protocol amendment are attached, including anonymous statements giving reason(s) for nonconcurrence or abstention (if the recommendation of the committee is not unanimous).

By vote of ___ for, ___ against, ___ abstaining, with ___ members disqualified from review and ___ members absent, we recommend to:

Approve implementation of modification. See attached minutes for detailed minor modifications needed.

Return to principal investigator for specific revision before resubmission. See attached minutes for requirements.

Disapprove. See attached minutes for reason(s).

The Committee recommends the first scheduled review on

Completed signature pages will be attached.

RECOMMENDATION OF COMMANDING OFFICER

1. I concur with the recommendation of the Institutional Review Board (IRB).
2. I concur with the recommendation of the IRB, but recommend additional modifications or restrictions (See attached)
3. I disagree with the recommendation of the IRB and recommend the following. (See attached)

First Name, Middle Initial, Last Name
Rank, Corps
United States Navy
Commanding Officer

DATE:

APPROVAL AUTHORITY OF COMMANDING OFFICER

1. I concur with the recommendation of the Institutional Review Board Subjects (IRB).
2. I concur with the recommendation of the IRB, but recommend additional modifications or restrictions. (See attached)
3. I disagree with the recommendation of the IRB and recommend the following. (See attached)

First Name, Middle Initial, Last Name
Rank, Corps
United States Navy
Commanding Officer

DATE:

INSTITUTIONAL REVIEW BOARD RECOMMENDATION

For: ADVERSE EVENT

Date of review:

Brief Description of Event:

Date of event/ Date reported

DoD number and Protocol Title:

Principal Investigator:

Participating NMRC Investigator:

Work Unit Number:

Unless otherwise noted below, it is our opinion that the research and safeguards described in the research protocol still meet the standards set forth in 32 CFR 219, DoD Directive 3216.2, SECNAVINST 3900.39C, BUMEDINST 3900.6B, and NAVMEDRSCHCENINST 3900.6A (and local instructions, as applicable) – namely, that the participation of humans as experimental research volunteers is limited to those situations in which voluntary informed consent is obtained; and that such participation is confined to research projects and clinical investigations which are necessary, scientifically sound, reasonably safe, and in which the benefit to be derived clearly justifies the risk incurred by the research volunteer. Minutes of our deliberations concerning the review of this adverse event report are attached, including anonymous statements giving reason(s) for nonconcurrence or abstention (if the recommendation of the committee is not unanimous).

By vote of ___ for, ___ against, ___ abstaining, with ___ members disqualified from review and ___ members absent, we recommend to:

Accept the adverse event report.

Accept the adverse event report pending review and acceptance of minor revisions and/or clarifications (See attached minutes for requirements).

Return the adverse event report to investigators for revision. Resubmitted report requires review by full committee. (See attached minutes for requirements.)

AND:

Continue the research.

Suspend the research. (See attached minutes for reasons and requirements.)

Terminate the research. (See attached minutes for reasons.)

Completed signature pages will be attached.

RECOMMENDATION OF COMMANDING OFFICER

1. I concur with the recommendation of the Institutional Review Board (IRB).
2. I concur with the recommendation of the IRB, but recommend additional modifications or restrictions (See attached)
3. I disagree with the recommendation of the IRB and recommend the following. (See attached)

First Name, Middle Initial, Last Name
Rank, Corps
United States Navy
Commanding Officer

DATE:

APPROVAL AUTHORITY OF COMMANDING OFFICER

1. I concur with the recommendation of the Institutional Review Board Subjects (IRB).
2. I concur with the recommendation of the IRB, but recommend additional modifications or restrictions. (See attached)
3. I disagree with the recommendation of the IRB and recommend the following. (See attached)

First Name, Middle Initial, Last Name
Rank, Corps
United States Navy
Commanding Officer

DATE:

Appendix (6)

INSTITUTIONAL REVIEW BOARD RECOMMENDATION

For: CONTINUING REVIEW

Date of review:

Date research started:

No. of previous reviews:

DoD number and Protocol Title:

Principal Investigator:

Participating NMRC Investigator:

Work Unit Number:

Unless otherwise noted below, it is our opinion that the research and safeguards described in the research protocol still meet the standards set forth in 32 CFR 219, DoD Directive 3216.2, SECNAVINST 3900.39C, BUMEDINST 3900.6b, NAVMEDRSCHCENINST 3900.6a (and local instructions, as applicable) – namely, that the participation of humans as experimental research volunteers is limited to those situations in which voluntary informed consent is obtained; and that such participation is confined to research projects and clinical investigations which are necessary, scientifically sound, reasonably safe, and in which the benefit to be derived clearly justifies the risk incurred by the research volunteer. Minutes of our deliberations concerning the review of this continuing review report are attached, including anonymous statements giving reason(s) for nonconcurrence or abstention (if the recommendation of the committee is not unanimous).

By vote of ___ for, ___ against, ___ abstaining, with ___ members disqualified from review and ___ members absent, we recommend to:

Accept the continuing review report.

Accept the continuing review report pending review and acceptance of minor revisions and/or clarifications (See attached minutes for requirements).

Return the continuing review report to investigators for revision. Resubmitted report will require review by full committee. (See attached minutes for requirements.)

AND:

Continue the research.

Suspend the research. (See attached minutes for reasons and requirements.)

Terminate the research. (See attached minutes for reasons.)

The Committee recommends the next scheduled review on:

Completed signature pages will be attached.

RECOMMENDATION OF COMMANDING OFFICER

1. I concur with the recommendation of the Institutional Review Board (IRB).
2. I concur with the recommendation of the IRB, but recommend additional modifications or restrictions (See attached)
3. I disagree with the recommendation of the IRB and recommend the following. (See attached)

First Name, Middle Initial, Last Name
Rank, Corps
United States Navy
Commanding Officer

DATE:

APPROVAL AUTHORITY OF COMMANDING OFFICER

1. I concur with the recommendation of the Institutional Review Board Subjects (IRB).
2. I concur with the recommendation of the IRB, but recommend additional modifications or restrictions. (See attached)
3. I disagree with the recommendation of the IRB and recommend the following. (See attached)

First Name, Middle Initial, Last Name
Rank, Corps
United States Navy
Commanding Officer

DATE:

Appendix (7)

Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure As Authorized under the Bureau of Medicine and Surgery

1. Applicability

Research activities that present no more than minimal risk to human subjects, and involve only procedures listed in one or more of the categories below, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110, 32 CFR 219.110 and 21 CFR 56.110.

The activities listed below are those approved by federal authorities but have also been specifically refined by higher authorities of the Bureau of Medicine and Surgery. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

2. Research Categories

Research Categories Eligible for Expedited Review. The following categories of research may be eligible for expedited review. This list derives from categories published in the Federal Register but takes precedence over it as it is more restrictive per direction from higher BUMED authorities. These categories apply regardless of the age of the subjects, except as noted.

A. Expedited Review Category 1. Clinical studies of drugs and medical devices when either condition (1) or (2) is met.

(1). Research on drugs for which an investigational new drug application is not required. (Note: Research on marketed drugs in which the research exposure would significantly increase the risks or decrease the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(2). Research on medical devices for which either:

(a). An investigational new device exemption application is not required; or

(b). The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/ approved labeling.

B. Expedited Review Category 2. Collection of blood samples by finger stick, heel stick, ear stick or venipuncture according to the restrictions in the applicable category:

(a). Healthy nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period, and the collection may not occur more frequently than 2 times per week.

(b). Other adults and all children. Considering the age, weight, and health of the subjects, the collection procedure, the amount of blood collected, the frequency with which it will be collected, the amount drawn may not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period, and collection may not occur more frequently than 2 times per week.

C. Expedited Review Category 3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

(1). Hair and nail clippings collected in a non disfiguring manner;

(2). Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

(3). Permanent teeth if routine care indicates a need for extraction;

(4). Excreta and external secretions (including sweat);

(5). Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;

(6). Placenta removed at delivery;

(7). Amniotic fluid obtained at the time of rupture of the membrane prior to or during delivery;

(8). Supra- and subgingival dental plaque and

calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

(9). Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

(10). Sputum collected after saline mist nebulization.

D. Expedited Review Category 4. Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays, microwaves, or potentially injurious directed energy such as lasers. When medical devices are employed, they must be cleared or approved for marketing. (Note: Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples of activities that may be eligible for expedited review include:

(1). Physical sensors that are applied either to the surface of the body or at a distant and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

(2). Weighing, and testing sensory acuity;

(3). Magnetic resonance imaging;

(4). Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;

(5). Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

E. Expedited Review Category 5. Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes, such as medical treatment or diagnosis.

F. Expedited Review Category 6. Collection of data from voice, video, digital, or image recordings made for research purposes.

G. Expedited Review Category 7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus groups, program evaluation, human factors evaluation, or quality assurance methodologies.

H. Expedited Review Category 8. Continuing review of greater-than-minimal risk research that was previously approved by the full IRB may be conducted using expedited review procedures if it falls into any one of the following categories:

(1). Where all three of the following conditions are met:

(2). The research is permanently closed to the enrollment of new subjects; and

(3). All subjects have completed all research-related interventions; and

(4). The research remains active only for long-term follow-up of subjects.

(5). Where no subjects have yet been enrolled and no additional risks have been identified since IRB review; or

(6). Where all remaining research activities are limited to data analysis.

I. Expedited Review Category 9. Continuing review of approved minimal risk research may be conducted using expedited review procedures when the research was originally reviewed by the full IRB only because it did not fit into Categories 2 through 7, as long as:

(1). The research was not conducted under an investigational new drug application or investigational device exemption, and

(2). No additional risks have been identified since the full IRB review.

Appendix (8)

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.

Appendix (9)

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/NMRI 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:

Appendix (10)

**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:

3. 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?

Yes

No

If No, briefly comment.

V. SUBJECT POPULATION:

10. 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.*

13. 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.

Yes

No

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.

C. Special Considerations:

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.

VIII. GENERAL OR MISCELLANEOUS COMMENTS:

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 copies.*

Appendix (11)

Institutional Review Board

New Proposal or Modification Administrative Review

Upon receipt of a new protocol or a modification to an approved protocol, the Executive Administrator places the submission on the agenda for the next time-qualifying meeting. The Executive Administrator provides an administrative critique using the following assessment items. Unless otherwise indicated below, the Executive Administrator is to consult with the IRB Chair to determine the means by which outstanding items are to be addressed before final disposition. Investigators are to be advised by the Executive Administrator that a protocol is approved only when the approving authority has signed the protocol and notified the investigator by official communication. Volunteers cannot be enrolled until all protocol requirements (e.g. host country approvals, assurance signatures etc) have been completed in full.

DoD Protocol Number: _____

Protocol Abbreviated Title: _____

NMRC Investigator(s): _____

Full Work Unit Number: _____

Adapt the following questions for use with a new protocol or modification submission.

1. Has the protocol or modification package been properly routed? Has the investigator documented review and approval of program and department directors? *(If program and department directors have not seen, approved, and initialed the protocol submission, materials are to be sent to the appropriate office for review before further processing.)*

2. Has the investigator included the required cover memorandum to the Chair? Does the cover letter, if applicable, contain required justifications for waivers, time requirements or exemptions? If applicable, does the cover letter from the investigator include all modification materials in the same categories from the originally approved protocol? Do modifications exceed original authorized parameters? (If so, IRB review and approval are required; if not, the Chair must review materials, notify the investigator of approval, notify the IRB in the next agenda, and place materials in the original protocol file.)

3. Does the cover page contain all required information including full work unit number, number of enrollees, project period dates, associate investigators, collaborating institutions etc?

4. Have all required signatures been obtained, dated and included on the signature page? *(If required signatures are incomplete, the Executive Administrator is to inform the investigator immediately that IRB approval cannot be given and enrollment cannot begin until signature requirements are completed.)*

5. Has scientific review been obtained and certified through signature with date on the required signature page? Is the scientific review official one of the investigators named in the protocol? *(Protocols lacking a signature/certification for scientific review are to be returned to the investigator immediately. Protocols cannot be processed for IRB review until scientific review is finalized. All questions concerning potential conflict of interest in the area of scientific review are to be remanded to the IRB Chair, IRB Administrator or Executive Secretary.)*

6. Does the protocol list the number of potential enrollees where required? Is the number of enrollees consistently referenced throughout the submitted materials?

7. Does the protocol directly or indirectly indicate any exclusions to the enrollee population? Is justification given for exclusions? In the case of pediatric enrollees, does the investigator cite the required direct benefit to children?

8. Does the protocol contain an explicit research organizational plan? In the case of collaborative research efforts, is a lead agency identified? In the case of research being performed overseas, has host country approval documentation been provided? *(Regarding host country approvals, the Executive Administrator is to notify investigators immediately that final IRB approval and the beginning of enrollment depend directly on the final disposition of host country approval. Enrollment of volunteers cannot begin until host country approval has been obtained and received by the IRB.)*

9. Does the protocol appear to fall under the categories of "exempted" research activities? *(If so, the protocol must be assessed by the IRB Chair and IRB Executive Administrator. If exempt, the Chair must write a memorandum to the Commanding Officer with recommendation and request for concurrence/signature that exempt status is granted.)*

10. Does the protocol list potential risks? Do protocol materials attempt to address risks and take steps for their minimization?

11. Is a medical monitor named? If so, is the medical monitor an investigator on the protocol? If no medical monitor is named, has a request for medical monitor exemption been made in the protocol and/or the cover memorandum from the investigator?

12. Does the investigator cite detailed methods to ensure the confidentiality of enrollees?

13. Does the protocol cite measures for the disposition, storage and safeguarding of records, data, consent forms and related materials both during and after the project period?

14. Does the protocol contain the required consent form with all its constitutive elements? Is the consent form in layperson, non-technical language? For international or domestic studies done with enrollees who are not English-fluent, are foreign language translations and required independent back translations included in submitted materials? Does the protocol list names and contact information for those preparing foreign language and back translations?

15. If enrollees are U.S. citizens or foreign nationals admitted to the U.S., is a Privacy Act Statement included? Does it contain the required elements? If there are no enrollees who are U.S. citizens or foreign nationals admitted to the U.S., is all mention of the Privacy Act excluded?

16. Is the Investigator Assurance Form included with all signatures and dated accordingly by each signee? *(The Executive Secretary is to inform investigators immediately that signatures must be obtained before final IRB approval and the enrollment of volunteers.)*

17. Are there other miscellaneous areas that should be brought to the attention of the IRB Executive Administrator or IRB Chair before IRB review?

Notes:

Final review:

Executive Secretary

Date: _____

Final review:

Director, Office of Research Administration

Date: _____

Final Review:

Chair, IRB

Date: _____

Appendix (12)

Informed Consent: Principles and Critical Elements

PRINCIPLES:

As directed by 10 USC 980, informed consent is a Department of Defense requirement for the ethical protection of human subject participants from research risks.

Informed consent is both a process and a procedure. The process of informed consent takes place in the professional relationship or interaction of trust between research/medical staff and enrollees beginning with any and all enrollment provisions or initiatives. The procedures of informed consent, unless a specific waiver is granted, are constituted by written documentation. However, though a waiver of written informed consent may be obtained with extensive and clear justification for *bona fide* reasons none of which can compromise the rights and welfare of human subjects, the obtaining of informed consent in written form is the normative experience.

The use of implied consent is expressly prohibited.

Requirements for informed consent documents are found below. These are set to provide participants with the essential information to make and express a free, un-coerced and moral choice about one's enrollment into a particular research study. Signed informed consent documents (including third party witnessing and/or childhood assent documentation where applicable) provide a documented record that meets ethical and legal requirements for certifying that enrollees have been given all requisite information regarding the scope of work and risks/benefits involved in a research study, that information provided has been rendered in a way completely comprehensible to individual enrollees, and that an enrollee's agreement to participate is completely free, voluntary and un-coerced.

All statements and information must be written from the perspective of the individual enrollee. The level and choice of language to be used must be that of the enrollee/population and not that of the medical or research staff. Therefore, complex scientific vocabulary, concepts and language patterns are required to be translated to understanding of participants. Finally informed consent documents can never include any exculpatory language that would in any way suggest that enrollees would waive any of their rights nor waive the

liability of researchers, staff, institutions and research sponsors.

CRITICAL ELEMENTS:

The required critical elements and standards to follow are derived from 32 CFR 219. In addition, DoD Directive 3912.2, and paragraph 6.c of SECNAVINST 3900.39C delineate specific requirements that must be met when shaping and enacting informed consent processes and documents including those that would deal with child or other third party assent for vulnerable populations.

Basic elements of informed consent: 32 CFR 219

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are not experimental;

(2) A description of any reasonably foreseeable *risks or discomforts* to the subject;

(3) A description of any benefits to the subject or to others, which may reasonably be expected from the *research*;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any that might be advantageous to the subject;

(5) A statement describing the extent, if any to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal *risk*, an explanation as to whether any compensation and/or medical treatment are available if *injury occurs* and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which

the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional elements of informed consent. In addition to the above, the following must be included when deemed appropriate.

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are presently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject without prejudice to the subject. In all instances where abrupt withdrawal would be hazardous to the subject; e.g., medication regimens which gradual reduction, appropriate safe discontinuation procedures will be followed, and the subject advised;

(5) A statement that major new findings developed during the course of the research, which may relate to the subjects willingness to continue participation, will be provided to the subject;

(6) The approximate number of subjects involved in study; and

(7) A statement that informs the subject that the Food and Drug Administration (FDA) may inspect the research records, in projects where this is applicable.

Appendix (13)

SPECIAL STUDY STANDARD 1:

Research Involving Investigational Drugs, Biologics or Devices

Use of investigational drugs, biologics or devices requires compliance with NAVMEDCOMINST 6710.4. In addition:

1. If a research protocol involves the use of investigational drugs, biologics or devices, approval by both NMRC and the Naval Investigational Drug Review Board 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 United States, approval of the host country government is also required.

2. In the event that 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 research that either (1) is not commercially available in the United States or (2) 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 U.S. Food and Drug Administration (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 NAVMEDCOMINST 6710.4. 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 a FDA approved process.

4. Supplementation of an existing Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE) with a new research protocol is desirable. This requires concurrence of the current responsible individual (holder of the IND or IDE) and approval by the FDA.

Appendix (14)

SPECIAL STUDY STANDARD 2:

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 the U.S. Food and Drug Administration (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 research volunteers, 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 NAVMEDCOMINST 6710.4.

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. If the research meets the criteria of the FDA regulations pertaining to Investigation New Drug Applications, 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 that is 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 that use of the drug product;

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

(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 Investigational New Drug Application (IND).

b. The consent form 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; and

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

Appendix (15)

SPECIAL STUDY STANDARD 3:

Research Involving Testing of Research Volunteers Suspected to be Infected with the Human Immunodeficiency virus

The following comments pertain to research protocol involving testing of research volunteers for infection with the human immunodeficiency virus (HIV), and whose test results can be, associated with personal identifiers (i.e. are not anonymous):

1. Research volunteers must be told in advance that 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 volunteers must be told that the investigators are obligated to make test results available to the individual research volunteer. If a research volunteer 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 volunteer is informed that he or she has tested positive for infection with the HIV, the investigators are obligated to ensure that the research volunteer is provided with the opportunity for appropriate counseling about the disease and infectivity.
4. If research volunteers are foreign nationals and research is conducted under the auspices of a host government, it remains the responsibility of NMRC investigators to ensure that research volunteers 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, without participation of NMRC investigators in the process such that investigators could verify that the ethical and legal responsibilities of the NMRC investigators have been properly executed, is prohibited. This policy does not require NMRC investigators to personally and exclusively inform and counsel research volunteers, nor does it preclude appropriate delegation of these responsibilities. This policy does require that NMRC investigators participate in the process to the extent that they can verify that their research volunteers are being appropriately informed and counseled.
5. One of the greatest potentials for harm to a research volunteer involves disclosure of the confidential information

regarding the research volunteer's HIV positive status. Considerations for protection of data and confidentiality are of particular importance in research involving research volunteers with HIV infection. These considerations and safeguards must be fully disclosed in the research protocol and consent form.

Appendix (16)

SPECIAL STUDY STANDARD 4:

Research Involving Physiological Stress

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

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

a. A completely equipped "emergency cart" is to be immediately available at the site where the research volunteer 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 NMRC or contracting 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% 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 volunteer. At the conclusion of the study, the medical officer (or civilian physician) will clear each research volunteer for release and resumption of normal activities.

d. At least one member of the research team will be continuously with the research volunteer from the beginning of the study until the research volunteer is released by a medical officer (or civilian physician). 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 volunteers, specific criteria for termination of an individual research volunteer'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.

Appendix (17)

SAFETY PROVISIONS FOR THE ENROLLMENT OF NON-PREGNANT WOMEN

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 volunteer is allowed. The consent form will include a statement that there is no known risk to a pregnant woman, embryo or fetus in the event that the research volunteer is unknowingly pregnant or becomes pregnant during the course of the study. The consent form 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 volunteer, embryo or fetus, the consent form will include a statement describing in detail the risks to a pregnant research volunteer, embryo or fetus in the event that the research volunteer 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 that the volunteer is unlikely to be pregnant. In addition, investigators must objectively demonstrate that the volunteer is not likely to be pregnant as described below:

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

a. The test must be sensitive enough to detect 25 milli International Units per milliliter (mIU/ml) of human chorionic gonadotrophin (hCG), or less. This level of HCG may detect pregnancy as early as 10 to 12 days after conception, before the first missed menstrual period.

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

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

4. In cases where the adverse effects of experimental exposure in pregnancy warrant a higher degree of certainty that the female research volunteer 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 volunteer in any potentially hazardous activity, or whenever the research volunteer, 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.

5. In cases where the adverse effects of experimental exposure in pregnancy warrant the highest degree of certainty that the female research volunteer is not pregnant, the experimental exposure should occur during the first ten 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.

6. 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 volunteer tested.

7. 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 volunteers of childbearing potential.

8. The research volunteer will be advised of risks associated with becoming pregnant during the course of the study. If she thinks that 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 form.

12. Requests for waiver of these requirements are to be submitted in accordance with instruction and through the chain of command. A waiver may be granted in situations where the potential risk to the volunteer and her embryo or fetus is clearly outweighed by the expected benefit.

Appendix (18)

REVIEW CRITERIA
PROGRAM: 7.2

COMMAND: _____

PROTECTION OF HUMAN SUBJECTS

REFERENCES: 10 USC 980
32 CFR 219
DoD Directive 3216.2
SECNAVINST 3900.39B
SECNAVINST 5212.5D
SECNAVINST 5215.1C
NAVMEDRSCHDEVCOMINST 3900.2
NAVMEDRSCHCENINST 3900.6
NAVMEDRSCHCENINST 3902a
NAVMEDRSCHCEN ltr 3900 Ser 00R/038014 of 24 AUG 99

GENERAL INFORMATION

YES NO N/A

7.2.1 The activity performs research efforts involving human subjects and has active human use protocols.

Total number of active protocols: _____

Total number of active protocols that are greater than minimal risk: _____.
Represents ____% of total active protocols.

Total number of active protocols that are minimal risk: _____.
Represents ____% of total active protocols.

Total number of active protocols that are approved as exempt: _____.
Represents ____% of total active protocols.

7.2.2 The activity has established its own IRB in accordance with regulations.

Date of last BUMED assurance under authority of 32 CFR 219: _____

If the activity performs research involving human subjects and does not have its own IRB, state IRB the activity uses and the assurance under which the IRB is established:

SECTION A: POLICY, PROGRAM AND EDUCATION

YES NO N/A

7.2.3	Does activity have an instruction that implements human subject protections policies, regulations, statutes, instructions and directives of higher authorities?	_____	_____	_____
7.2.4	Has activity's instruction been updated or reissued in appropriate time frames?	_____	_____	_____
7.2.5	Does activity maintain a separate manual of standard operating procedures and updates this resource regularly?	_____	_____	_____
7.2.6	To maintain human subject protections as an all hands responsibility, does activity have instruction and standard operating procedures manual available for all personnel?	_____	_____	_____
7.2.7	Does activity make higher agency documents and related literature available to professional personnel?	_____	_____	_____
7.2.8	Does activity allocate resources for maintenance and development of a IRB office and program? Are resources sufficient? If not, provide requirements data in appendix form.	_____	_____	_____
7.2.9	Does activity provide continuing education for IRB Members and leadership? For general professional personnel?	_____	_____	_____
7.2.10	Does activity uphold and require norms for IRB certification for all personnel at the principal and associate investigator level? Does activity require IRB certification registration numbers on protocols and other documents?	_____	_____	_____

SECTION B: PROTOCOLS

YES NO N/A

- | | | | | |
|--------|--|-------|-------|-------|
| 7.2.11 | Does the activity employ a protocol format that includes categories and required information as detailed by regulations and higher agencies? | _____ | _____ | _____ |
| 7.2.12 | Is scientific review required and performed by a duly appropriate body separate from the ethical review body? Is scientific review completed prior to ethical review? | _____ | _____ | _____ |
| 7.2.13 | Do protocols clearly and consistently detail the approximate number of subjects anticipated as being enrolled? Is the population number justified by power calculation or other appropriate means to demonstrate compliance with lowering risks? | _____ | _____ | _____ |
| 7.2.14 | Do protocols clearly state exclusions and inclusions for subject populations? Are exclusions justified clearly? | _____ | _____ | _____ |
| 7.2.15 | Do protocols name medical monitors and are medical monitor qualifications required? If a medical monitor is not required, is a waiver sought, justified and obtained in accordance with regulations? | _____ | _____ | _____ |
| 7.2.16 | Do protocols completely provide for informed consent processes and procedures? Do protocols describe how informed consent will be obtained? | _____ | _____ | _____ |
| 7.2.17 | Are informed consent documents required to be shaped in non-technical language and appropriate for use by subjects? | _____ | _____ | _____ |
| 7.2.18 | Do informed consent documents contain all required critical elements? | _____ | _____ | _____ |
| 7.2.19 | Do informed consent files indicate that research staff is using the approved versions of informed consent documents? | _____ | _____ | _____ |
| 7.2.20 | Do informed consent processes and procedures require third party consent for particularly vulnerable populations such as pediatric enrollees? | _____ | _____ | _____ |

	YES	NO	N/A
7.2.21 Do informed consent processes and procedures that require third party consent further require and obtain childhood assent where mandatory?	_____	_____	_____
7.2.22 Are foreign translation consent forms and documents prepared and certified appropriately?	_____	_____	_____
7.2.23 Do protocols clearly address all risks and benefits and further clearly deal with minimizing risks and maximizing benefits?	_____	_____	_____
7.2.24 Are all protocols linked to active work units or in some analogous fashion clearly demonstrate mission relevance of research effort?	_____	_____	_____
7.2.25 Are all protocols provided with the required DoD Assurance Number as delegated by higher authorities?	_____	_____	_____
7.2.26 Are Investigator Assurance Agreements signed by all required personnel?	_____	_____	_____
7.2.27 Do protocols make provision for a clear organizational plan and designation of lead IRB responsibility when multiple agencies are involved in research efforts?	_____	_____	_____
7.2.28 Do consent form documents include provision for the Privacy Act for U.S. citizens or non-U.S. citizens legally admitted to the U.S.?	_____	_____	_____

SECTION C: IRB AFFAIRS

YES NO N/A

- | | | | | |
|--------|--|-------|-------|-------|
| 7.2.29 | Does the activity have a duly constituted IRB? | _____ | _____ | _____ |
| 7.2.30 | Are the Chairperson and Recording or Executive Secretary appointed by the Commanding Officer in writing? Are provisions made for alternate Chairpersons and Secretaries so that committee affairs are always possible? | _____ | _____ | _____ |
| 7.2.31 | Are IRB members appointed in writing by the Commanding Officer for appropriate terms of appointment? | _____ | _____ | _____ |
| 7.2.32 | Does committee membership represent a diversity of interests and subject area expertise?
(e.g. scientific disciplines, medical practice, ethical theory, administration, law, community affairs, minority affairs etc) | _____ | _____ | _____ |
| 7.2.33 | Does the committee include at least one member who is unaffiliated with the activity and who is a federal employee equivalent (GS, military, PHS, IPA)? | _____ | _____ | _____ |
| 7.2.34 | Does the committee include at least one member whose main area of expertise is not in scientific affairs? | _____ | _____ | _____ |
| 7.2.35 | Does each IRB meeting have the required quorum so as to perform valid reviews? | _____ | _____ | _____ |
| 7.2.36 | Do OCONUS activities have at least one member of the local Ministry of Health appointed to the committee as a consultant? Do minutes clearly reflect the assessment of the MOH representative regarding a protocol's suitability in the local culture? | _____ | _____ | _____ |
| 7.2.37 | Does the committee have sufficient numbers and alternates so that regular meetings are always held and ethical reviews and oversight functions are performed without delays or delinquencies? | _____ | _____ | _____ |

SECTION D: REVIEW PROCEDURES

YES NO N/A

- | | | | | |
|--------|--|-------|-------|-------|
| 7.2.38 | Are review procedures based upon instruction and clearly detailed in the activity's standard operating procedures document? | _____ | _____ | _____ |
| 7.2.39 | Does review include certification that scientific review has taken place prior to ethical review? | _____ | _____ | _____ |
| 7.2.40 | Do review minutes clearly give evidence that reviews are germane to the ethical protection of the rights and welfare of human subjects in accordance with higher authorities? | _____ | _____ | _____ |
| 7.2.41 | Do protocol reviews and recommendations take place in a timely fashion that allows for mature ethical reflection and does not impede scientific necessities? | _____ | _____ | _____ |
| 7.2.42 | Do pertinent IRB members and local approval authorities recuse themselves or abstain from voting in cases where there may be a conflict of interest? | _____ | _____ | _____ |
| 7.2.43 | Are exempt protocols reviewed in accordance with recommendations and regulations? | _____ | _____ | _____ |
| 7.2.44 | Do exempt protocols receive review of annual status reports and final reports by the Chair and local approval authority? | _____ | _____ | _____ |
| 7.2.45 | Do all review procedures allow for assessment of risk level, provisions for the protection of rights and welfare of subjects, assessment of qualifications of pertinent professional personnel etc. | _____ | _____ | _____ |
| 7.2.46 | Do review procedures promote the assessment of important critical factors regarding vulnerable subjects, military subjects and the need for freedom from coercion, and special medical considerations such as disease reporting through the military chain or public health system as may be applicable? | _____ | _____ | _____ |
| 7.2.47 | Do review procedures provide for assessment of sensitive issues such as provisions for subjects in biomedical efforts who test positive for HIV? | _____ | _____ | _____ |

	YES	NO	N/A
7.2.48 Do review procedures include certification that all relevant personnel serving as principal or associate investigators have completed required training, education and registration?	_____	_____	_____
7.2.49 Are accurate minutes maintained for each meeting? Are minutes and recommendation sheets signed as required? Are copies of minutes and recommendation sheets maintained in protocol files?	_____	_____	_____
7.2.50 For efforts involving multiple agencies, does committee review confirm or establish lead IRB/IRB status to avoid duplication of overall effort?	_____	_____	_____
7.2.51 Are finalization of review and approval certified to investigators before enrollment of subjects?	_____	_____	_____
7.2.52 For OCONUS studies, is Ministry of Health approval obtained in writing before enrollment of subjects and the initiation of research?	_____	_____	_____
7.2.53 Are continuing reviews of protocols performed minimally on an annual basis?	_____	_____	_____
7.2.54 Does the IRB maintain a clear calendar for continuing reviews? Are timely notices given to professional personnel to avoid non-compliance? Are investigators notified if a continuing review requirement has lapsed? Are appropriate actions taken?	_____	_____	_____
7.2.55 Does the IRB require copies of continuing review from collaborative agencies for multiple agency efforts? Are these maintained in protocol files?	_____	_____	_____
7.2.56 Are adverse events or untoward complications reported according to regulations?	_____	_____	_____
7.2.57 Are adverse events or untoward complications given appropriate review especially for relatedness to study procedures and/or products etc? Are FDA and sponsor norms adhered to for relevant situations?	_____	_____	_____

	YES	NO	N/A
7.2.58 Are permissions given by the Commanding Officer or Officer in Charge for consultant participation by professional personnel acting in a non-investigator status?	_____	_____	_____
7.2.59 Are waivers from requirements requested through the chain of command in accordance with regulations prior to action?	_____	_____	_____

SECTION E: RECORDS

YES NO N/A

- | | | | | |
|--------|--|-------|-------|-------|
| 7.2.60 | Are protocol files maintained appropriately?
Do files contain copies of the IRB protocol,
study designs, research documents, copies of
minutes, modifications, approval notices,
continuing reviews, final reports,
adverse event reports and other related
documents? | _____ | _____ | _____ |
| 7.2.61 | Are original informed consent and informed
consent related documents maintained
in permanent files with due regard for
issues of privacy and confidentiality? | _____ | _____ | _____ |
| 7.2.62 | Is a protocol information database maintained
for IRB protocol records? | _____ | _____ | _____ |
| 7.2.63 | Is a volunteer registry database maintained
in accordance with regulations? | _____ | _____ | _____ |
| 7.2.64 | Are protocol files archived in a manner
that is appropriate and in keeping with
standards? | _____ | _____ | _____ |

SUMMARY

Point of Contact: _____

Reviewer's Comments:

RATING:

- ___ N/A Not applicable in this Inspection/Activity
- ___ 1 Satisfactory
- ___ 2 Satisfactory with Recommendation Requiring Mandatory Follow-up. (Complete below.)
- ___ 3 Unsatisfactory with Corrective Action Requiring Mandatory Follow-up. (Complete below.)

Reviewer Information

Name
Title/Position, Department
Institution
Street Address
City, State, Zip Code

Reviewer's Signature

Date

Discussion:

Recommendation or Corrective Action (circle one):

Appendix (19)

A HISTORICAL, ETHICAL AND REGULATORY OVERVIEW

1. The requirement for the development of specific policy requirements on the local level for the ethical protection of the rights and welfare of human subjects can only truly be understood and appreciated from the perspective of history and regulatory development.

a. Historical Background

(1) During the historical development of contemporary biomedical research, one concern has emerged over time with increasing interest and ethical concern, namely the protection of the rights and welfare of human subjects from research risks. Beginning with concerns over potential physical or psychological harms or those touching upon personal confidentiality and privacy, modern ethical standards have come to delineate ever increasing areas of ethical consideration such as the protection of human subjects from risks related to social or cultural concerns, gender issues, economic or political concerns etc. These evolving concerns are in development with an evolving and dynamic understanding of the nature of the human person and the nature of human society.

(2) Of critical historical and moral importance, the driving energy behind the most contemporary human subjects' protections and resulting bodies of regulations and laws was the evidence of misuse and research atrocities. With the revelations of the Nazi atrocities during the Nuremberg Trials of 1947, the Nuremberg Code was the first major international articulation of the rights and protections due to participants in medical research efforts. This was followed by the 1964 first edition of the Declaration of Helsinki that has itself been revised over the ensuing years. International concerns have likewise resulted in declarations of the Council for International Organizations of Medical Sciences. In the United States the evidence of other research misuses (e.g. The Tuskegee Experiments, the Willowbrook Experiments, the Fernald School Cold War Experiments etc.) resulted in the publication of an increasingly large body of literature and scholarly concern over the ethical protection of human subjects. These public discussions and concerns eventually bore fruit in regulatory requirements. In 1979 The Belmont Report articulated the foundational principles of human subjects ethical protections that are found at the end of this chapter.

(3) While legal concern over the rights of human subjects in research can be traced back even into court cases of

the late nineteenth century, between the 1980's and the 1990's United States law saw the issuance of human subjects protections requirements in the Code of Federal Regulations. The first of these, reference (a), was issued for and adopted by the federal agency that is currently the Department of Health and Human Services (DHHS). This was the first systematic and comprehensive codification of human subjects protections within the Code itself. In 1991, reference (a) was adopted by sixteen other federal agencies as "The Common Rule." The Department of Defense (DoD) adopted The Common Rule as reference (b). Reference (d) subsequently directed that all DoD activities are required to comply with Subparts B, C and D of reference (a) so as to provide for the protection of particularly vulnerable populations, namely in research involving fetuses, pregnant women, human *in vitro* fertilization, incarcerated persons and children.

(4) In the contemporary situation, the continuing development of human subject protections' concerns has resulted in a variety of new national studies and policy drafts developed by the National Bioethics Advisory Commission. In addition, in the late 1990's, the former Office for the Protection from Research Risks (OPRR) at the National Institutes of Health (NIH) was made a special assistant to the Secretary DHHS and renamed as the Office for Human Research Protections (OHRP) with a mission of leadership for the development of greater and more effective human subject protections policies and requirements.

(5) These studies and policy drafts affected the development of specific norms and regulations within DoD and the Department of the Navy (DoN). Under reference (b), during the 1980's and 1990's the Department of Defense promulgated its own directives and regulations as found in references (c) and (d). These were in turn implemented under specific instructions of the Secretary of the Navy and on lower echelon levels such as those found in references (g) and (j). This present instruction implements the norms, regulations and directives of the Office of the Surgeon General of the Navy regarding human research and development efforts as distinct from other regulations for clinical investigations. Reflecting wider national patterns and the directives of higher authority, the policies to follow will always be in a state of dynamic development in response to new and emergent needs.

b. Regulatory Background

(1) Pursuant to reference (b) and following upon reasonable expectations regarding professional codes of conduct for scientific research, references (c), (g) and (j) require that each Navy activity must implement the regulations and directives of all higher authorities in local policies and standard operating procedures for the ethical protection of the rights and welfare of human subjects from research risks where such research investigations are conducted or where they may reasonably be expected to be performed.

(2) These same references require that each Navy activity which conducts research involving the participation of human subjects must have a comprehensive ethics process in line with all regulations and that includes a review committee that will make advisory recommendations to the Commanding officer and/or official with approval authority.

(3) No study involving human subjects will be initiated unless the protocol covering the study has positive ethical review by a duly constituted valid IRB and approval from the appropriate authority. Enrollment of human subjects in research efforts cannot begin until approval from the appropriate authority has been granted and official written notification of the same has been received by the principal investigator or other relevant submitting individual.

(4) The essential elements in the protection of human research volunteers are: a) the ethical review of the research protocol by an IRB; b) determination that the benefits from the research clearly outweigh all risks regardless of the nature of the risk itself; c) approval of the protocol; d) implementation of all reasonable safety measures and means to reduce risk to research subjects; e) provision for easily accessible points of contact for the participants concerning the research itself, medical issues where applicable, ethical concerns, and the Commanding Officer; and, f) provision for a complete informed consent process and procedures for each research subject being enrolled.

(5) In all cases and without exception, review and approval processes must maintain an unimpeachable and demonstrable commitment to the highest ethical standards for the protection of the rights and welfare of human subjects. This includes meeting the foundational principles found in The Belmont Report of 1979 mentioned above namely:

(a) Respect for persons: Guarantees the absolute inviolability of the human person, individual liberty and freedom and personal autonomy with due provisions for those persons and populations who would have diminished autonomy.

(b) Beneficence: Orders all research toward bringing about a maximum of benefits and the honoring of the commitment of physicians to "do no harm" as the paradigm under which all research regardless of discipline must be accomplished.

(c) Justice: Requires that the access to the benefits of research be equally available to all persons unless specific exclusions are essential or unavoidable. Justice also demands that the risks of research be shared equitably without the exploitation of others because of the availability or vulnerability.

Supplement
Interim Policies

Special Supplemental Policies and Revisions
to BUMEDINST 3900.6b

Revised Human Use Policy #2.1

Adverse and Serious Adverse Events

Revised 21 Feb 2002

1. PURPOSE.

- 1a. This memo proposes policies and procedures for reporting of adverse and serious adverse events relating to research conducted or supported by the Department of Navy for which MED-26H has responsibility. These policies will form the basis for revisions to the BUMED Protection of Human Subjects instruction and the Human Use Guidebook.
- 1b. This is a final policy; it updates Human Use Policy #2 and its provisions should be implemented locally pending receipt of formal guidance.
- 1c. Please provide comments, suggestions and recommendations to CDR David McGowan, MED-26H, at (202/DSN) 762-3508, fax -0976, or e-mail dgmcgowan@us.med.navy.mil.

2. DEFINITIONS.

- 2a. ADVERSE EVENT means any untoward sign, result, event, misadventure, injury, dysfunction, adverse drug reaction or other undesirable happening that involves any volunteer human subject and could be reasonably related to participation in the study, regardless of whether it was listed on the informed consent document as an expected risk.
 - 2a(1). The adverse event could have occurred during any interaction with the subject including solicitation, screening, selection, training of volunteers, as well as during the actual experimental procedure or subsequent follow-ups.
 - 2a(2). Adverse events specifically include, but are not limited to, accidents, injuries, exacerbations of preexisting conditions and non-physical harms such as personal or socio-cultural embarrassment, financial hardship, and adverse administrative actions or career influences.
 - 2a(3). In the special case of surveillance or longitudinal epidemiologic studies, determination of what constitutes an adverse event requires consideration of the specific interventions of the research and not the characteristics of the underlying disease(s).

Revised Human Use Policy #2.1
Adverse and Serious Adverse Events

2b. SERIOUS ADVERSE EVENT (SAE) means any adverse event that has grave potential or effect. SAEs include, but are not limited to, occurrences that are fatal, life threatening, permanently disabling, require hospitalization, or are iatrogenic (such as administration of the wrong drug or of an excessive dose.)

2b(1). An SAE is considered expected if it was listed as an anticipated risk in the approved informed consent document (ICD). An SAE is unexpected if it was not included in the ICD.

2b(2). Different authorities overseeing research may have different definitions for what constitutes a SAE. For example, the "serious adverse drug experience" defined by the US Food and Drug Administration (FDA) is one type of SAE. When more than one authority has responsibility for a specific research protocol, the broader, more inclusive definition shall apply.

2c. OTHER EVENTS

2c(1). Occurrences, such as significant deviations from the protocol, enrollment of a subject who did not meet selection criteria, or failure to document an individual's informed consent are not considered as adverse events for these purposes. They are, however, breaches in the protocol or procedure that require review and corrective action.

2c(2). Reports of damage to property, personnel injuries and deaths, and significant public relation issues may require separate reporting within the chain-of-command to BUMED, Naval Safety Center, CNO, etc., in accordance with other regulations.

3. POLICY. Responsibility for the timely detection, reporting, and correction of adverse and serious adverse events rests with the Principal Investigator (PI) and the research activity's approving official. The research activity will make every effort to:

3a. Ensure the research protocol and the ICDs fully describe all foreseeable or anticipated risks or potential complications.

3b. Document, investigate, and review occurrences of adverse events and SAE, even though they may not initially appear to have a causal relationship to the research project.

Revised Human Use Policy #2.1
Adverse and Serious Adverse Events

- 3c. Ensure proper care is rendered to subjects harmed by participation in the research project and to take appropriate actions to avoid imposing harm on subsequent research participants.
- 3d. Collate the adverse event experience from all participating sites in multi-site studies, unless some central organization, such as a Data Safety Monitoring Board, exists to perform this function.

4. RESPONSIBILITIES

4a. The Institutional Review Board (IRB) shall:

- 4a(1). Ensure the timely review of adverse and SAEs reports at their regularly scheduled meeting. They may accept the PI's report and recommendations, request additional information, or impose additional requirements to minimize the risk to future subjects and maintain a favorable risk-benefit ratio for the research.
- 4a(2). Specifically determine if any unexpected SAE requires revision of the ICD to reflect a new risk and if previous subjects should be notified of the new information.
- 4a(3). Consider the adverse event experience as part of their continuing or completion reviews in perspective with other information relating to the study. Based on the overall experience with the research they may require modifications to the protocol or ICD, or may revise the time of the next continuing review.
- 4a(4). Specifically recommend re-approval of the research after required changes have been implemented if the research had been temporarily suspended.
- 4a(5). Retain records pertaining to adverse events as permanent records

4b. Reporting of Adverse Events

- 4b(1). The PI shall cumulate data concerning adverse events throughout the study at all sites, and provide a written summary to the IRB as part of each continuing review and as part of the project's completion report.
 - 4b(1)(a). This summary report shall include all adverse and SAEs to date, even if previously reported, and should clearly indicate any

Revised Human Use Policy #2.1
Adverse and Serious Adverse Events

significant findings, trends or patterns in the adverse event experience.

4b(1)(b). Adverse events may be logically grouped for convenience of analysis and reporting, but unforeseen or unexpected events should be clearly identified and discussed separately.

4b(1)(c). If an adverse event report is required by another agency (such as the FDA) that report may be submitted in lieu of writing a new report as long as it contains similar information and any additional information required herein is appended.

4b(2). Private personal identifying data should be not be included in adverse event reports, although when necessary anonymous codes may be used for clarification.

4b(3). The IRB should review the adverse event summary report as part of their continuing review or end-of-project review in perspective with other information relating to the performance of the study.

4c. Reporting of Serious Adverse Events (SAE)

4c(1). The PI shall:

4c(1)(a). Ensure necessary care is provided to the subject, and that appropriate actions are taken to avoid harm to other subjects and to prevent recurrences.

4c(1)(b). Inform the medical monitor and the IRB Chair of the SAE as soon as practicable and in a manner appropriate to its gravity and potential impact on other subjects.

4c(1)(c). Conduct a timely investigation into the SAE and provide a written report to the IRB Chair that includes at a minimum:

4c(1)(c)(i). A clear summary description of the SAE that places events in perspective so that its significance and import are understandable to non-medical and non-scientific personnel who may be within the chain of command.

4c(1)(c)(ii). A statement whether the SAE was expected or unexpected (that is, was it already included on the approved ICD?).

Revised Human Use Policy #2.1
Adverse and Serious Adverse Events

4c(1)(c)(iii). The investigator's opinion as to the causal relationship, if any, between the research and the SAE; and how this SAE affects the overall risk-benefit ratio of the research when considered in perspective with all previous adverse and serious adverse events;

4c(1)(c)(iv). Specific recommendations as appropriate for changes to the protocol, policies or operating procedures to minimize the risks of recurrence.

4c(1)(c)(v). Specific recommendations for modification of the ICD to ensure the fully informed consent of future subjects if the risk could reasonably be expected to recur;

4c(2). Expected SAE reports should be reviewed at the next regular IRB meeting, filed with the IRB minutes and endorsed, approved and submitted via the chain of command in a routine manner for oversight review by MED-26H.

4c(3). Unexpected SAEs:

4c(3)(a). The IRB Chair shall notify appropriate levels within the chain of command as soon as practicable of the unexpected SAE occurrence and the immediate corrective actions taken. The promptness of reporting and the command elements notified depend on such factors as the gravity of the unexpected SAE and the likelihood of its affecting other subjects.

4c(3)(b). The PI and medical monitor must implement appropriate action(s) in a timely manner to protect subjects and to minimize the chance of reoccurrence. The IRB Chair must either concur with the adequacy of these actions by specifically endorsing them or require additional safeguards.

4c(3)(c). The IRB Chair should temporarily suspend the research pending implementation of corrective actions if appropriate to protect other subjects. The approving official may re-approve the suspended research protocol only upon receipt of a favorable recommendation by the IRB following their review.

4c(3)(d). Each unexpected SAE shall be reviewed by the full IRB and the unexpected SAE report with endorsements shall be forwarded as a separate administrative action via the chain of

Revised Human Use Policy #2.1
Adverse and Serious Adverse Events

command to MED-26H for BUMED level review within 30 days.
Electronic transmission is acceptable.

5. DISCUSSION

- 5a. The intent of this policy is to encourage rapid, thorough and ongoing analysis of the overall adverse event experience by local experts; the goal is to minimize risks by implementing appropriate corrective action as early as possible.
- 5b. In obtaining informed consent, the PI should strive to identify and explain all known significant risks in order to assist the potential subject in making their decision regarding participation. Unanticipated problems will, however, occasionally occur and they need close scrutiny in order to identify means of mitigation and to provide updated informed consent to future subjects.
- 5c. Subjects should always be encouraged to freely report all concerns, injuries or side effects to the investigator, medical monitor or other suitable point of contact.
- 5d. Immediate evaluation of an unexpected SAE provides reevaluation of the risk experience and provides the opportunity to implement changes designed to minimize risks to future subjects. Additionally it serves as an opportunity to revise the ICD, providing future subjects with a more complete picture of the risks they might face. Periodic evaluation of the adverse event summary, on the other hand, provides the opportunity for viewing the research in a perspective that can not be obtained by considering each event in isolation.
- 5e. These policies are intended to focus on the research itself as a process, and specific application of these policies must consider the nature of the research and the experimental intervention. For example, consider a surveillance study of an infectious disease in which inadvertent release of research data led to a subject being fired. That would clearly be an adverse event related to the research and corrective actions should be taken to prevent its recurrence.
- 5f. It is particularly important to appreciate adverse events in an overall perspective and not as isolated or individual events. While it is not intended to suggest that an investigator must somehow obtain knowledge of every adverse event that occurs to a subject outside of the research environment, events that occur outside of the research environment (such as a fall at home) must be recorded as they come to

Revised Human Use Policy #2.1
Adverse and Serious Adverse Events

the attention of the investigator. The investigator should evaluate the overall experience in order to identify unanticipated patterns or trends. The goal is to appreciate the unexpected. A fever, for example, may be expected in a vaccine study, but the frequency, duration or severity of the reaction might be greater than anticipated. Similarly, there might in fact be a connection between a vaccination and a subject falling at home or wrecking their car, and that connection will not be appreciated never considered.

5g. MED-26H does not require immediate notification of the occurrence of an unexpected SAE, but expects all appropriate authorities to be notified in a timely manner depending on the nature of the event. We prefer to emphasize the need for thoughtful and thorough analysis of the event by local experts and timely action by local authorities to minimize the impact and chance of recurrence.

5h. It is not our intent to impose redundant reporting requirements on the investigator. A copy of a report required by another agency can be used in the report package if desired, as long as additional information is added as appropriate to meet these requirements.

5i. Significant deviation from the protocol, or enrollment of a subject who did not meet selection criteria or who did not receive properly documented informed consent, are not considered to be adverse events but are breeches in protocol. These occurrences, however, do indicate a problem with the responsible conduct of research and must be addressed and resolved. For example, following the inadvertent enrollment of an unqualified subject an inquiry might reveal that a worksheet did not list all of the disqualifying criteria; it is desirable to identify and correct this oversight rather than continue to recruit unqualified subjects.

6. This policy guidance shall be updated as required and remain in effect until issuance of the revised BuMed Instruction 3900.6C on Protection of Human Subjects.

Human Use Policy #3

EXEMPT RESEARCH

Revised 22 February 2002

1. PURPOSE

- 1a. This memo proposes policies and procedures relating to the exemption of certain categories of research conducted or supported by the Department of Navy for which MED-26H has responsibility. These policies will form the basis for revisions to the BUMED Protection of Human Subjects instruction and the Human Use Guidebook.
- 1b. This is a final policy and its provisions should be implemented locally pending receipt of formal guidance.
- 1c. Please provide comments, suggestions and recommendations to CDR David McGowan, MED-26H, at (202/DSN) 762-3508, fax -0976, or e-mail dgmcgowan@us.med.navy.mil.

2. BACKGROUND. Federal regulations provides that certain categories of innocuous research may be exempted from formal IRB review in order to lessen the regulatory burden without compromising the protections afforded to potential human research participants.

3. DEFINITION. Exempt research means that a specific project is both minimal risk and meets certain eligibility criteria for exemption.¹

4. POLICY

- 4a. Exempt research must meet all applicable requirements for the protection of human subjects, and investigators are specifically responsible for complying with applicable regulations. By BUMED policy, a protocol found to be exempt is given a DoD assurance number, subjected to annual continuing reviews, and tracked to completion to ensure that it continues to be eligible for exemption.
- 4b. The IRB is charged with making the determination of the level of risk involved in a research proposal and its eligibility for exemption. The investigator must submit a human use research protocol to the IRB Chair in sufficient detail to facilitate the determination and shall include all information relative to determining risk and issues of privacy. The submission should specify the exemption category that might apply, and

¹ Authorized in 32 CFR 219.101

Human Use Policy #3

EXEMPT RESEARCH

shall include signed Investigator's Assurance Statements from all investigators involved in the research.

- 4c. No research shall be classified as exempt that involves information obtained or recorded in such a manner that participants could reasonably be identified either directly or indirectly through one or more identifiers linked to the participants. Likewise, no research shall be classified as exempt that involves information which, even if unintentionally disclosed, could place the participant at risk of criminal or civil liability, or which could be damaging to the participant's financial standing, employability or reputation.
- 4d. It is not required to obtain advance informed consent when conducting exempt research as it is not considered research following 32 CFR 219 for purposes of compliance with 10 USC 980. However, the potential participant shall still be provided information explaining the purpose of the research, how privacy will be protected, and making it clear that participation is voluntary.
- 4e. Classified research or research involving prisoners, fetuses, pregnant women or human *in vitro* fertilization shall not be found to be exempt.
- 4f. Research involving children shall not be found to be exempt if the research involves surveys, interviews, or observations of public behavior if the investigator(s) participate in the activities being observed.²
- 4g. The PI remains responsible for protection of human subjects when conducting exempt research. Special emphasis should be placed on mitigating psychological, social and economic harms and in protecting the subject's privacy.
- 4h. All serious adverse events related to the exempt research must be reported in a timely manner following current policy.
- 4i. Exempt projects shall receive annual continuing review and re-approval. The PI shall submit a summary to the IRB in such time as to allow for the proper review and re-approval of the project prior to the end of the approval period. This summary shall include all pertinent portions of the summary required for continuing review including summary of progress to date, descriptions of all significant changes made in the research and any

² Note 1/ of 32 CFR 219.101 following subparagraph (i)

Human Use Policy #3

EXEMPT RESEARCH

factors that may affect either the risk-benefit ratio or exempt status of the project.

- 4j. The PI shall submit a notification of completion to the IRB at the end of the project.
- 4k. All actions relating to exempt research are subject to subsequent review by the IRB and approving official, and are further subject to oversight review by MED-26H.

5. RESEARCH CATEGORIES ELIGIBLE FOR EXEMPTION. To be exempt, a proposal must both involve no more than minimal risk and belong to one of the following categories:

- 5a. **Exempt Category 1:** Human use research focused on and conducted in established or commonly accepted educational settings involving normal educational practices.
- 5b. **Exempt Category 2:** Human use research involving the use of educational tests, survey procedures, epidemiologic practices, interview procedures or observation of public behavior, as long as
 - 5b(1). Information obtained is recorded in such a manner that participants can not be identified either directly or indirectly through one or more identifiers linked to the subject; and
 - 5b(2). The participant would not be placed at risk of embarrassment, criminal or civil liability or damage to their financial standing, employability or reputation if their responses were inadvertently disclosed.
- 5c. **Exempt Category 3:** Human use research involving the collection or study of data, documents, records, or pathological or diagnostic specimens that already exist at the time the research was proposed, if
 - 5c(1). These sources are publicly available, or
 - 5c(2). The information is recorded in such a manner that participants cannot be identified either directly or indirectly through one or more identifiers linked to the subject.
- 5d. **Exempt Category 4:** Human use research involving excreta or any specimen collected during the normal management of a patient as long as the sample cannot be identified.

Human Use Policy #3

EXEMPT RESEARCH

6. DISCUSSION

- 6a. Exempt research is not subject to full IRB review because of the inherent low risk associated with the research; however, it is NOT exempt from the requirements of this policy, nor does it release the investigator from ethical responsibilities to protect the subject's rights.
- 6b. If a specific project does not meet the Congressional definitions of both "research" and "human subjects," it is not human subjects research and is not covered by these regulations. If it is human use research, however, it might be eligible for exemption from full IRB review. Even if not exempt, it might still be eligible for expedited review. However, exemption is unrelated to expedited review, and (naturally) the eligibility categories for each are different. See also the policy on expedited review.
- 6c. Research may not be classified as exempt if it would be reasonably possible to identify the subject. Obviously, such personal identifiers as name, SSN, and birth date can lead to direct identification. But we must also consider the possibility of identification through combinations of research data, or combining research data with public data. For example, a study might refer to a 48-year old Navy Captain assigned to the USS Eversail during an at sea period in July of 1998. Anonymous in and of itself, but the public record shows that only one Captain was onboard at that time. So this research would not be exempt and would require review to ensure that adequate consideration was given to subject privacy. This does not mean "could the FBI figure it out if given enough time and money" but that it would be highly unlikely that privacy could be compromised by any reasonable examination of research and publicly available data.
- 6d. Likewise, research may not be classified as exempt if it involves information that could harm the subject if it were released for whatever reason or even by accident. For example, a survey investigating self-admitted past criminal behavior would not be exempt even if it did not include any personal identifying information. Although no one would intend to release the potentially harmful information, much less link it to a particular subject, IRB review is appropriate simply to ensure that protections are adequate.
- 6e. Even though documentation of informed consent is not required, it is still incumbent on the researcher to provide the potential participant with

Human Use Policy #3 EXEMPT RESEARCH

sufficient information to make an informed decision about participation. For surveys, as an example, this may take the form of a clearly understandable introduction laying out the purposes of the research, how privacy will be protected, and that participation is completely voluntary. This is, in effect, the informed consent process without an informed consent document.

7. This policy guidance shall be updated as required and remain in effect until issuance of the revised BuMed Instructions 3900.6C on Protection of Human Subjects.

Human Use Policy #4

Expedited Review and Approval Procedure

Revised 14 Feb 2002

1. PURPOSE

- 1a. This memo proposes policies and procedures relating to the expedited review and approval process for research conducted or supported by the Department of Navy for which MED-26H has responsibility. These policies will form the basis for revisions to the BUMED Protection of Human Subjects instruction and the Human Use Guidebook.
- 1b. This is a final policy and its provisions should be implemented locally pending receipt of formal guidance.
- 1c. Please provide comments, suggestions and recommendations to CDR David McGowan, MED-26H, at (202/DSN) 762-3508, fax -0976, or e-mail dgmcgowan@us.med.navy.mil.

2. DEFINITION

- 2a. EXPEDITED REVIEW¹ is the review of proposed research by either the IRB Chair or by one or more designated voting members of the IRB (rather than by the full IRB) in order to facilitate approval prior to the next regularly scheduled IRB meeting without sacrificing protections of the subjects.

3. POLICY

- 3a. Expedited review authority requires specific written delegation by the Institutional Assurance Issuing Authority (MED-26H). Expedited review authority may not be further subdelegated or assigned to a subordinate activity; however, the approving official may specifically subdelegate expedited review approval authority to the IRB Chair.
- 3b. Commands having expedited review authority may use the expedited review process to:
 - 3b(1). Review and approve minimal risk research protocols that fall within one of the categories included in paragraph 4.

¹ Authorized in 32 CFR 219.110 "Expedited Review Procedures for Certain Kinds of Research Involving No More Than Minimal Risk, and for Minor Changes in Approved Research."

Human Use Policy #3

Expedited Review and Approval Procedure

3b(2). Review and approve minor changes to previously approved research protocols.

3b(3). Conduct expedited continuing review and re-approval when the:

3b(3)(a). Initial protocol was reviewed using expedited review procedures; or

3b(3)(b). Protocol meets the criteria of either paragraph 4.H. or 4.I. below.

3c. Expedited review procedure shall not be used:

3c(1). For any classified research projects involving human subjects;

3c(2). For any greater than minimal risk research;

3c(3). For any research involving vulnerable classes of persons such as pregnant women, children or prisoners; or

3c(4). When even inadvertent or unintended identification of the subjects and/or their responses could place them at risk of criminal or civil liability, or could be stigmatizing or damaging to their financial standing, employability, insurability or reputation.

3d. Expedited review may be carried out by one or more experienced reviewers specifically designated by the Chair from among the voting members of the IRB. The reviewer(s) shall not be part of the research team, nor shall they have an apparent conflict of interest in the project.

3e. In conducting the expedited review, the expedited reviewer(s):

3e(1). Have the same responsibilities and may exercise all of the authorities of the IRB, except that they may not disapprove the research. Disapproval requires action by the full IRB.

3e(2). Must determine that there is no more than minimal risk involved and that the proposed activity is eligible for expedited review, citing the specific expedited review eligibility paragraph that applies.

3e(3). May request reasonable changes in the protocol designed to gain approval. They are not, however, obligated to recommend approval, and may refer the protocol to the full IRB at any time for any reason.

Human Use Policy #3

Expedited Review and Approval Procedure

- 3e(4). Must ensure that all requirements are met for obtaining advance informed consent.
- 3e(5). Must ensure that adequate safeguards are in place to protect the subjects and that appropriate precautions are taken to minimize risks related to invasion of privacy and breach of confidentiality.
- 3e(6). Must assign a date for continuing review that shall not be more than one year from the date of the expedited review.
- 3e(7). Shall forward their recommendations to the IRB Chair, who may then approve the research if so authorized in writing by the approving official. Research activities may then begin without awaiting for review by the full IRB.
- 3f. All actions taken under expedited review authority shall be reviewed by the full IRB at the next regular meeting. The full IRB must specifically confirm each action or take appropriate corrective action. Details of their review and votes on recommendations shall be included in the minutes and forwarded to the approving official for action. All actions related to expedited review shall be further subject to oversight review by MED-26H.
4. RESEARCH CATEGORIES ELIGIBLE FOR EXPEDITED REVIEW. The following categories of research may be eligible for expedited review. This list derives from the revised list of categories published in the Federal Register² but takes precedence over it as it is more restrictive. These categories apply regardless of the age of the subjects, except as noted.
- 4a. **Expedited Review Category 1.** Clinical studies of drugs and medical devices when either condition (1) or (2) is met.
- 4a(1). Research on drugs for which an investigational new drug application³ is not required. (Note: Research on marketed drugs in which the research exposure would significantly increase the risks or decrease the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
- 4a(2). Research on medical devices for which either:

² Federal Register Vol. 63, No. 216, November 9, 1998.

³ 21 CFR Part 312

Human Use Policy #3

Expedited Review and Approval Procedure

- 4a(2)(a). An investigational new device exemption application⁴ is not required; or
- 4a(2)(b). The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/ approved labeling.
- 4b. **Expedited Review Category 2.** Collection of blood samples by finger stick, heel stick, ear stick or venipuncture according to the restrictions in the applicable category:
- 4b(1). Healthy nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period, and the collection may not occur more frequently than 2 times per week.
- 4b(2). Other adults and all children⁵. Considering the age, weight, and health of the subjects, the collection procedure, the amount of blood collected, the frequency with which it will be collected, the amount drawn may not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period, and collection may not occur more frequently than 2 times per week.
- 4c. **Expedited Review Category 3.** Prospective collection of biological specimens for research purposes by noninvasive means. Examples:
- 4c(1). Hair and nail clippings collected in a non disfiguring manner;
- 4c(2). Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
- 4c(3). Permanent teeth if routine care indicates a need for extraction;
- 4c(4). Excreta and external secretions (including sweat);
- 4c(5). Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
- 4c(6). Placenta removed at delivery;

⁴ 21 CFR Part 812

⁵ Children are defined as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a).

Human Use Policy #3

Expedited Review and Approval Procedure

- 4c(7). Amniotic fluid obtained at the time of rupture of the membrane prior to or during delivery;
 - 4c(8). Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
 - 4c(9). Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
 - 4c(10). Sputum collected after saline mist nebulization.
- 4d. **Expedited Review Category 4.** Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays, microwaves, or potentially injurious directed energy such as lasers. When medical devices are employed, they must be cleared or approved for marketing. (Note: Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples of activities that may be eligible for expedited review include:
- 4d(1). Physical sensors that are applied either to the surface of the body or at a distant and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
 - 4d(2). Weighing, and testing sensory acuity;
 - 4d(3). Magnetic resonance imaging;
 - 4d(4). Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
 - 4d(5). Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
- 4e. **Expedited Review Category 5.** Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes, such as medical treatment or diagnosis.

Human Use Policy #3

Expedited Review and Approval Procedure

- 4f. **Expedited Review Category 6.** Collection of data from voice, video, digital, or image recordings made for research purposes.
- 4g. **Expedited Review Category 7.** Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus groups, program evaluation, human factors evaluation, or quality assurance methodologies.
- 4h. **Expedited Review Category 8.** Continuing review of greater-than-minimal risk research that was previously approved by the full IRB may be conducted using expedited review procedures if it falls into any one of the following categories:
- 4h(1). Where all three of the following conditions are met:
- 4h(1)(a). The research is permanently closed to the enrollment of new subjects; and
 - 4h(1)(b). All subjects have completed all research-related interventions; and
 - 4h(1)(c). The research remains active only for long-term follow-up of subjects.
- 4h(2). Where no subjects have yet been enrolled and no additional risks have been identified since IRB review; or
- 4h(3). Where all remaining research activities are limited to data analysis.
- 4i. **Expedited Review Category 9.** Continuing review of approved minimal risk research may be conducted using expedited review procedures when the research was originally reviewed by the full IRB only because it did not fit into Categories 2 through 7, as long as:
- 4i(1). The research was not conducted under an investigational new drug application or investigational device exemption, and
 - 4i(2). No additional risks have been identified since the full IRB review.

5. TRANSITIONAL GUIDANCE DUE TO RECENT IMPLEMENTATION OF EXPEDITED REVIEW AUTHORITY

Human Use Policy #3

Expedited Review and Approval Procedure

- 5a. Current federal regulations require the full IRB to perform a CR if the original protocol was reviewed by the full IRB. However, reasonable consideration would suggest a modification to that rule since expedited review has only been recently authorized in the Navy.
- 5b. If your activity holds expedited review authority, and if the protocol would have initially been eligible for expedited review, then the CR may be conducted using expedited review procedures. This special exception must be clearly annotated for every case in the minutes for the benefit of future auditors.
- 5c. This transitional guidance will expire and shall not be used after 31 December 2003.

6. DISCUSSION

- 6a. What's the difference between expedited review and exempt research? Isn't exempt research just approved after expedited review?

6a(1). Not exactly. Expedited review and exempt research are distinct concepts and don't really relate to one another. This summary may help clarify the differences.

6a(2). When a study is first proposed, the IRB Chair determines if it meets the federal definitions of both "research" and "human subjects." If it does meet both definitions, it is by law human use research, and by BUMED policy the proposal is assigned a DoD assurance number and tracked to completion.

6a(3). Next, the IRB Chair determines the level of risk involved. If greater than minimal risk, the proposal must have full IRB review in the usual manner.

6a(4). However, if a proposal involves only minimal risk, it may be eligible for **exemption** if it meets certain specific criteria.

6a(4)(a). The protocol must meet one of the specific criteria for exemption listed in the separate policy on Exempt Research. Those are (naturally) different from the criteria relating to expedited review contained in this document, and care must be taken not to confuse them.

6a(4)(b). By BUMED policy, even an "exempt" protocol is given a DoD assurance number, received annual continuing review and is tracked to completion. This ensures that the research continues to meet the criteria for exemption.

Human Use Policy #3

Expedited Review and Approval Procedure

- 6a(5). If a proposal does not meet the criteria for exemption it requires formal review. This review, however, may either be the usual review by the full IRB or the proposal may be eligible for **expedited review**. To be eligible for expedited review, a protocol must meet the specific eligibility criteria for expedited review herein.
- 6b. What's the difference between the expedited review process and a primary reviewer system? Doesn't a primary reviewer just do the expedited reviews?
- 6b(1). No. A **primary reviewer** specifically facilitates the work of the full IRB, and by definition does not engage in expedited review. The primary reviewer studies a more complex protocol in depth and resolves administrative details prior to consideration by the full IRB. Use of a primary reviewer system allows the full IRB to focus on issues of importance without being buried in administrative detail, but this is separate from expedited review.
- 6b(2). Use of the **expedited review process** allows for quick approval of benign protocols. One or more IRB members are specifically appointed to conduct an expedited review prior to the next regular IRB meeting. They make a recommendation to the IRB Chair, who, if specifically so authorized, may approve the research. This allows the PI to begin at once without having to wait for the next IRB meeting.
- 6c. Like all administrative actions taken by the Chair, expedited review and approval actions must undergo subsequent formal review by the IRB and confirmation by the approving official. Approval using expedited review procedures is only intended only for use in obviously benign cases and is not intended to fast-track approval of a complex or risky protocol facing a deadline.
- 6d. Appropriate consideration must be given to potential non-physical harms when determining the level of risk; these include, but are not limited to, criminal or civil liability, social stigmatization, damage to the subject's financial standing, employability, insurability or reputation.
- 6e. Consideration should be given to requiring destruction of visual or voice data after analysis to prevent unintended misuse. Potentially sensitive research material of any sort would suggest the need for a full IRB review.
- 6f. What about informed consent?

Human Use Policy #3

Expedited Review and Approval Procedure

6f(1). The requirement to obtain advanced informed consent from every subject involved in human use research is absolute⁶ and cannot be waived (except for certain emergency research) even if the research is eligible for expedited review.

6f(2). However, the same does not apply to exempt research; exempt research is not human use research for legal purposes and therefore does not require informed consent.

6g. If my research is listed in Paragraph 4, doesn't that make it minimal risk? No. The types of research activities listed in paragraph 4 are only *eligible* for expedited if the specific protocol involves no more than minimal risk. Inclusion in this list only means that the activity is eligible for expedited review. Similarly, there is no obligation to use expedited review procedures just because a project is eligible.

6h. Does every protocol that was initially reviewed by the IRB have to have continuing review done by the full IRB too?

6h(1). No, some protocols that originally received review by the full IRB can have expedited continuing review. These cases must fit into categories 8 or 9 of paragraph 4, which in effect say:

6h(1)(a). Expedited Review Category 8 – Greater-than-minimal risk research can have expedited continuing review if there is either nothing left to do that is risky, or when nothing has happened yet.

6h(1)(b). Expedited Review Category 9 – Some minimal risk research really should be eligible for expedited review, but doesn't fit into any of the authorized categories. By law these projects must initially receive full IRB review, but the IRB can clearly state that this specific protocol is eligible for expedited continuing review.

7. APPLICATION FOR EXPEDITED REVIEW AUTHORITY. Activities wishing to request local expedited review and approval authority must apply in writing to MED-26H via their chain of command. Requests should specify the expiration date of their Institutional Assurance and specifically state whether or not the IRB Chair will be delegated expedited review approval authority.

⁶ 10 USC 980 amended 28 Dec 01

Human Use Policy #3 Expedited Review and Approval Procedure

8. This Expedited Review policy guidance shall be updated as required and will remain in effect until issuance of the revised BuMed Instruction 3900.6C on Protection of Human Subjects.

Human Use Policy #3 Expedited Review and Approval Procedure

SAMPLE EXPEDITED REVIEW REQUEST LETTER

3900
Ser

From:

To: Chief, Bureau of Medicine and Surgery (MED-26H), 2300 E Street NW,
Washington, DC 20372

Via:

Subj: REQUEST FOR LOCAL EXPEDITED REVIEW AUTHORITY FOR THE
PROTECTION OF HUMAN SUBJECTS

Ref: (a) BUMEDINST 3900.6B Ch-1, Protection of Human Subjects
(b) 32 CFR 219, Protection of Human Subjects (The Common Rule)
(c) DoD Directive 3216.2, Protection of Human Subjects and Adherence to
Ethical Standards in DoD-Supported Research (revision pending signature)
(d) SECNAVINST 3900.39C, Protection of Human Subjects
(e) Human Use Policy #4, Expedited Review and Approval Procedure, revised 14
Feb 02

Encl: (1) [Local written policies regarding expedited reviews]

1. As authorized by reference (a), I request delegation of local expedited review authority to be utilized in support of our program for the protection of human subjects. We will conduct expedited review consistent with the requirements specified in reference (b) through (e) as well as any future guidance from the Chief, Bureau of Medicine and Surgery (MED-26H). My local policies are complete and consistent with this guidance, and are attached as enclosure (1) for your convenience.

2. I understand that expedited review authority depends on our maintaining an institutional assurance issued by the Bureau of Medicine and Surgery, which will expire on _____. If approved, I [do not] intend to subdelegate expedited review approval authority to my IRB Chair, Dr. _____. I further understand that this authority may not be further subdelegated or transferred.

3. My point of contact for the protection of human subjects is _____.

Signature

Copy to:

Human Use Policy #5

CONTINUING REVIEW

Revised 14 February 2002

1. PURPOSE

- 1a. This memo proposes policies and procedures relating to the continuing review process for research conducted or supported by the Department of Navy for which MED-26H has responsibility. These policies will cumulatively form the basis for revisions to the Bureau of Medicine and Surgery (BUMED) Protection of Human Subjects instruction and the Human Use Guidebook.
- 1b. This is a final policy and its provisions should be implemented locally pending receipt of formal guidance.
- 1c. Please provide comments, suggestions and recommendations to CDR David McGowan, MED-26H, at (202/DSN) 762-3508, fax -0976, or e-mail dgmcgowan@us.med.navy.mil.

2. DEFINITIONS

- 2a. CONTINUING REVIEW (CR) is a periodic administrative reevaluation of a human use research project based on requirements in 32 CFR 219.109(e).

3. POLICY

- 3a. CR shall be performed on all ongoing human subject research regardless of the level of risk involved. This specifically includes research found to be exempt. CR involves a complete reevaluation of the risk-benefit ratio based on the actual experience with the conduct of the research and considering recent experience with related work done elsewhere. As experience is gained during the actual conduct of a project, the institutional review board (IRB) shall require revision of the informed consent document (ICD) as necessary to reflect the new understanding of the risks. Only copies of the ICD showing the "Approved" stamp and expiration date shall be used.
- 3b. Monitoring of the actual conduct of the research or the adequacy of the informed consent process is part of the ongoing responsibility of the IRB to ensure the safety of the subjects. The IRB may at any time observe or have a third party observe any part of the consent process or of the research itself.

Human Use Policy #5

CONTINUING REVIEW

4. CONTINUING REVIEW REQUIREMENTS

- 4a. Activities must have clear written local policies fully explaining their CR procedures and specifying the required contents of the principal investigator's summary report.
- 4b. The principal investigator (PI) is responsible for submitting a summary report and supporting documents to the IRB in sufficient time to allow for appropriate continuing review and approval before the end of the current approval period.
- 4c. Human subject research shall not be conducted outside of an approval period. If the approval period expires, federal law requires that the IRB temporarily suspend the project and that work involving human subjects temporarily cease. Administrative extension of the approval period is prohibited. CR must be properly completed and re-approval granted before the end of the approval period in order to avoid interruption of the research.
- 4d. Prolonged suspension due to failure of the PI to provide required documentation shall result in permanent termination of the research. If a project is terminated, a complete initial submission, scientific peer review, IRB review and formal approval (as for a new project) will be required before the work can be resumed.
- 4e. The IRB Chair must temporarily suspend any research in which there is a substantial concern for the safety of subjects, significant deviation from approved procedures, or in which the balance of the risk-benefit ratio appears to have become unfavorable, pending a thorough review of all material information.
- 4f. Approval letters and informed consent documents must clearly state the date of the end of the approval period.
 - 4f(1). This expiration date shall not be more than one year from the date of the convened meeting at which the IRB voted to recommend approval, regardless of when the project was actually approved or started.
 - 4f(2). The duration of the approval period should be based on the level of risk and the specifics of the research; the approval period should not always be a full year but shortened as necessary to help ensure the safety of the subjects. In determining the date of the next CR, consideration must be given to the experience with the research to date, the number of human subjects involved and the level of confidence in the safety of the

Human Use Policy #5 CONTINUING REVIEW

procedures used in the research as well as the nature of the adverse effects that may be anticipated.

4g. It must be clear which IRB holds primary responsibility for ongoing monitoring of research and the conduct of the periodic continuing reviews when the project involves more than one activity, collaborative or cooperative research efforts or joint review agreements.

4g(1). The primary or lead IRB should share its CR report and recommendations with other participating activities to minimize duplication of effort.

4g(2). When the CR is performed by a primary IRB which is outside BUMED's jurisdiction, the responsible naval IRB must still perform CR and make a recommendation regarding re-approval. In conducting their review, they are encouraged to consider the CR report from the primary IRB.

4h. The PI shall submit a summary report to the IRB for its CR that contains at least the following information:

4h(1). A summary of progress to date, significant events, and problems encountered; an explanation for unplanned delays; and a description of all significant changes made in the protocol.

4h(2). A summary of demographics, to include:

4h(2)(a). The total number of subjects who signed a consent form, regardless of whether they actually completed the research,

4h(2)(b). The number of males and of females, and

4h(2)(c). The number of each racial group (Caucasian, African American, Hispanic, Other). This requirement is waived if the original protocol was approved without a specific requirement that this information be obtained from subjects.

4h(3). A description and explanation of all deviations or variances from the approved protocol since the last CR.

4h(4). A description and explanation of any subjects who were inappropriately enrolled in the research; that is, those who either did not meet selection criteria or who met exclusion criteria but were enrolled anyway.

Human Use Policy #5

CONTINUING REVIEW

4h(5). A summary of any recent literature or professional knowledge as well as any special circumstances or considerations that may affect the perception of the risk-benefit analysis.

4h(6). A description of and schedule for work remaining to be done.

4h(7). An accounting of all subjects who signed an informed consent document, identifying factors that affected their participation in the research.

4h(7)(a). Number of subjects who completed the project as expected without problems, complications, or complaints.

4h(7)(b). Number of subjects who did not complete the project and the reason(s) for their failure to finish. This specifically includes accounting for voluntary withdrawals, "no shows" and those lost to follow-up as well as medical disqualifications, deaths, or injuries, even if previously reported.

4h(8). A summary of all complaints relating to the research from any subject, investigator or other person and the action taken to address them.

4h(9). A cumulative summary of all adverse events experienced in the research at all sites since the initiation of the project, with an indication of the importance of any trends or unexpected findings.

4h(10). The PI's analysis of and comments on the project, explaining and providing perspective as appropriate to assist the IRB in understanding and appreciating implications.

4h(11). Documentation of all changes in investigator personnel; attach signed Investigator Assurance statements for new researcher if not previously submitted.

4h(12). An updated version of the ICD reflecting any new information, and including an updated revision number and date in the footer even if there are no changes.

4h(13). Appointment and approval letters for the current medical monitor if a change has occurred.

4i. In conducting the CR, the IRB shall:

4i(1). Review all the information submitted by the PI.

Human Use Policy #5 CONTINUING REVIEW

- 4i(2). Determine that the risk-benefit ratio has not changed unfavorably.
- 4i(3). Consider whether subjects have been able to complete the protocol as planned, and whether the actual risks are as originally anticipated.
- 4i(4). Determine if the study requires verification from sources other than the PI that no new material changes have occurred.
- 4i(5). Determine if the informed consent process has been both adequate and appropriately documented and that only approved informed consent documents are being used, and make recommendations to correct any deficiencies.
- 4i(6). Revise the ICD to reflect new findings, knowledge, or adverse effects, and determine what specific information must be communicated to past subjects who have not previously been given this new information.
- 4i(7). Verify that subjects enrolled fit selection and exclusion criteria, and review subject demographics to ensure compliance with federal gender and diversity requirements.
- 4i(8). Consider whether there has been adequate protection of the subjects' privacy and of the confidentiality of the data, including storage and handling of previously collected personally identifiable data.
- 4i(9). The IRB must specifically approve a new updated ICD.
- 4j. The IRB must document its discussions, recommendations, and votes on each CR separately in the minutes, including individual reviews of exempt projects. Separate packages for approving official action are required for each minimal risk or greater than minimal risk protocol, but administrative actions related to re-approval of exempt protocols may be handled collectively.
- 4k. A primary reviewer system may be used to facilitate review by the full IRB. The primary reviewer should provide a summary to the full IRB, directing the IRB's attention to specific items or considerations of importance. When using a primary reviewer system, each IRB member must receive the complete CR package for each protocol sufficiently in advance to allow for evaluation before the IRB meeting.
- 4l. CR may be conducted using expedited review procedures provided that the activity holds specifically delegated local expedited review authority AND either

Human Use Policy #5 CONTINUING REVIEW

4l(1). the protocol was initially reviewed using an expedited review procedure, or

4l(2). the only activities remaining in the study are eligible for expedited review.

4m. CR using expedited review procedures is not required at any time, and special circumstances may suggest a CR by the full IRB even if the protocol was originally reviewed using an expedited process.

4n. All administrative actions, reports, and documents relating to CR must be submitted to MED-26H for BUMED oversight review.

5. TRANSITIONAL GUIDANCE DUE TO RECENT IMPLEMENTATION OF EXPEDITED REVIEW AUTHORITY

5a. Current federal regulations require the full IRB to perform a CR if the original protocol was reviewed by the full IRB. However, reasonable consideration would suggest a modification to that rule since expedited review has only been recently authorized in the Navy.

5b. If your activity holds expedited review authority, and if the protocol would have initially been eligible for expedited review, then the CR may be conducted using expedited review procedures. This special exception must be clearly annotated for every case in the minutes for the benefit of future auditors.

5c. This special variance will expire and shall not be used after 31 December 2003.

6. DISCUSSION

6a. Human use research is an ongoing process, and it requires continuous vigilance to ensure the safety of the subjects throughout the project. Review and consideration is not "complete" upon approval, and the activity must immediately suspend approval as warranted to protect the volunteer subjects.

6b. The initial IRB recommendations are based on the PI's best assessment about anticipated results, risk, and procedures before starting the study. The CR provides an opportunity to reassess the actual experience while integrating any new information that may have become available from other sources.

6c. Monitoring involves the ongoing or episodic observation of the process for obtaining informed consent and/or of any aspect of the research by representatives of the IRB. Monitoring should be utilized in a degree and

Human Use Policy #5 CONTINUING REVIEW

manner appropriate to the degree of risk. CR, on the other hand, is a formal periodic reevaluation conducted at specific intervals.

6d. The CR due date and the end of the approval period are the same thing. Research cannot legally continue beyond this date.

6e. Regarding specific administrative requirements for the ICD.

6e(1). Some research will uncover additional risks during the course of the project and so ICDs must be revised to reflect this new knowledge. Every ICD must include a footer on each page saying "This is revision # ___ of [date]."

6e(2). After approval the IRB Administrator stamps the current version of the ICD with the statement

"APPROVED [date]. This document may NOT be used after [date]."

This last date must be the date that the current approval period expires. These measures will help ensure that only the appropriate ICD is used, and that it is not used beyond the end of the approval period.

6e(3). A new version of the ICD must be submitted for CR even if there are no changes in the text so that the expiration date can be updated.

6f. When does the "one year" for CR start? According to 32 CFR 219.109(e), CR is required "at intervals appropriate to the degree of risk, but not less than once per year." The reference date is, however, not clear. In concert with other federal agencies, we interpret and standardize this requirement to refer only to the documented date that the IRB made its formal vote recommending approval at a convened meeting; it does not matter when the protocol was finally approved, or when the PI actually gets around to starting the work. Some examples may help.

6f(1). Consider a protocol submitted on 01 January 2001 for an IRB meeting on 15 January. The protocol is discussed and the board votes to recommend approval without changes. The approving official approves the protocol on 20 January and assigns a CR due date of 14 January 2002 – one year from the date that the board voted to recommend approval. The research may be conducted on 14 January 2002, but may not be continued after the 14th without formal re-approval. Continuing with this example, while the PI has permission to begin the research as of 20 January, let's say that equipment

Human Use Policy #5 CONTINUING REVIEW

or funding problems prevent starting until 10 May; the CR is still due on 14 January.

6f(2). Consider another protocol reviewed at an IRB meeting on 15 February 2001. The protocol was deficient, however, and was returned for rewrite without a vote to recommend approval. The IRB then considers the revised protocol at their next meeting on 15 March, and the protocol is recommended for approval. The approving official signs it off on the 20th with a CR due date of 14 March 2002. Continuing with this example, the PI's funding is delayed and he or she still has not started by the following March but does have plans to begin in May. He or she must submit a CR summary and the IRB must perform a CR in order for the protocol to be re-approved before CR due date of 14 March 2002. Obviously the CR report would show that no subjects were enrolled (due to funding problems), but there should still be a re-evaluation of the risk-benefit ratio in light of any new experience that may have been gained in similar research done elsewhere.

6f(3). Consider a protocol reviewed at an IRB meeting on 18 April 2001. The IRB votes to recommend approval but requires minor changes, and specifically authorizes the IRB Chair to review and accept the revisions without it having to be re-reviewed by the full IRB. The PI finally satisfies the requirements by 01 May, and the Chair submits the package to the approving official for action. It is approved on 10 May. While the PI may not begin the research until after its approval on 10 May 2001, the next CR is still due no later than 17 April 2002 since that was one year from the date of the meeting at which the IRB voted to recommend approval.

6g. In making the summary report, the PI should not list each subject individually and provide an explanation of their individual outcome. If more than one subject was dropped or lost for the same reason, it is sufficient to report the number of subjects in that group. For example -- Subjects who signed an ICD: 100. Subject who started the research: 92. (8 did not start because of personal schedule conflicts.) Subjects who completed project: 88. (4 could not complete because of equipment problems.)

6h. The IRB must determine how soon it needs to reevaluate the research in order to minimize the number of subjects who may be exposed to an unknown risk. Consider research involving a new and untried procedure with some appreciable risk of delayed adverse effects. In order to ensure proper evaluation of the early experience, the IRB could require CR in three months, and further add the restriction that no more than ten subjects shall be enrolled.

Human Use Policy #5

CONTINUING REVIEW

- 6i. Regular CR is required for exempt projects to ensure that no significant changes have occurred during the course of the research that would affect its exempt status. The PI could appropriately submit a brief memo describing the actual experience with the research and showing that it continues to qualify for exemption. The CR could be handled by expedited review, with subsequent confirmation by the full IRB at a regular meeting.
- 6j. Each CR is intended to provide a complete overview of the project from its beginning and from all sites of performance. To obtain a complete perspective, the IRB should consider not only new information but the overall experience with the research since its beginning.
- 6k. The best protection of volunteers will occur in a cooperative atmosphere with an ongoing dialogue between the PI, the IRB, and the Command united in their desire to identify and correct problems at the earliest possible time. An "annual inspection" mentality where the PI works in isolation until the time of CR diverts from the primary goal of protecting the volunteer subjects, while tending to encourage a focus on details that just happen to be easy to inspect.
- 6l. It is the PI's responsibility to submit the summary report to the IRB for CR in a timely manner. The IRB Administrators may choose to remind PIs in advance, but it is the PI's responsibility to obtain re-approval. Data obtained outside of an approval period may not be acceptable for publication, presentation, or inclusion in overall analysis.
- 6m. The expedited review process is not the same thing as using a primary reviewer system.
- 6m(1). A **primary reviewer** simply facilitates the work of the full IRB by making an in-depth analysis in advance and resolving straight forward administrative deficiencies before the meeting. The primary reviewer thus allows the board to focus on specific points of interest without being buried in administrative detail. The IRB must not simply accept the primary reviewer's recommendations without proper consideration.
- 6m(2). Under **expedited review** one or more specifically designated IRB members conduct a review in advance of a regular IRB meeting. They ensure compliance with all requirements and make a recommendation to the IRB Chair for action. If authorized by the approving official, the Chair may then permit the PI to begin the research before review by the full IRB. The expedited review is then presented to the full IRB at the next regular meeting and is subject to their confirmation and eventual approving official action. Expedited review authority is not automatic and

Human Use Policy #5 CONTINUING REVIEW

must be specifically delegated in writing from BUMED, and further, the local approving official must specifically authorize the IRB Chair to directly authorize start of the research. See the specific policy on expedited review.

6m(3). Expedited CR could be appropriate for a project in which the only remaining activity would itself qualify for expedited review, even if that project involved greater than minimal risk. For example, expedited CR would be appropriate for a project in which no subjects have yet been enrolled, or for a meningitis treatment study in which the only remaining activity is the long-term follow-up of recovered subjects.

7. This policy may be revised as required.