

Naval Medical Research Center

Institutional Review Board



**Policies and Procedures for the
Protection of Human Subjects in
Research**

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INTRODUCTION

The Naval Medical Research Center (NMRC) Institutional Review Board (IRB) Standard Operating Procedures (SOP) for the Protection of Human Subjects in Research is a reference for IRB members and investigators. This SOP details the policies and procedures governing human subjects' research and the requirements for submitting research protocols for review by the NMRC IRB and approval.

The full ethics documents, applicable regulations and standards referenced in these SOPs are available at the NMRC ORA website, <http://www.nmrc.navy.mil/ora/index.htm> or by contacting the NMRC Office of Research Administration.

IMPORTANT NOTE: Unless specifically stated to the contrary, reference to the NMRC facilities, employees and agents includes its Detachment in Lima, Peru.

For additional reference materials and resource, IRB members and investigators are always welcome to visit or contact the Office of Research Administration.

Chapter 1

Ethical Mandate for Protecting Human Subjects

NMRC human subject research must be carried out in an ethical manner (32 CFR 219.103(b)(1)). The documents discussed in this chapter represent important milestones in the evolving acceptance of ethical principles for the conduct of and development of protections for human subject research¹.

- a. **The Nuremberg Code.** The modern history of human subject protections begins with the post World War II discovery of atrocities committed by Nazi doctors in war-related human research experiments. The Nuremberg Military Tribunal developed ten principles as a means of judging their “research” practices, known as *The Nuremberg Code*. The *Code* is significant because it established the necessity for requiring the voluntary consent of the human subject and placed personal culpability for ensuring the quality of consent on any individual “who initiates, directs, or engages in the experiment.”
- b. **The Declaration of Helsinki.** The Nuremberg Code’s principles were later expanded to further protect subjects. The World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects (1964, latest revision 2000) calls for prior approval and ongoing monitoring of research by independent ethical review committees.
- c. **The Belmont Report.** In the early 1970s, a 40-year United States Public Health Service *Study of Untreated Syphilis in the Negro Male at Tuskegee* and other ethically questionable research resulted in 1974 legislation calling for regulations to protect human subjects and the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to examine ethical issues related to human subject research. The Commission’s final report, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (79 FR 12065, April 17, 1979)*, defines the ethical principles and guidelines for the protection of human subjects. *The Belmont Report’s* most important contribution is its elucidation of three basic ethical principles:
 1. **Respect for Persons** maintained by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations;
 2. **Beneficence** preserved by weighing risks and benefits; and
 3. **Justice** protected by the equitable selection of subjects.

The Belmont Report also provides important guidance regarding the boundaries and interface between biomedical research and the practice of medicine.

¹ The full ethics documents are available at the NMRC ORA website <http://www.nmrc.navy.mil/ora/index.htm> or by contacting the NMRC Office of Research Administration.

Chapter 2 Regulatory Mandate for Protecting Human Subjects

The Federal regulations require specific protections for human subjects. The following is an overview of the most applicable regulations.²

- a. **Department of Health and Human Services (DHHS) Regulations (45 CFR Part 46).** In May 1974, the Department of Health, Education, and Welfare (later divided to form the DHHS and the Department of Education) codified its basic human subject protection regulations at 45 CFR Part 46, Subpart A. Revised in 1981 and 1991, the DHHS regulations, enforced by the Office for Human Research Protections (OHRP), presently include additional protections for pregnant women, human fetuses and neonates (Subpart B); prisoners (Subpart C); and children (Subpart D).

DHHS regulations at 45 CFR Part 46 Subpart A constitute the Federal Policy (Common Rule) for the protection of human subjects. This Common Rule applies to any human subject research supported by any of the seventeen Federal agencies, including DoD, that support human subject research (see Table 2.1).

Table 2.1 Federal Common Rule Departments and Agencies	
Department / Agency	CFR Citation
▪ Department of Agriculture	▪ 7 CFR Part 1c
▪ Department of Energy	▪ 10 CFR Part 745
▪ National Aeronautics and Space Administration	▪ 14 CFR Part 1230
▪ Department of Commerce	▪ 15 CFR Part 27
▪ Consume Product Safety Commission	▪ 16 CFR Part 1028
▪ International Development Cooperation Agency, Agency for International Development	▪ 22 CFR Part 225
▪ Department of Housing and Urban Development	▪ 24 CFR Part 60
▪ Department of Justice	▪ 28 CFR Part 46
▪ Department of Defense	▪ 32 CFR Part 219
▪ Department of Education	▪ 34 CFR Part 97
▪ Department of Veterans Affairs	▪ 38 CFR Part 16
▪ Environmental Protection Agency	▪ 40 CFR Part 26
▪ Department of Health and Human Services	▪ 45 CFR Part 46
▪ National Science Foundation	▪ 45 CFR Part 690
▪ Department of Transportation	▪ 49 CFR Part 11
▪ Central Intelligence Agency	▪ Executive Order
▪ Social Security Administration	▪ Authorizing Statute

² The applicable parts of Titles 21, 32 and 45 of the Code of Federal Regulations are available at the NMRC ORA website <http://www.nmrc.navy.mil/ora/index/.htm> or by contacting the NMRC Office of Research Administration.

- b. Department of Defense (DoD) Regulations (32 CFR Part 219).** In January 1991, the DoD joined 16 other Executive Branch Departments and Agencies in simultaneously adopting the Common Rule. Codified by the DoD at 32 CFR Part 219, the Common Rule is the same as that codified by DHHS as Subpart A of the DHHS regulations at 45 CFR Part 46, but does not include the additional DHHS Subparts. However, DoD and Navy policies, at DoD Directive 3216.2 4.4.1 and SECNAV Instruction 3900.39C 6.b (7), respectively, require that research involving pregnant women, fetuses, neonates, prisoners and children meet the additional protections of 45 CFR Part 46 Subparts B, C and D. The Surgeon General of the Navy through the Human Research Protection Program (Code M00HR) at the Bureau of Medicine and Surgery enforces DoD regulations for naval research activities.

DoD human subject regulations apply to all human subject research conducted by a DoD Component (i.e., intramural) and other research that is supported by a DoD Component (i.e., extramural) through a contract, grant, cooperative agreement or other arrangement. (DoD Directive 3216.2 2.2).

Note: Investigators receiving support from other Federal agencies, such as the National Institutes of Health (NIH), as well as other DoD components such as the Army and Air Force, must meet both those agencies' and Navy requirements for the protection of human subjects.

- c. Food and Drug Administration (FDA) Regulations (21 CFR Parts 50 and 56).** FDA has codified informed consent (21 CFR Part 50), IRB (21 CFR Part 56), and child protection (61 FR 20589 and 21 CFR Part 50, Subpart D) regulations that are almost identical to the DHHS regulations. Additional FDA regulations to protect human subjects address Investigational New Drugs (21 CFR Parts 312 & 314), Radioactive Drugs (21 CFR Part 361), Biological Products (21 CFR Parts 600 & 601), and Investigational Devices (21 CFR Parts 812 & 814).

In general, FDA human subject regulations apply to clinical investigations and other research involving FDA-regulated products, including food and color additives, drugs, medical devices, and biological products for human use, and electronic products, regardless of funding source.

Note: DoD Directive 3216.2 deems the use of investigational new drugs, biological products or devices for purposes of Force Health Protection as non-research activities. Such activities are governed by DoD Directive 6200.2.

Prospective IRB review and approval are required for all clinical investigations and all other research involving FDA-regulated products for human research, even where an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) is not required.

Chapter 3

Command Commitment to Protecting Human Subjects

The Common Rule requires that every institution engaged in Federally-supported human subject research file an “Assurance” to formalize its commitment to protect of human subjects (32 CFR 219.103(a)). NMRC and its detachment, NMRC in Lima, Peru, must provide written assurance to Federal agencies that each one will comply with all Federal laws and regulations governing the protection of human research subjects. As part of this Assurance, NMRC and NMRC must develop procedures for conducting human subject research in a responsible and ethical fashion. The procedures for implementing these requirements are provided in this and subsequent chapters of this manual.³

- a. DoD Navy Assurance.** As a matter of institutional policy, NMRC and NMRC meet the requirements of the DoD human subject protection regulations for all research, without regard to funding source or other support. DoD requires that any Naval or Marine Corps activity conducting, supporting, or participating in a human research effort, regardless of sponsor or subject area, hold a current DoD Navy Assurance as granted by the Surgeon General of the Navy.

NMRC maintains DoD Navy Assurance DoD-N40028 for which the NMRC Commanding Officer serves as the Institutional Signatory Official.

NMRC maintains DoD Navy Assurance DoD-N40029 for which the NMRC Officer-in-Charge serves as the Institutional Signatory Official. NMRC has designated the NMRC IRB for review of research under its DoD Navy Assurance.

- b. Federalwide Assurance and IRB Registration.** Because NMRC’s and its detachment’s activities involve research supported by or in collaboration with other Federal agencies, NMRC must have an assurance accepted by those agencies. Accordingly, NMRC maintains a Federalwide Assurance of Protection for Human Subjects (FWA00000152) approved by the DHHS Office for Human Research Protections (OHRP). The NMRC Commanding Officer is the Institutional authority for establishing and empowering the NMRC IRB and serves as the Institutional Human Subject Signatory Official (Institutional Official or IO) for the NMRC FWA.

NMRC currently operates, and has designated under its FWA, one Institutional Review Board (IRB) (registered as IRB00001008) to accommodate the major portion of NMRC and NMRC human subject research. The NMRC IRB is the “IRB of record” for NMRC human subject research conducted within NMRC facilities, including NMRC, and by NMRC and NMRC employees and agents.

The NMRC FWA also lists the following designated IRBs: NIDBR in Great Lakes, Illinois, NAMRU-2 in Jakarta, Indonesia, and NAMRU-3 in Cairo, Egypt.

³ The terms of the DoD Navy Assurance and Federalwide Assurance will be made available to IRB members and investigators and institutional officials and copies are available at the NMRC Office of Research Administration.

These IRBs serve as the designated IRB of record for NMRC human subject research conducted within facilities of the respective organizations.

c. NMRC FWA Covered Facilities. An “institution” includes both the main facility and any satellite facilities. Accordingly, for purposes of the NMRC FWA, NMRC is comprised of the following facilities:

- C.W. Bill Young Marrow Donor Recruitment and Research Facility in Rockville, Maryland
- Biological Defense Research Directorate Annex in Rockville, Maryland
- Combat Casualty Care Directorate Annex at the Armed Forces Radiobiology Research Institute in Bethesda, Maryland
- Malaria Clinical Trial Center in Bethesda, Maryland
- Naval Medical Research Center Detachment (NMRC D) in Lima, Peru
- NMRC D Field Lab in Iquitos, Peru

NMRC’s Echelon 4 Commands currently rely on NMRC’s FWA: NIDBR in Great Lakes, Illinois, NAMRU-2 in Jakarta, Indonesia, and NAMRU-3 and (its detachment) in Cairo, Egypt.

Chapter 4

Human Subject Research vs. Non-Research Activities

This chapter is intended to provide a reference to assist in determining when an activity is research involving human subjects.

- a. **Important Definitions for the Protection of Human Subjects in Research.** The following important definitions relating to human subject protections are provided here for convenience.
 1. **Research.** DoD regulations at 32 CFR 219.102(d) and the Common Rule define research as “**a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.**” *Note: FDA regulations at 21 CFR 56.102(c) define research as “any experiment that involves a test article and one or more human subjects.” FDA regulations note that “[t]he terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.”*
 2. **Human Subject.** DoD regulations at 32 CFR 219.102(f) and the Common Rule define human subject as “**a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information.**” Navy policy, at SECNAV Instruction 3900.39C 6.b (10), clarifies that human subjects may also include investigators when they serve a “subject” role. *Note: FDA regulations at 21 CFR 56.102(e) define **human subject** as “an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.”*
 3. **Research Involving a Human Being as an Experimental Subject.** Federal statutes at 10 USC 980 refers to research involving human beings as experimental subjects. Enclosure 2 of DoD Directive 3216.2 defines research involving a human being as an experimental subject as “an activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction (32 CFR 219.102(f).” This does not include (i) activities carried out for diagnosis, treatment or prevention of injury and disease in members of the Armed Forces and other mission essential personnel under Force Health Protection programs; (ii) authorized health and medical activities as part of the reasonable practice of medicine or other health professions; (iii) organizational monitoring and compliance programs; and (iv) research satisfying the exempt categories at 32 CFR 219.101(b).

The Office of General Counsel in a 22 October 2004 Memorandum, “Applicability of Human Research Subject Protections to Certain Activities,” further clarified that “research involving a human being as an experimental

subject should be understood as **an activity with all of the following** attributes:

- There is a non-routine intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction;
 - It is part of a systematic investigation to test an hypothesis and permit conclusions to be drawn, usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective; and
 - Its overall primary purpose is to contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships.)”
4. **Private Information.** Federal regulations at 32 CFR 219.102(f) define private information as **any information that an individual can reasonably expect will not be made public, and any information about behavior that an individual can reasonably expect will not be observed or recorded.**
 5. **Identifiable.** Federal regulations at 32 CFR 219.102(f) define identifiable to mean that **the identity of the individual subject is or may readily be ascertained by the investigator or may be associated with the information.**
 6. **Minimal Risk.** Federal regulations at 32 CFR 219.102(f) and 21 CFR 56.102(i) define minimal risk to mean that **the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.**
 7. **Minimal Risk for Prisoners.** In the case of research involving prisoners, federal regulations at 45 CFR 46.303(d) define minimal risk as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Note: The involvement of prisoners of war as human subjects of research is prohibited (DoD Directive 3216.2 4.4.2).

8. **Institutional Review Board (IRB).** An IRB is an appropriately constituted group that has been formally designated to review and monitor research involving human subjects. In accordance with the DoD regulations, the Common Rule, and FDA regulations, the IRB recommends protocol approval, requires modification to secure approval, or disapproves research. The IRB also is authorized to suspend or terminate research for continued non-compliance with the DoD regulations, the Common Rule, FDA regulations, or its own findings, determinations, and initial and continuing review procedures.

- b. Independent Verification that Project is Not Human Subject Research.** NMRC requires that all planned projects involving interaction (direct or indirect) with humans or the use of human specimens or data must be evaluated to determine if the project constitutes research involving human subjects. The investigator may not make the determination unless it is obvious that it is human subject research, in which case, the investigator should proceed directly with protocol development and submission for Scientific Review Board (SRB) and Institutional Review Board (IRB) review.

Determining if a given project is considered human subject research can be subtle and difficult. Accordingly, investigators are to submit relevant information to the IRB Chair or Vice Chair for review and evaluation using the Determination of Human Subject Research Status form (HRPP Form 1). As part of the evaluation, the reviewer must answer two questions: (1) is the project research as defined above; and (2) does the project involve human subjects as defined above. If the answer to both questions is yes, then the project is human subject research and investigators must develop a protocol for review by the SRB and IRB. (See NMRC's *Guide for Researchers: Determination of Human Subject Research* in Appendix I).

For projects that do not meet the definition of human subject research, the IRB Chair or Vice Chair may make recommendations to safeguard the welfare and rights of the involved individuals.

- c. Types of Human Subject Research.** The following examples illustrate common types of human subject research. These are examples only, and are not exhaustive of all human subject research.
- 1. Clinical Research.** Clinical research involves the evaluation of biomedical or behavioral interventions related to disease processes or normal physiological functioning. Clinical research often, but not always, includes drugs, devices, or biological products regulated by the FDA.
 - 2. Biomedical Research.** Biomedical research involves research (i) to increase scientific understanding about normal or abnormal physiology, disease states, or development; and (ii) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials and medical device research are both types of Biomedical Research.
 - 3. Social and Behavioral Research.** The goal of Social and Behavioral Research is similar to that of Biomedical Research—to establish a body of knowledge and to evaluate interventions—but the content and procedures often differ. Social and Behavioral Research involving human subjects focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention. (See also, Chapter 14, “Social and Behavioral Research.”)

4. **Pilot Studies.** Pilot studies are preliminary investigation to assess feasibility or to assist in generating a hypothesis (e.g., provide better estimate for sample size in the future studies). Pilot studies involving human subjects are considered human subject research and require IRB review.
5. **Epidemiology Research.** Epidemiology research targets specific health outcomes, interventions, or disease states and attempts to reach conclusions about cost-effectiveness, efficacy, interventions, or delivery of services to affected populations. Some epidemiology research is conducted through surveillance, monitoring, and reporting programs—such as those employed by the Centers for Disease Control and Prevention (CDC)—whereas other epidemiology research may employ retrospective review of medical, public health, and/or other records. Because epidemiology research often involves aggregate examination of data, it may not always be necessary to obtain individually identifiable information. When this is the case, the research may qualify for exemption or expedited review. In all cases, **the IRB, not the individual investigator, will determine when IRB review of the activity is required.** (See also, Chapter 16, “IRB Considerations Regarding Study Design”).
6. **Repository Research, Tissue Banking, and Databases.** Research utilizing stored data or materials (cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB review. When data or materials are stored in a bank or repository for use in future research, the IRB must review a protocol detailing the repository’s policies and procedures for obtaining, storing, and sharing its resources, for verifying informed consent provisions, and for protecting subjects’ privacy and maintaining the confidentiality of data. The IRB may then determine the parameters under which the repository may share its data or materials with, or without, IRB review of individual research protocols.
7. **Human Genetic Research.** Genetic studies include but are not limited to: (a) pedigree studies (to discover the pattern of inheritance of a disease and to catalogue the range of symptoms involved); (b) positional cloning studies (to localize and identify specific genes); (c) DNA diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); (d) gene transfer research (to develop treatments for genetic disease at the DNA level), (e) longitudinal studies to associate genetic conditions with health, health care, or social outcomes, and (f) gene frequency studies. Unlike the risks presented by many biomedical research protocols considered by IRBs, the primary risks involved in the first three types of genetic research are risks of social and psychological harm, rather than risks of physical injury. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion.

- d. Public Health Surveillance or Response to Outbreak Activities vs. Human Subject Research.** 10 USC 1074(f) refers to the medical tracking system for members deployed overseas. Health surveillance is part of the medical care and public health care functions of the military Health System. It is not human subjects research under 10 USC 980 and the Common Rule. Thus, it is permissible to require military personnel to participate in health surveillance activities.

In cases where the intent of the activity changes after it has begun (e.g., findings from an activity intended solely for internal purposes lead to a desire to generalize and disseminate the results for general application, the activity becomes research at the moment the intent to generalize the findings is formed, and the IRB should be contacted immediately. In such cases, the IRB will determine the conditions under which the investigator may pursue the relevant research objectives.

Investigators must submit a *Determination of Human Subject Research* form (HRPP Form-1) to ORA for activities involving human specimens or data or the interaction or intervention with living human beings. The submission will be evaluated to determine whether the activity meets the definition of human subject research and requires SRB and IRB review. (See Appendices for the forms and guidance).

- e. Quality Assurance Activities vs. Human Subject Research.** Quality Assurance activities attempt to measure the effectiveness of programs or services. Quality Assurance activities constitute human subject research, and require IRB review, when they are designed or intended, at least in part, to develop or contribute to generalizable knowledge.

On the other hand, Quality Assurance activities that are designed solely for internal program evaluation purposes, with no external application or generalization, usually do not constitute human subject research, and usually do not require IRB review.

For example, an occupational health physician conducts a review of personnel files and then contacts employees to assess adequacy of preventive measures (e.g., as a survey). If the sole intent is to improve preventive measures within the facility, then the activity is not human subject research. If the intent is to share the results of the survey with other institutions, then this may be human subject research requiring IRB review.

In cases where the intent of the activity changes after it has begun (e.g., findings from an activity intended solely for internal NMRC purposes lead to a desire to generalize and disseminate the results for application outside NMRC), the activity becomes research at the moment the intent to generalize the findings is formed, and the IRB should be contacted immediately. In such cases, the IRB will determine the conditions under which the investigator may pursue the relevant research objectives.

For example, activities covered by 10 USC 1102 and DoD Directive 6025.13,

“Medical Quality Assurance in the Military Health System,” 4 May 2004 are not generally deemed to be research. Certain program evaluations which assess the success of established program in achieving objectives when the assessments are for the use of DoD program managers, for example, a survey to determine if program beneficiaries are aware of the availability of program services or benefits – generally not considered research. However, as clarified by Office of General Counsel Memorandum, “Applicability of Human Research Subject Protections to Certain Activities,” if it were an assessment carried out for publication in general literature regarding non-DoD programs of a similar type, it would be for a research purpose.

Where any disagreement arises about whether a Quality Assurance activity constitutes human subject research, the IRB, not the individual investigator, will determine when IRB review of such activities is required.

- f. Research Activities vs. Medical Case Reports.** Generally speaking, a case report is not usually considered research because it is not usually “a systematic investigation designed to develop or contribute to generalizable knowledge;” therefore, it does not come under the rubric of the IRB. Further, the case report presentation, whether by lecture or publishing, is executed by the physician of record, meaning that the patient's own physician is reporting the case and already has identified the patient and has access to the clinical data. If the presentation uses photographs, initials, or any other information that may possibly identify the patient, then written permission or a separate consent form for this purpose is required.

There does not appear to be a limit on the number of cases from one's own patients that form a case report and if exceeded, moves the situation into the category of retrospective chart review and then requires IRB approval. Usually, a non-research case report summarizes one case (or occasionally two, or at most three, cases) to emphasize a discrete instance of disease. However, it is the nature of the report, not the absolute number of cases, which determines whether or not the activity involves human subject research. A non-research case report may not involve a systematic investigation characterized as developing or contributing to generalizable knowledge. A non-research case report is limited to an account of an observation or a description of a disease process that has little scientific merit and is not subject to scientific analysis. It is not presented as a systematic investigation designed to contribute to generalizable knowledge. A non-research case report should be presented in such a way that it is readily distinguishable from a research report, which usually contains data with statistical analysis, or at least a systematic qualitative analysis, that substantiates the science and the conclusion and thus constitutes a contribution to generalizable knowledge.

- g. Research Activities vs. Laboratory Services.** NMRC facilities and laboratories may occasionally provide tests or other services to non-NMRC researchers solely on a non-research basis (e.g., NMRC performs assays for non-NMRC investigators as a reference laboratory).

Provision of such services solely on a reference laboratory basis does not

constitute NMRC human subject research and does not require NMRC IRB review, provided that all of the following conditions are met:

- The research is not otherwise conducted at NMRC;
- The research does not otherwise involve NMRC employees or agents (e.g., as co-investigators, in planning or analysis, or receiving publication credit);
- The services are genuinely non-collaborative, meriting neither professional recognition nor publication privileges;
- The services adhere to commonly recognized professional standards for maintaining privacy and confidentiality; and
- The services are conducted under a valid contract or other agreement.

However, if NMRC personnel are involved in any way that is more than merely providing a service, then prospective review and approval of the NMRC IRB is required.

Chapter 5

Shared Responsibilities for Protecting Human Subjects

The ethical conduct of research is a shared responsibility. It requires cooperation, collaboration, and trust among NMRC administrators, investigators and their research staff, the subjects who enroll in research, and the IRB members and staff. Organizational charts related to the Human Research Protection Program at NMRC are provided in Appendix I.

- a. **NMRC Institutional Responsibilities (32 CFR 219.103).** As part of its commitment to responsible and ethical research efforts and in compliance with its written DoD Navy Assurance (DoD-N) and Federalwide Assurance (FWA), NMRC has developed this Standard Operating Procedure for conducting human subject research, including how the IRB will review research, how investigators report unanticipated problems to the IRB and appropriate regulatory bodies, and other issues.
- b. **NMRC Commanding Officer.** The NMRC Commanding Officer serves as the Institutional Signatory Official for NMRC's FWA and DoD-N Assurance. Consequently, the NMRC Commanding Officer is fully responsible for supervising the protection of human subjects within NMRC and its Detachment, including:
 - Overseeing the development and implementation of NMRC policies governing the NMRC IRB, all NMRC human subject research, and all NMRC investigators and research personnel.
 - Maintaining open channels of communication among all parties involved in the NMRC human subject protection process.
 - Ensuring that the NMRC IRB has sufficient meeting space and staff to support its substantial review and record keeping responsibilities.
 - Overseeing the operation and administration of the NMRC IRB and determining that the IRB complies with all Federal, State, and local laws and regulations that govern research involving human subjects.
 - Assuring that IRB members and investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and all applicable regulations.
 - Ensuring that DoD, DoN, or other funds for research involving human subjects are not expended unless the requirements of the DoD Navy Assurance have been satisfied.
 - Developing and implementing an educational plan for IRB members, staff and investigators.

- Establishing and maintaining policies to ensure that the Commanding Officer and IRB Chair are promptly notified regarding (i) any unanticipated problem involving risks to subjects or others; (ii) any serious or continuing non-compliance with IRB requirements by research investigators; or (iii) any for-cause suspension or termination of IRB approval.
 - Ensuring notification of the BUMED, OHRP and FDA of such incidents in accordance with applicable Federal regulations. Such notice will be accomplished in coordination with the Director of the Office of Research Administration and IRB Chair.
 - Overseeing implementation of a research compliance monitoring process that provides monitoring reports, as appropriate, to the Institutional Signatory Official and IRB Chair.
 - For NMRC initiated research requiring an IND, serving as the IND holder and sponsor representative signing the FDA Form 1571.
 - Forwarding the following to the Assistant Secretary of the Navy, Research, Development and Acquisition (ASN(RDA)) for approval: (i) research involving severe or unusual intrusions, either physical or psychological, on human subjects (e.g., consciousness-altering drugs, abnormal environments involving extreme risk); (ii) research involving prisoners; (iii) requests for waiver of requirements not otherwise permitted by federal codes and regulations (e.g., exception from informed consent requirements for emergency research); and (iv) research with potential political or public embarrassment to the DoN or DoD.
- c. **NMRC D Officer-in-Charge.** Under the terms of the NMRC D DoD Navy Assurance, the NMRC D Officer-in-Charge is responsible for supervising and monitoring the conduct of human subject research conducted at NMRC D or by NMRC D employees or agents.

As part of this effort, all submissions to the NMRC IRB must be routed through the NMRC D Officer-in-Charge. (See NMRC D's "*Policies and Procedures for Monitoring and Overseeing Human Subject Research at Naval Medical Research Center Detachment*".)

- d. **Directors and Department Heads.** Directors and Department Heads are best positioned to oversee investigators under their supervision as well as determine whether resources such as space, personnel, etc., are appropriate to properly conduct the research. All submissions for IRB review must be routed through investigator's chain in command.
- e. **Director, Office of Research Administration (ORA Director).** The ORA Director is delegated responsibility for managing the NMRC Human Research Protection Program, including the operations of the IRB. The ORA Director:

- ensures that properly executed institutional assurances in accordance with OHRP procedures and DoD regulations are submitted
- recommends appointment of IRB members to the IRB Chair and Commanding Officer
- develops and updates policies, procedures and forms related to the protection of human subjects
- liaises with other institutions to negotiate research review agreements
- develops, implements, and maintains compliance and training activities for the NMRC research program

The ORA Director also works closely with the IRB Chair, members, staff and researchers to ensure compliance with laws and regulations to ensure the protection of human subjects in research. To this end, the ORA Director's responsibilities also include:

- serving as the primary resource concerning compliance issues,
 - coordinating communication with the Bureau of Medicine and Surgery (BUMED) on human studies,
 - responding to the BUMED's requests or those of higher authority,
 - coordinating site visits as may occur by DoD, FDA, or OHRP.
- f. **Scientific Review Board (SRB).** The SRB is NMRC's committee charged with conducting a scientific review of all human subject research including research exempt from the human subject protection regulations conducted by NMRC and NMRC investigators. (See NMRC Instruction 3900.4). The SRB review differs from IRB review in that it involves assessing the research's scientific quality and the investigator's qualifications. All research protocols must receive scientific review before submission to the NMRC IRB and the SRB Chair will determine whether reliance on another institution's scientific review is appropriate.
- g. **Institutional Review Board (IRB).** The NMRC IRB is formally designated to review and monitor research involving human subjects to protect the rights and welfare of the subjects. It also provides oversight and monitoring of such protections. In accordance with the Common Rule, DoD and FDA regulations, the NMRC IRB recommends approval, requires modification to secure approval, or disapproves research.

NMRC IRB review all human subject research conducted (i) completely or partially at NMRC; (ii) in approved off-site locations, facilities; and/or (iii) by NMRC employees or agents while on official duty time, regardless of whether the research is funded or regulated by any government agency.

In limited circumstances (i.e., collaborative research ventures) and at the discretion of the NMRC Commanding Officer, NMRC may rely on the

collaborative institution's IRB in lieu of NMRC IRB review. (See also, Chapter 10 on collaborative research). In such circumstances, NMRC retains responsibility for monitoring the conduct of research at NMRC facilities by its employees and agents.

The NMRC IRB must report any serious unanticipated problems involving risks to subjects or others, serious or continuing non-compliance, suspensions or terminations of IRB approval to the Commanding Officer, any other relevant official or committee of the NMRC, BUMED and any other applicable sponsors or agencies.

- h. Principal Investigators (PI).** As the individual responsible for the implementation of research, the PI bears direct responsibility for protecting every research subject. This responsibility starts with protocol design, which must minimize risks to subjects while maximizing research benefits and continues through the life of the project, including the informed consent process, regardless of which members of the research team actually obtain and document consent. Finally, the PI and all members of the research team must comply with the findings, determinations, and requirements of the IRB.

For DON-supported intramural research, a PI must be a current federal employee (uniformed or civilian, staff, or trainee), covered under the Intergovernmental Personnel Act (IPA), or a consultant consistent with the requirements established by 5 USC 3109. Status as a contractor or federal retiree is not sufficient to qualify individuals as a PI for such research.

For DoN-supported extramural research, the PI must meet the criteria established by the institution that receives the award.

Principal Investigators must:

- Review the terms of NMRC's FWA and DoD Navy Assurance, this IRB SOP or the Investigator Guidebook, DoD regulations and requirements for the protection of human research subjects, relevant DHHS and FDA regulations, and the Belmont Report.
- Ensure at all times that the research complies with all applicable Federal, State, and Local regulatory requirements and with the determinations of the NMRC IRB.
- Ensure that all human subject research conducted at NMRC and/or on official duty time, has received prospective review and approval by the NMRC IRB.
- Ensure that continuing IRB review and approval of the research are secured in a timely fashion.
- Ensure that no changes in approved research are initiated without prior review by the NMRC IRB and approval, except where necessary to

eliminate apparent immediate hazards to subjects; and that no research is continued beyond the IRB-designated approval period.

- Ensure that the NMRC IRB is notified in a timely manner of (i) any injuries or unanticipated problems involving risks to subjects or others; (ii) any serious adverse events experienced by subjects; (iii) any adverse events reported to the study sponsor; and (iv) any serious or continuing non-compliance with applicable regulatory requirements or determinations of the IRB of which they become aware.
- Report all events to the Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), if used, and report a summary of the DSMB/DMC findings to the NMRC IRB.
- Maintain complete and accurate records regarding all communications with the NMRC IRB, the sponsor, and any Federal Agency, and make such records available to the NMRC Institutional Official and/or delegate immediately upon request.
- Make a final report to the NMRC IRB and to the sponsor within 90 days after the completion or discontinuance of a research project, or of withdrawal of the exemption for a research project.
- Provide the NMRC IRB with copies of any reports or correspondence to or from any regulatory or compliance enforcement Federal agency, such as BUMED, OHRP, or FDA, that exercises oversight over the protection of human subjects in research in which they are involved.

If the investigator leaves NMRC or NMRCDD, the original research records must be retained at the facility. Additionally, the investigator must submit a protocol amendment to change the Principal Investigator as appropriate.

- i. **NMRC/NMRCDD Lead Investigators.** A NMRC/NMRCDD Lead Investigator is required if the Principal Investigator is not a NMRC or NMRCDD employee. Lead Investigators will serve as the point of contact for research submitted to the NMRC IRB and will be responsible for the conduct of research at NMRC or NMRCDD. Specifically, Lead Investigators are responsible for ensuring compliance with applicable DoD and DoN regulations and requirements, as well as NMRC policies and procedures for the protection of human subjects.
- j. **Co-Investigators (or Associate Investigators).** Co-investigators are individuals who significantly contribute to the creation and/or conduct of the study. Co-investigators work under the supervision of the Principal and/or Lead Investigator.
- k. **Other Members of the Research Team.** Every member of the research team is responsible for protecting human subjects. Study coordinators, nurses, research assistants, and all other research staff have a strict obligation to comply with all IRB determinations and procedures; adhere rigorously to all protocol requirements; inform investigators of all adverse reactions or unanticipated problems involving risks to subjects or others; oversee the adequacy of the

informed consent process; and take whatever measures are necessary to protect the safety and welfare of subjects.

Researchers at every level are responsible for notifying the NMRC IRB promptly of any serious or continuing non-compliance with applicable regulatory requirements or determinations of the NMRC IRB of which they become aware, whether or not they themselves are involved in the research. Researchers may also notify the IRB Chair or ORA Director directly of any compliance concerns.

- l. Research Subjects.** Subjects are expected to make every effort to comprehend the information researchers present to them so that they can make an informed decision about their participation in good faith. While participating, they should also make every reasonable effort to comply with protocol requirements and inform the investigators of unanticipated problems. Subjects always have the right to withdraw their participation in research at any time and for any reason without penalty or loss of benefits to which they would otherwise be entitled.
- m. Additional Institutional Committees.** NMRC requires that all human subject research also be reviewed by (i) the WRAMC Safety Radiation Committee if the research involves ionizing radiation exposure; and/or the (b) Institutional Biosafety Committee if the research using recombinant DNA.

The Commanding Officer may establish additional reporting relationships between the NMRC IRB and other officials, including the ORA Director, or other committees, as appropriate.

Chapter 6

IRB Roles and Authorities

An Institutional Review Board (IRB) is an appropriately constituted group that has been formally designated to review and monitor research involving human subjects.

- a. **Subject Protections under Federal Regulations.** DoD regulations at 32 CFR Part 219 require that institutions engaging in human subject research devise mechanisms for the protection of human subjects in accordance with the Common Rule. The regulations require that each institution conducting human subject research file a written “Assurance” of protection for human subjects and designate one or more Institutional Review Boards (IRBs) to review its human subject research.

The NMRC IRB must comply with the requirements of all relevant regulatory agencies including BUMED and other DoD offices, DHHS Office for Human Research Protections (OHRP), and the Food and Drug Administration (FDA). Copies of any reports or correspondence to or from such agencies must be provided by the NMRC IRB to the Institutional Official.

- b. **Oversight of the NMRC IRB.** The NMRC Commanding Officer, who serves as the Institutional Official, is responsible for oversight of regulatory compliance for all human subject research activities conducted under the auspices of NMRC. The NMRC Commanding Officer is empowered to give final approval for initiation of a study recommended for approval by the IRB, or disapproval of a study recommended for approval by the IRB. The Commanding Officer cannot overturn an IRB decision for disapproval, nor impose less human subjects’ protections in a project without IRB recommendation for approval.

The NMRC IRB will regularly forward copies of its meeting minutes, which will include information on IRB findings and actions, to the Commanding Officer for review. The NMRC IRB must report any unanticipated problem involving risks to subjects or others to the NMRC Institutional Official for reporting to BUMED and other agencies as required.

The NMRC IRB will regularly forward copies of its meeting minutes and documentation supporting its findings to BUMED for headquarters level administrative review.

- c. **Purpose and Mission of the IRB.** The IRB’s primary responsibility is to protect the rights and welfare of participants involved in human subject research (32 CFR 219.109). In doing so, the IRB monitors human subject research to determine that it is conducted ethically, and in compliance with applicable DoD and Federal regulations, applicable State law, NMRC’s DOD Navy and Federalwide assurances, memoranda of agreement (e.g., joint research review agreements), and NMRC’s policies and procedures for protecting human subjects.

The IRB fulfills these responsibilities by conducting prospective and continuing

review of human subject research, including review of the protocol and grant applications or proposals (regardless of funding source), the informed consent process, procedures used to enroll subjects, and any adverse events or unanticipated problems reported to the IRB. Prospective review and approval of research or changes to previously approved research ensures that research is not initiated without IRB review and approval.

In communications to investigators, the NMRC IRB will make investigators aware of the requirement to submit protocol changes to the IRB for review and approval before initiation of such changes except where necessary to eliminate apparent immediate hazards to the subject.

d. Scope of the IRB's Review Authority. The NMRC IRB has regulatory authority to take any action necessary to protect the rights and welfare of human subjects in the NMRC research program. Pursuant to DoD regulations at 32 CFR 219.109(a), the NMRC IRB has authority to:

- recommend approval, require modification to secure approval, or disapprove human subject research.
- suspend or terminate research for continued non-compliance with the Common Rule, DoD, DHHS and FDA regulations, or its own findings, determinations, and requirements (32 CFR 219.113).
- observe and/or monitor NMRC research to whatever extent it considers necessary to protect human subjects.

NMRC retains the authority to prohibit conduct of research within its facilities or by its employees or agents that it deems not to be in its best interests (e.g., research that is not consistent with the mission of NMRC, the Naval Service or DoD; research that would require skills or resources that are not readily available; or research that might result in unacceptable fiscal or reputational risks).

- 1. Requirement for Prospective Review and Approval.** All human subject research conducted at any NMRC facility or by any NMRC employee or agent must be prospectively reviewed and recommended for approval by the NMRC IRB. No human subject research may be initiated or continued at any NMRC component or by any NMRC employee or agent without prospective approval of the NMRC IRB.
- 2. Adding a New Site to an Existing Approved Protocol.** Any NMRC component or investigator desiring to add a new site to an existing IRB-approved protocol must submit the request with all required materials to the NMRC IRB for prospective review and approval.
- 3. Power to Take Action.** The NMRC IRB is empowered to take any action necessary to protect the rights and welfare of human subjects participating in NMRC research.

4. **Power to Suspend or Terminate Enrollment.** The NMRC IRB may suspend or terminate the enrollment and/or ongoing involvement of human subjects in research as it determines necessary for the protection of those subjects, especially in instances of serious or continuing non-compliance.
 5. **Cases of Serious or Continuing Non-compliance.** In cases of serious or continuing non-compliance, the NMRC IRB may: (i) disqualify an investigator from conducting a particular research project or research altogether at the institution; (ii) require education and training in the ethics and regulations of human subject research; or (iii) take any other reasonable and appropriate action necessary to protect research subjects. (See also Chapter 19, “Managing Allegations of Serious or Continuing Non-Compliance.”)
 6. **Access to Regulatory Correspondence.** All persons conducting research within any NMRC or NMRCDC facility, and all persons acting as employees or agents of NMRC or NMRCDC regardless of location, must promptly provide the NMRC IRB with copies of any reports, audit findings, or correspondence to or from any regulatory agency (such as OHRP or FDA) that bear upon the protection of human subjects in research in which they are involved. The IRB will review such correspondence to determine if action is needed to protect human subjects.
 7. **Access to Institutional Officials.** The NMRC IRB or any IRB member may bring any matter directly to the attention of the NMRC Institutional Official or the Director of the Office of Research Administration when warranted.
- e. **Command Approval Authority.** For Naval research, the review and approval authorities are two responsibilities. The NMRC Commanding Officer serves as the NMRC IRB Approval Authority. In the absence of the Commanding Officer, the Executive Officer and/or Acting Commanding Officer may serve as the Approval Authority if he/she has completed the requisite training and education required for institutional officials and approval authorities.
- The NMRC IRB Chair has been delegated review authority for research eligible for expedited review under 32 CFR 219.110. All actions conducted via expedited procedures must be reported to the IRB at the next convened meeting. The IRB and the Commanding Officer may require additional information or revisions to safeguard subjects.
- f. **IRB Relationships within NMRC.** The NMRC IRB may require that human subject research also be reviewed by other NMRC committees as appropriate, including the Scientific Review Board, the Institutional Biosafety Committee, and the WRAMC Radiation Safety Chair, etc.
 - g. **Appeal of IRB Determinations.** No NMRC or NMRCDC committee or official may set aside or overrule a determination by the NMRC IRB to disapprove or require modifications in human subject research. No NMRC or NMRCDC committee or official may permit the conduct of human subject research that has not been approved by an IRB officially designated by NMRC. The NMRC IRB must

provide the research investigator with a written statement of its reasons for disapproving or requiring modifications in proposed research and must give the investigator an opportunity to respond in person, by teleconference, or in writing. The NMRC IRB will evaluate the investigator's response in reaching its final determination.

- h. Relationship of NMRC IRBs to Other Institutions.** The NMRC IRB may be designated for review of research under another institution's FWA (or other Assurance) only with the written agreement of NMRC's Institutional Official and in accordance with applicable SECNAV requirements. Any such designation must be accompanied by a written agreement specifying the responsibilities of the facility and its IRB under the other institution's FWA (or other Assurance). The NMRC IRB has no authority over, or responsibility for, research conducted at other institutions in the absence of such a written agreement.
- i. Relationship of the NMRC IRB to IND/IDE Sponsors.** Unless specifically required by an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) sponsor or by the IRB, no written notifications of IRB decisions will be provided to IND/IDE sponsors by the IRB. The Principal Investigator serves as the communications link between the IRB and the sponsor for this purpose. For FDA-regulated test articles, such a liaison is permitted when the PI and sponsor sign the FDA Form 1572, Statement of Investigator.
- j. Headquarters Level Administrative Review.** For naval research, a headquarters level administrative review is defined as a post-approval review of research protocols for the purpose of quality improvement and quality assurance. The review will assess that NMRC IRB has completed all items as required under pertinent regulations. Headquarters level administrative reviews are required for all new protocols, continuing reviews, amendments, deviations, unanticipated problems to subjects or others, adverse events, and final reports.
- k. Ongoing Monitoring Initiatives.** The NMRC IRB is responsible for reviewing all audit findings or other reports (e.g., medical monitor, DSMB or DMC reports) related to any NMRC research. In doing so, the NMRC IRB should determine and document in IRB records whether or not corrective action may be warranted. This may be conducted via expedited procedures, except that where more than a minor change may be needed to protect human subjects, the review will be referred to the convened IRB.

In addition to the regular reporting to the IRB, NMRC's ongoing monitoring program also includes the following initiatives:

- 1. Investigator Protocol File Audits.** ORA, in collaboration with the IRB Chair or Vice Chair will audit at least six investigator protocol files or 20% of the IRB portfolio, whichever is greater each year. The audit will consist of meeting with the investigator, conducting an audit of the signed informed consent documents, and reviewing his/her research protocol documentation, to verify that investigators maintain, at a minimum, the following research documents:

- Research protocol, including all supporting documents (data abstraction forms, recruitment materials, advertisements, etc.) approved by the IRB.
- Informed Consent Document, if applicable, approved by the IRB.
- Approval letter, including IRB approval, to start the research.
- Continuing review reports, amendments, other reports (unanticipated problems or adverse events), and the final report.
- Letters approving continuing review and amendments.
- All correspondence between investigators, NMRC IRB and other reviewing IRBs.
- Host country approvals, if applicable.

The audit will also verify that research documents and databases are secured to maintain privacy and confidentiality as described in the research protocol. Additionally, the audit may also include verifying that investigators are appropriately tracking selected options regarding the future use of specimens, etc., as laid out in the protocol and informed consent document.

- 2. Publication Clearance Program.** NMRC requires that all manuscripts, abstracts and presentations related to human subject research be routed through the Command for clearance. ORA is charged with administering the Command clearance program. As part of the clearance process, ORA will compare the publication with the protocols on file. Any discrepancies will be reported to the IRB Chair.

(See also Chapter 19, “Managing Allegations of Serious or Continuing Non-Compliance.”)

- 1. IRB Self-Assessments & Monitoring.** The NMRC IRB will conduct regular self-assessments to identify areas of review and operations which may require further enhancement and strengthening.

Chapter 7

IRB Structure and Membership

The NMRC IRB shall have sufficient expertise to review the broad variety of research in which NMRC commonly becomes involved, shall be knowledgeable about all relevant regulatory requirements, and strive to remain impartial and objective in its reviews.

- a. **IRB Membership Requirements.** In compliance with DoD regulations at 32 CFR 219.107, the Common Rule, and FDA regulations, and additional Department of the Navy (DoN) requirements, the NMRC IRB must satisfy the following requirements:
- The IRB shall have at least five members.
 - IRB members shall possess varying professional backgrounds to promote complete and adequate review of research activities commonly conducted at or by NMRC investigators. For example, because FDA regulated research is conducted at NMRC and NMRCDC, FDA requires a licensed physician on the IRB.
 - IRB members shall be sufficiently diverse relative to race, gender, cultural background, and sensitivity to community attitudes so as to promote respect for the IRB's advice and counsel in safeguarding the rights and welfare of human subjects.
 - IRB members shall include persons able to ascertain the acceptability of proposed research in terms of institutional commitments, regulations, applicable law, and standards of professional conduct and practice.
 - The NMRC IRB will not consist entirely of members of one profession.
 - The NMRC IRB shall include at least one member whose primary concerns are in scientific areas.
 - The NMRC IRB shall have at least one member whose primary concerns are in non-scientific areas. This person **must** always be present to have a quorum. (See discussion of quorum.)
 - The NMRC IRB shall include at least one member who is not otherwise affiliated with NMRC and who is not part of the immediate family of a person who is affiliated with the NMRC.
 - The NMRC shall include at least one member who is active duty military.
 - IRB members must be current federal employees, individuals assigned under the Intergovernmental Personnel Act (IPA), or consultant consistent with the requirements established by 5 USC 3109. Status as a

contractor or federal retiree is not sufficient to qualify as a federal employee for the purpose of IRB membership.

- b. Appointment of IRB Members, Length of Service, and Duties.** New members of the NMRC IRB are nominated by the ORA Director and IRB Chair, and formally appointed by the Commanding Officer. The Commanding Officer must officially appoint members in writing. Members serve 2-year staggered terms and may be reappointed indefinitely.

Members are responsible for ensuring that the rights and welfare of research subjects are protected. Members vote to approve, require modifications in, disapprove, or defer research submitted to the IRB. Members are expected to attend IRB meetings on a regular basis, serve as Primary Reviewers for research within their areas of expertise, and serve as general reviewers on all research discussed at convened meetings. Members may also be asked to participate in other subcommittees, audits, and education, as long as there is no conflict of interest with the IRB responsibilities.

Any member of the NMRC IRB may be removed by the NMRC Commanding Officer (i) for failure to perform the duties of an IRB member, including failure to attend at least 2/3 of the IRB meetings held within any 12-month period; or (ii) for scientific misconduct or conflict of interest.

- c. Appointment of IRB Chair, Length of Service, and Duties.** The Chair of the NMRC IRB is formally appointed in writing by the Commanding Officer. The IRB Chair's appointment will be reflected in his/her position description indicating the percentage of his/her official time to be reserved for IRB related matters. In addition to the responsibilities of IRB membership, the Chair has primary responsibility for the following:

- Conducting each meeting in an orderly manner. The Chair is responsible for chairing the meeting, conducting business so that each proposal is fairly and completely reviewed, seeing that the IRB reaches a decision on the disposition of each proposal and ensuring that these decisions are communicated to the individuals who submitted the proposal.
- Reviewing and approving research utilizing expedited review procedures in accordance with DoD and FDA regulations.
- Reviewing, as needed and as delegated by the IRB in appropriate circumstances, responses from investigators to determine if they respond sufficiently to the IRB's concern to allow approval under expedited review procedures and without being returned to the fully convened IRB.
- Signing correspondence on behalf of the IRB.
- Recommending the Vice Chair(s) for appointment by the Commanding Officer. The Vice Chair will be a senior member of the IRB who will assume the responsibilities of the Chair during any period of the Chair's absence.

- Reviewing IRB policies and procedures at least annually to confirm current compliance with all Federal, State, and local requirements for the protection of human subjects.

The Commanding Officer may relieve an individual as IRB Chair for failure to fulfill the duties listed above. The Commanding Officer may remove the Chair from the IRB (i) for failure to perform the duties an IRB member, including failure to attend at least 2/3 of the IRB meetings held within any 12-month period; or (ii) for scientific misconduct or conflict of interest.

- d. **Alternate IRB Members.** The NMRC IRB, at its discretion, may recruit alternate members to substitute for regular members of the IRB. The backgrounds of alternate members should be similar to the member they are replacing or they should be able to represent similar interests. Alternate members must be listed on the IRB's official membership roster, which must specify which member (or members) the alternate is qualified to replace. *Note: Although an alternate may be qualified to replace more than one regular member, only one such member may be represented by the alternate at any convened meeting.*

Alternate members are expected to attend all meetings and serve as primary and secondary reviewers similar to regular members of the IRB. Alternate members will have voting rights, except that they may not vote at meetings attended by their respective regular members. Alternate members will be included in determining or establishing quorum at meetings when their respective regular members are absent, but not when those regular members are present.

Procedures for appointment, terms of appointment, length of service, and duties are the same as for regular IRB members.

- e. **Research Administrative Officials May Not Serve as IRB Voting Members.** Research administration personnel including, but not limited to the Research Services Director, ORA Director, and ORA staff, may not serve as voting members of the IRB.
- f. **Consultants to the IRB.** At its discretion, the NMRC IRB may recruit (non-voting) consultants (sometimes referred to as "non-voting" or "ex officio" members) whose presence at the meetings would aid the IRB in conducting its duties.
1. **Ad Hoc Consultants.** Ad Hoc Consultants serve on an as-needed basis and generally attend IRB meetings only when their special expertise is needed. Ad Hoc Consultants may have access to all documents submitted to the NMRC IRB that are pertinent to the research under review, may participate in IRB deliberations, and make recommendations to influence IRB determinations. However, Ad Hoc Consultants may not vote on IRB determinations. Ad Hoc Consultants will not be included in determining or establishing quorum at IRB meetings.

- 2. Continuing Consultants.** Continuing Consultants generally attend all IRB meetings. They may have access to all documents submitted to the NMRC IRB, may participate in IRB deliberations, and make recommendations to influence IRB determinations. However, Continuing Consultants may not vote on IRB determinations. Continuing Consultants will not be included in determining or establishing quorum at IRB meetings.
 - 3. ORA Director.** The ORA Director serves as a resource, providing special expertise in regulatory compliance in human subject research. In this capacity, the ORA Director will advise the IRB as to fulfilling its function to protect the rights and welfare of human subjects in a manner consistent with the regulatory requirements of the Federal, State and Local laws and regulations as well as additional DoD requirements.
- g. Secret Clearance Requirement for Review of Classified Research.** Classified research with human subjects is held to the same ethical principles and human subject protection. However, classified research is not eligible for review using expedited procedures. In order to review research, all reviewing NMRC IRB members must have secret clearance. At this time, not all members of the NMRC IRB have secret clearance and until such clearance has been established, all classified will be referred to a higher research approval authority for review.
- h. Conflicts of Interest.** No IRB member may participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB (32 CFR 219.107(e)). IRB members, including the Chair, who have conflicting interests are required to disclose such interests and to absent themselves from deliberations, quorum counts, and votes on the relevant protocol. Such absences are recorded in the meeting's minutes. (See also, Chapter 18).

While many IRB members also conduct research, it remains their ongoing responsibility to disclose any real or apparent conflicting interests to appropriate NMRC officials and to absent themselves appropriately from any IRB deliberations which presents a conflict.

- i. Education and Professional Development of IRB Members.** The terms of the DoD-Navy Assurance and the Federal-Wide Assurance (FWA) specify that NMRC and NMRCDC is required to have a plan to provide education about human subject protections for IRB members. Upon receiving an appointment to the IRB, a member receives comprehensive reference materials (including this SOP) necessary to review research from an ethical and regulatory perspective. IRB members will also be required to complete education modules as directed by BUMED (see also NMRC Policy and Procedures on Human Subject Protection Training). New members will have the opportunity to observe several IRB meetings before they are assigned studies as primary or secondary reviewer.

Members will periodically be provided with continuing education opportunities within NMRC, NMRCDC or at neighboring institutions, and resources will be made available each fiscal year for one or more IRB members to attend national or regional human subject protection meetings. Additional continuing education

requirements may be established as deemed necessary by the NMRC **Institutional Official or by BUMED.**

- j. Compensation of IRB Members.** The NMRC does not provide monetary compensation to IRB members for their service on the IRB. However, it is acknowledged that service on the IRB requires a significant investment of time for all IRB members and especially for IRB Chairs.
- k. Liability Coverage.** Actions for alleged negligence or wrongful acts or omissions of Federal employees come within the provisions of the Federal Tort Claims Act (FTCA). The coverage extends to the federally employed IRB members acting in performance of their duties, including individuals assigned to NMRC or NMRCDC under the Intergovernmental Personnel Act (IPA). The coverage does not extend to individuals appointed to the IRB under 5 USC 3109.

***Note:** Such protections may be provided on a case-by-case basis at the discretion of the DoD and the Department of Justice. For more information, please contact the IRB Office or NMRC's Legal Office.*

Chapter 8

IRB Administrative Support

The Department of Defense (DoD) regulations at 32 CFR 219.103(b)(2) and the Common Rule require that NMRC provide its IRB with sufficient meeting space and staff to support the IRBs' review and record keeping responsibilities.

- a. **Resource Allocation.** The Commanding Officer is ultimately responsible for ensuring the protection of human subjects at the NMRC and NMRC research program. To this end, the Research Services Director, in consultation with the ORA Director, shall allocate on an annual basis sufficient resources to support the IRB review and record keeping responsibilities, according to the terms and conditions of the DoD Navy Assurance and the Federal-Wide Assurance (FWA).

The NMRC IRB will be supported by at least one IRB Administrator with part-time administrative support.

- b. **Reporting Lines and Supervision.** Relative to human subject protection issues, the IRB Administrator takes direction from the IRB Chair. For administrative purposes, the IRB Administrator reports to the ORA Director. IRB support staff takes direction from the IRB Administrator and ORA Director.
- c. **Initial Training, Continuing Education, and Professional Development of IRB Staff.** NMRC is required under its assurances to have a plan to provide education about human subject protections for IRB staff. DoD policy requires a continuing education plan for human subject protections for IRB staff per the terms and conditions of the FWA. At a minimum, all IRB staff and the ORA Director, must complete the initial educational modules as directed by BUMED (see, NMRC *Research Education: Policies and Procedures for Human Subject Protection Education and Training*). IRB staff and the ORA Director will be provided resources to attend national or regional human subject protection conferences on a periodic basis. NMRC strongly encourages IRB staff to become Certified IRB Professionals and/or Certified IRB Managers.
- d. **IRB Administrator Duties.** The IRB Administrator, with administrative support, is responsible for ensuring that the following IRB functions are accomplished in a professional fashion compliant with all relevant regulatory requirements:
- Developing and implementing procedures to effect efficient document flow and maintenance of all SRB and IRB records
 - Maintaining the official roster of IRB members
 - Scheduling IRB meetings
 - Distributing pre-meeting materials
 - Compiling the minutes of IRB meetings in compliance with regulatory requirements

- Promptly reporting changes in IRB membership to BUMED and OHRP
- Assisting new IRB members in completing orientation procedures and meeting required education standards
- Maintaining all IRB documentation and records in accordance with regulatory requirements
- Ensuring that all IRB records are secured and properly archived
- Ensuring that documentation of IRB activities and decisions fully satisfies all regulatory requirements
- Ensuring that IRB actions are promptly reported to BUMED for HQ level administrative review
- Facilitating communication between investigators and the IRB
- Tracking the progress of each research protocol submitted to the IRB
- Maintaining an electronic database for tracking purposes
- Serving as a resource for investigators on general regulatory information, and providing guidance about forms and submission procedures
- Maintaining training documentation and reference materials related to human subject protection requirements
- Drafting reports and correspondence to research investigators on behalf of the IRB(s) or IRB Chair(s) regarding the status of the research, including conditions for approval of research and cases of adverse events or unanticipated problems
- Assisting in drafting reports and correspondence directed to research facility officials, federal officials, and others on behalf of the IRB(s) or IRB Chair(s)
- Maintaining quality control of IRB support functions
- Assisting in evaluation, audit, and monitoring of human subject research as directed by the IRB and the ORA Director
- Keeping manuals and Standard Operating Procedures up to date
- Assisting during regulatory inspections and site visits

Chapter 9

IRB Recordkeeping & Required Documentation

Federal regulations require that NMRC implement written policies and procedures to govern the operations and direct the activities of its IRB (32 CFR 219.103(b)(4)). This IRB SOP addresses that requirement.

- a. **Record Retention.** SECNAV Instruction 3900.39C requires that research records be maintained as “Project Case Files” following SECNAV Instruction 5212.5D (Navy and Marine Corps Record Disposition Manual, Section 3900, Paragraph 5, Page III03-63 of 22 Apr 98).

SECNAV Instruction 5212.5D defines project case files as those files maintained by project managers at laboratories and other activities responsible for research and development functions. The file is a complete history of each project from initiation through research, development, design and testing, to completion.

Included are:

- project authorization documents (e.g., IRB correspondence and approvals, Command approvals)
- technical characteristics (e.g., research protocols)
- test and trial results (i.e., research data)
- all technical and progress reports (including reports received from contractors, related publications)
- notices of completion (e.g., final review reports)
- correspondence influencing the direction or course of action taken on a project

Project case files will be maintained in ORA for 5 years. Forward inactive project case files to nearest Federal Records Center (FRC) when 5 years old or when no longer needed for reference, whichever is later. Transfer to the nearest National Archive Center when 25 years old.

- b. **Access to IRB Records.** All IRB records should be secured in locked filing cabinets or locked offices. Access to IRB records is limited to the IRB, SRB, IRB staff, authorized DoD representatives, and officials of Federal and state regulatory agencies, including BUMED, OHRP and FDA. Research investigators shall be provided reasonable access to files related to their research. All other access to IRB records is limited to those who have legitimate need for them, as determined by the Commanding Officer.
- c. **IRB Records Defined.** At a minimum, IRB records must include all information required under DoD, DHHS and FDA regulations at 32 CFR 219.115, 45 CFR 46.115 and 21 CFR 56.115, respectively, and as recommended by official (i.e.,

written) DoD, OHRP and FDA guidance and instructions.

IRB files will be organized such that the following information may be readily accessed:

- Written IRB operating procedures
 - Current and past IRB membership rosters
 - Training records
 - All correspondence to and from the IRB
 - IRB research protocol files
 - Documentation of determinations of human subject research status
 - Documentation of exemptions from federal regulations
 - Documentation of exemptions and exceptions from FDA regulations
 - Documentation of expedited reviews
 - Documentation of IRB findings and review categories for the involvement of pregnant women, fetuses, neonates, prisoners, and children in research
 - Documentation of IRB findings and justifications for waiver of informed consent and waiver of documentation of informed consent
 - Information for all approved research addressing each of the eight criteria for Approval under Federal regulations at 32 CFR 219.111 and 21 CFR 56.111
 - IRB meeting minutes
 - DoD Navy and Federalwide Assurances
 - Documentation of cooperative review agreements, e.g., memorandum of agreements
 - Documentation of review by another institution 's IRB, as applicable
 - Adverse event reports
- d. **IRB Membership Rosters.** The IRB Administrator shall ensure that current IRB Membership rosters are maintained and that any changes in IRB membership are reported promptly by the IRB Administrator to BUMED and OHRP.

All IRB membership rosters shall include the following information required by BUMED and OHRP:

- Names of IRB members.

- Names of alternate members and the corresponding regular member(s) for whom each alternate may serve.
 - Earned degrees of each member and alternate, where applicable.
 - Specific scientific qualifications (such as board certifications and licenses) or other relevant experience sufficient to describe each member's chief anticipated contribution to IRB deliberations.
 - Any employment or other relationship with the NMRC or with collaborating institutions (e.g., full or part time employee, stockholder, member of governing board, paid or unpaid consultant).
- e. **Education and Training Records.** BUMED requires a plan for continuing education in human subject protections for research investigators, IRB members and staff. ORA shall ensure that accurate records are maintained listing research investigators, IRB members, IRB staff who have fulfilled the facility's human subject protection initial and continuing training requirements.
- f. **IRB Protocol Files.** The IRB will maintain a separate file for each research protocol that it receives for review. Protocols will be numbered by the institution followed sequentially by fiscal year, in the order in which they are initially received, e.g., the first NMRC protocol submission received in fiscal year 2002 will be numbered "NMRC.2002.0001" and the second will be numbered "NMRC.2002.0002", etc. Such files will be kept at NMRC for a period of five years after closure and after which, when no longer needed for reference, ORA will transfer the files to the Federal Records Center (FRC) with instructions to forward to the National Archive Center after 25 years. (See item "a" above.)

Each IRB protocol file will contain at least the following materials:

- Protocol
- Documentation of scientific review board review and approval
- Documentation of type of IRB review
- The IRB-approved informed consent document, with the beginning and ending dates of the current approval period clearly displayed on each page
- Sponsor or cooperative group protocols and sample informed consent documents, if any
- Advertising or recruiting materials, if any
- Applications for protocol amendments or modifications
- Continuing review progress reports and related information
- Reports of unanticipated problems involving risks to subjects or others

- Reports of injuries to subjects and adverse events occurring within NMRC or NMRC D or involving NMRC or NMRC D employees or agents and reported to any regulatory agency
 - Reports of external adverse events and/or safety reports received from sponsors or cooperative groups
 - Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) reports, if any
 - Results of any internal quality control and monitoring activities, if any
 - All IRB correspondence to and from research investigators, government agencies, data monitoring boards, or sponsors
 - All other IRB correspondence related to the research
 - Documentation of all IRB review, including initial and continuing convened (full) or expedited IRB review, and NMRC approvals
 - Documentation of type of IRB review
 - Documentation of host country approval, if applicable
 - Documentation of local ethics review, if applicable
 - Documentation of statements of significant new findings provided to subjects
 - Documentation of project closeout
 - IRB reviewer checklists
 - Transmittal documentation to BUMED for HQ level administrative review
- g. Protocol Tracking System.** The Research Services Director will provide the IRB with access to a centralized reliable IRB research tracking system. The IRB Administrator shall ensure the maintenance of the system.

The system shall include the following information:

- Protocol number
- Protocol title
- Names of principal investigator and/or lead investigator where appropriate
- Work unit number
- Sponsor

- Date of initial approval
- Date of most recent continuing approval
- End of current approval period
- Type of review (expedited, full board review or exempt)
- Involvement of children, prisoners, pregnant women, fetuses or neonates
- Current status (pending IRB review, approved, deferred, modifications required, disapproved, closed)

h. Documentation of Exemptions and Exceptions. Identification of research activities that are exempt from the human subject regulations requires a sophisticated level of expertise and is not left to individual investigators.

Other than the emergency use of a test article (see below), all exemptions claimed for research conducted at NMRC or by employees or agents of NMRC or NMRC must be reviewed by the IRB Chair or Vice Chair. In reviewing exemption requests, the reviewer must receive enough information from the investigator to ascertain whether the claimed exemption genuinely applies.

Documentation of verified exemptions consists of the reviewer's written concurrence in the IRB protocol file that the activity described in the Investigator's request for exemption satisfies the conditions of the cited exemption category (see IRB Form 1-A, Request for Exemption).

Other than the emergency use of a test article (see below), the exemptions do not apply to research involving prisoners. The exemptions do apply to research involving pregnant women, fetuses, and neonates. The categories of exempt research are stipulated in the Federal Policy (Common Rule) and in DoD regulations at 32 CFR 219.101(b)(1-6).

Exemptions and exceptions including the following:

- 1. Exempt Research in Educational Settings.** Research conducted in established or commonly accepted educational settings that involves normal educational practices is exempt from Federal regulations in accordance with 32 CFR 219.101(b)(1). This exemption does not apply if the setting is not commonly recognized as an educational one, or if other than normal educational practices are employed. Even if the research is exempt, the investigator has an ethical obligation to respect and safeguard students' rights and welfare.
- 2. Exempt Research Using Educational Tests (Cognitive, Diagnostic, Aptitude, and Achievement Tests), Survey Procedures, Interview Procedures, or the Observation of Public Behavior.** Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is ordinarily exempt under Federal regulations at 32 CFR 219.101(b)(2).

When the subjects are **adults**, this exemption applies **unless**: (a) information is recorded in an identifiable manner (either directly or indirectly using codes or other identifying links); **and** (b) disclosure of the information would place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation. ***Note:** The research is exempt unless both (a) and (b) apply; i.e., the research is exempt unless the information collected is both identifiable and sensitive, except in the case of children as follows.*

This exemption applies to research involving **children, except** that: (a) research involving survey or interview procedures with children is **not exempt**; and (b) research involving observation of the public behavior of children is **not exempt** if the investigator participates in the actions being observed.

- 3. Exempt Research Using Educational Tests (Cognitive, Diagnostic, Aptitude, and Achievement Tests), Survey Procedures, Interview Procedures, or the Observation of Public Behavior.** If not exempt under the conditions described above, research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is exempt under 32 CFR 219.101(b)(3) where: (a) the subjects are elected or appointed public officials or candidates for public office; or (b) Federal statutes require without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. ***Note:** Condition (b) regarding Federal statutes rarely applies. The NMRC IRB will consult with BUMED and/or OHRP if it receives an exemption request based on absolute confidentiality under a Federal statute.*

If not exempt under the conditions described above, the IRB may sometimes utilize expedited procedures for review and approval of research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior.

- 4. Exempt Use of Existing Materials.** Retrospective studies involve research conducted by reviewing materials (data, documents, records, or specimens) collected in the past (e.g., medical records, school records, or employment records) and existing at the time the research is proposed and initiated may be exempt from IRB review and informed consent requirements.

Such research may be exempt under DoD regulations at 32 CFR 219.101(b)(4) if the information is publicly available or if the information is recorded in such a manner that subjects cannot be identified, either directly or through identifiers (e.g., codes) linked to the subjects. If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects.

Retrospective studies using existing materials occasionally entail greater than minimal risks to subjects and require review by the convened IRB (e.g.,

where the research reveals previously undisclosed illegal drug use and the expedited reviewer had concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators).

5. **Exempt Research and Demonstration Projects with Approval of Department or Agency Heads.** Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (a) Public benefit or service programs; (b) procedures for obtaining benefits or services under those programs; (c) possible changes in or alternatives to those programs or procedures; or (d) possible changes in methods or levels of payment for benefits or services under those programs.
6. **Exempt Taste and Food Quality Evaluation and Consumer Acceptance Studies.** Taste and food quality evaluation and consumer acceptance studies are exempt from IRB review if: (a) wholesome foods without additives are consumed or (b) a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration (FDA) or approved by the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the U.S. Department of Agriculture. This also applies to FDA regulated research.
7. **Exception from Informed Consent Requirement for Emergency Use of a Test Article.** FDA regulations at 21 CFR 50.23 permit the use of a test article without the informed consent of the subject (or the subject's legally authorized representative) where the clinical investigator and a physician, not otherwise involved in the research, certify in writing that (i) the subject is confronted with a life threatening emergency; (ii) informed consent cannot be obtained because of an inability to communicate; (iii) time is not sufficient to obtain consent from the subject's legally authorized representative; and (iv) there is no alternative approved or generally recognized therapy that provides equal or greater likelihood of saving the life of the subject.

This written certification must be submitted to the IRB within 5 working days of the use of the test article. This reporting must not be construed as an approval for the emergency use by the IRB. The IRB Administrator is responsible for maintaining this documentation in IRB records.

NMRC requires that the clinical investigator notify the IRB Chair prior to the emergency use where at all possible. Emergency use of test articles is discussed in greater detail in Chapter 13.

Emergency use of investigational drugs requires that the patient become a participant in a research protocol (21 CFR 50.3(g)).

8. **Exemption from IRB Review Requirement for Emergency Use of a Test Article.** FDA regulations at 21 CFR 56.104(c) permit the emergency use of a test article without IRB review. Emergency use is defined as use of a test

article on a human subject in a life threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)). All of the following conditions must be met for this type of emergency use: (i) an individual is in a life-threatening situation; (ii) no standard acceptable treatment is available; (iii) there is insufficient time to obtain IRB approval; and (iv) the emergency use must be reported in writing to the IRB within 5 working days. This reporting must not be construed as an approval for the emergency use by the IRB. The IRB Administrator is responsible for maintaining this documentation in IRB records. NMRC requires that the clinical investigator notify the IRB Chair prior to the emergency use where at all possible. Emergency use of test articles is discussed in greater detail in Chapter 13.

***Note:** DoD regulations at 32 CFR 219.116(f) and DHHS regulations at 45 CFR 46.116(f) have two regulatory objectives: to make sure that emergency medical care for **patients** may be provided without regard to IRB review and approval; and to require IRB review and approval prior to initiation of **research involving human subjects**. Confusion can arise when both objectives appear to pertain to the same person. OHRP has provided the following clarification. Whenever emergency care is initiated without prior IRB review and approval, the patient may not be considered to be a research subject. Such emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity. In other words, this section of the regulations for the protection of human subjects does not permit research activities to be started even in an emergency, without prior IRB review and approval. If emergency care involves drugs, devices, and biologics that are considered to be investigational by the FDA, it is necessary to meet FDA requirements to use the investigational article for emergency purposes.*

- i. **Documentation of Expedited Reviews.** DoD regulations at 32 CFR 219.110 state that expedited IRB review procedures may be employed for (i) minor changes in previously approved research during the specified approval period; and (ii) research activities that fall within the FDA/DHHS specified categories (63 FR 60353-20356 and 60364-60367, November 9, 1998) and involve no more than minimal risk to subjects. Documentation for expedited reviews will be maintained in IRB records and will include the category and circumstances that justify using expedited procedures. Such documentation is ordinarily provided through the reviewer's written concurrence in the IRB reviewer's checklist on the investigator's request for expedited review (see IRB Form 1-B "Request for Expedited Review"). Expedited reviews are conducted by the IRB Chair or Vice Chair.
- j. **Documentation of IRB Meetings – Minutes of IRB Meetings.** IRB staff will compile the minutes of IRB meetings. The IRB meeting minutes will be submitted to the members of the IRB for review and approval at a subsequent convened IRB meeting.

The IRB Chair or Commanding Officer who serves as the approving official will ordinarily implement protocol approvals and other IRB actions immediately

following the IRB meeting at which the action took place and need not wait for the approval of the minutes. Any errors in IRB meeting minutes will be rectified as soon as possible after they are identified.

The following specific information will be recorded in the meeting minutes:

1. Attendance. IRB minutes will list attendance as follows:

- Names of members present
- Names of absent members
- Names of alternates attending in lieu of specified (named) absent members (alternates may substitute for specific absent members only as designated on the official IRB membership roster)
- Names of non-voting members and consultants present
- Name of investigators present
- Names of guests present

2. Quorum requirements. IRB minutes will include a statement of “Quorum Requirements” based on the following standards:

- A majority of the IRB members (or their designated alternates), including at least one member whose primary concerns are in nonscientific areas, must be present in order to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting;
- Members may be present in person or audio (telephone) or audio-visual teleconference. Members present via teleconference will be noted as such in the meeting minutes, which will also indicate that the members received all pertinent information prior to the meeting and were able to actively and equally participate in all discussions;
- IRB minutes will include documentation of quorum and votes for each IRB action by recording votes as follows: Total Number Voting (); Number voting for (); Number voting against (opposed) (); Number abstaining ();
- Members absenting themselves due to conflicting interests may not be counted toward quorum requirements (i.e., may not be counted among those voting or abstaining); and
- No individual who is not listed on the official IRB membership roster may vote with the IRB.

3. Actions Taken by the Convened IRB. IRB minutes will include all actions taken by the convened IRB and the votes underlying those actions (32 CFR

219.109) on the initial or continuing review of research; review of protocol or informed consent modifications or amendments; unanticipated problems involving risks to subjects or others; adverse event reports; reports from sponsors, cooperative groups, or DSMB/DMCs; reports of continuing non-compliance with the human subject regulations or IRB determinations; suspensions or terminations of research; and other actions. IRB actions for initial or continuing review of research include those listed below.

IRB actions for initial or continuing review of research include the following:

- **Approved as submitted.** Approved as submitted, with no changes (or no additional changes). The research may proceed.
 - **Approved with minor changes.** Approved with minor changes to be reviewed by a designated IRB member and the IRB Chair or Vice Chair. Such minor changes must be clearly delineated by the IRB so the investigator may simply concur with the IRB's stipulations. The research may proceed after the required changes are verified and the protocol approved by the designated reviewer. IRB staff and so-called non-voting members of the IRB may not approve these changes. Such changes require the approval of a voting IRB member.
 - **Approved with substantive changes.** Approved with substantive changes to be reviewed by the convened IRB. The research may proceed only after the convened IRB has reviewed and approved the required changes to the research.
 - **Deferred.** Deferred pending receipt of additional substantive information. The IRB determines that it lacks sufficient information about the research to proceed with its review. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.
 - **Disapproved.** The IRB has determined that the research cannot be conducted at NMRC or NMRCO or by employees or agents of NMRC or NMRCO.
4. **Separate votes for other IRB actions.**
 5. **The basis for requiring changes in or disapproving research.** The minutes of IRB meetings will include the basis for requiring changes in or disapproving research (32 CFR 219.109(d)). This information will also be provided in writing to the investigator, who will be given an opportunity to respond in person, via conference call or in writing.
 6. **Summary of Controverted Issues at Convened Meetings.** The minutes of IRB meetings will include a summary of the discussion of all controverted issues and their resolution (32 CFR 219.115(a)(2)).
 7. **Required IRB Findings and Determinations.** The following IRB findings and determinations, including protocol-specific information justifying each finding

or determination, will be documented in IRB meeting minutes, either directly or by reference to specific IRB records:

- The level of risk of the research.
- The approval period for the research, including identification of research that warrants review more often than annually.
- Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research.
- Justification for waiver or alteration of informed consent, addressing each of the 4 criteria at 32 CFR 219.116(d). Briefly, the criteria that the IRB must find and document are: (1) the research involves no more than minimal risk to subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.
- Justification for waiver of the requirement for written documentation of consent in accordance with the criteria at 32 CFR 219.117(c).
- Justification for approval of research involving pregnant women, human fetuses and neonates, addressing each of the criteria specified under Subpart B of the DHHS human subject regulations.
- Justification for approval of research involving prisoners, addressing each of the categories and criteria specified under Subpart C of the DHHS human subject regulations. The IRB Chair is responsible for providing certification of the IRB's findings to OHRP.
- Justification for approval of research involving children, addressing each of the categories and criteria specified under Subpart D of the DHHS, or Subpart D of the FDA human subject regulations in the case of FDA regulated research. The IRB Chair is responsible for providing notification to BUMED of the IRB's findings concerning research requiring review by a panel of experts. For FDA regulated research similar notification shall go to the FDA Commissioner.
- Special protections warranted in specific research projects for groups of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research.
- Justification for approval of research planned for an emergency setting, with specific reference to the criteria specified under the special FDA exception at 21 CFR 50.24. **Note:** *Planned emergency research must be*

approved by the Assistant Secretary of the Navy, Research, Development and Acquisition (ASN(RDA)).

- Any IRB discussions or determinations regarding (i) unanticipated problems involving risks to subjects or others; (ii) serious adverse events; and (iii) any other items on which the IRB takes formal action.
- 8. Report of Expedited Reviews.** The minutes should identify research approved or other action since the last meeting utilizing expedited review procedures.
- 9. Recusals.** IRB minutes must state the name of persons who recused themselves and relevant protocol.
- 10. Duration of the meeting** by recording when the meeting came to order and when the meeting was adjourned.
- k. Documentation of Review by Another Institution's IRB.** When NMRC relies on the review by another institution's IRB, ORA will maintain a protocol file to include copies of the following:
- Copy of the applicable Memorandum of Agreement or in Joint Research Review Agreement, etc.
 - NMRC's approval for the investigator's participation in the research
 - Copy of the approved protocols and reviewing IRB's approval
 - Copy of any reports of non-compliance, unanticipated problems involving subjects or others, suspensions or terminations
 - Copy of the final report

Such documentation will be obtained either directly from the reviewing institution or from the investigator.

Chapter 10

Procedures for IRB Review

All human subject research conducted completely or partially in NMRC or NMRC D facilities, conducted in approved off-site locations, facilities; and/or conducted by NMRC or NMRC D researchers while on official Navy time, regardless of whether the research is funded or regulated by any government agency, must be prospectively reviewed by an IRB. Claimed exemptions from NMRC IRB review must be verified by the IRB Chair or Vice Chair. No human subject research may be initiated or continued at any NMRC or NMRC D facility or by any NMRC or NMRC D employee or agent without prospective approval of an IRB officially designated under the NMRC DoD Navy or Federalwide assurances. Regardless of the type of review (approved as exempt, expedited or review at a convened meeting), the investigator is notified in writing of the IRB's determinations.

- a. **Review by the Convened IRB.** DoD regulations at 32 CFR 219.108(b), the Federal Policy (Common Rule) for the Protection of Human Subjects, and FDA regulations require that the NMRC IRB conduct initial and continuing reviews of all non-exempt research at convened meetings at which a majority of the members are present, unless the research falls into one or more of the categories appropriate for expedited review (as discussed later in this chapter).

The entire IRB file shall be available to all members prior to and during the convened meeting. All IRB members will be afforded full opportunity to discuss each research proposal during the convened meeting.

A majority of the IRB members (or their designated alternates), including at least one member whose primary concerns are in nonscientific areas, must be present in order to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting.

The NMRC IRB meeting schedule with submission due dates will be made available to investigators and IRB members.

- b. **Special IRB Meetings.** Generally, all IRB actions will take place at a regularly scheduled IRB meeting. However, as necessary, the IRB Chair, any IRB member, or the Commanding Officer, may call a special IRB meeting to consider any matter concerned with the rights and welfare of any subject requiring urgent attention.
- c. **Telephonic and Video Conferencing.** IRB members may participate in convened IRB meetings via telephonic and/or video conferencing in accordance with applicable guidance from BUMED, OHRP and FDA.
- d. **Initial Review by the Convened IRB.** Upon receipt of a complete set of IRB application materials, the IRB Administrator will designate a Primary Reviewer and a Secondary Reviewer for the proposed research. As discussed later in this

chapter, the Primary and Secondary Reviewer will provide an exhaustive review of the applications assigned to them, fill out the appropriate Initial Reviewer forms, and lead the discussion of the proposed research at the convened meeting of the IRB.

Except for unusual circumstances, at least three weeks prior to the convened meeting, the Primary and Secondary Reviewers will be provided detailed initial review materials describing each project to which he or she is assigned. The purpose of encouraging Primary and Secondary Reviewers to contact the investigators before the meeting is to attempt to resolve significant issues with the intent of reducing the number of protocols that are deferred or approved with significant changes. When working with the investigators, if the revisions can be incorporated into the submission before the agenda and meeting materials are circulated to the other IRB members, then the investigator should be encouraged to do so. In the alternative, the primary and secondary reviewers can describe their discussions with the investigator at the IRB meeting.

Except for unusual circumstances, at least one week prior to the convened meeting, all IRB members will be provided detailed initial review materials describing each proposed research project to be discussed at the convened meeting. The purpose is to provide sufficient time for IRB members to review each proposed project before the meeting so they can discuss each project adequately and determine the appropriate action during the convened review.

1. **IRB Member Initial Review Materials.** Initial review materials provided to all IRB members at least one week prior to the meeting will include:
 - The research protocol and initial review application forms (which includes information about subject recruitment and selection, the research plan, risks and benefits, privacy and confidentiality protections, safety monitoring, informed consent procedures, and protections for vulnerable subjects) and requested attachments
 - The proposed informed consent document (translations or back-translations, if applicable) *Note: Because the IRB often requests changes to the informed consent documents and translations do tax limited resources of the NMRCDD translation department, investigators may submit translations or back-translations following the IRB's review of the original English version. In such instances, the investigator must then promptly submit translations and back-translations following receipt of the reviewed informed consent documents for review by the IRB Chair or Vice Chair and approval.*
 - Any recruitment materials (including advertisements to be seen or heard by potential subjects)
 - Any surveys, questionnaires or other instruments

2. Additional Materials for Primary and Secondary Reviewers. The Primary and Secondary Reviewers will be provided with the following additional materials with their review packets at least three weeks prior to the meeting:

- The full industry protocol or sponsor protocol, with the NMRC Human Subject Protection Addendum if the protocol does not include information outlined in the addendum. For NMRC or NMRC initiated research, the complete protocol using the NMRC protocol template or equivalent format.
- Initial Review Application form (IRB Form 1) and supplemental forms as appropriate
- The Clinical Investigator's Brochure (if applicable)
- For PHS funded research, the full grant application or proposal without appendices
- Any other information relevant to the approval criteria described in the regulations.

If Primary and Secondary Reviewers are not appointed, or if both the Primary Reviewer and the Secondary Reviewer are absent from the convened meeting, each IRB member must receive and review the above materials prior to the meeting. Otherwise discussion of the proposed research will be deferred to a subsequent meeting.

The minutes of IRB meetings will document separate deliberations, actions, and votes for each protocol undergoing initial review by the convened IRB.

e. Continuing Review by the Convened IRB. The NMRC IRB is required to conduct "substantive and meaningful continuing review" of research at intervals appropriate to the degree of risk, but not less than once per year (32 CFR 219.103 & 16.109(b)(4)). Continuing reviews will be conducted by the convened IRB unless the research falls into one or more of the categories appropriate for expedited review (as discussed later in this chapter).

Except for unusual circumstances, at least three weeks prior to the convened meeting, the Primary and Secondary reviewers will be provided detailed initial review materials describing each project to which he or she is assigned. Additionally, except for unusual circumstances, at least one week prior to the convened meeting, each IRB member will be provided with detailed continuing review materials sufficient to conduct substantive and meaningful reviews. These materials will include the currently approved informed consent document, the proposed informed consent document, and the IRB Continuing Review Report (IRB Form 4), which is comprised of the following:

- A summary of the research providing sufficient information to address the approval criteria found at Section 111 of the DoD and FDA human subject regulations

- A status report on the progress of the research
- The number of subjects enrolled and withdrawn
- A description of any unanticipated problems involving risks to subjects or others, reasons for the withdrawal of subjects, and complaints about the research since the last IRB review
- A summary of adverse events
- A summary of relevant recent literature, interim findings, and amendments or modifications since the last review, relevant multi-center trial reports,
- Other information considered relevant by the investigator, especially information about risks

At least one member of the IRB (i.e., a Primary Reviewer) will receive a copy of the complete protocol including any modifications previously approved by the IRB. Upon request, any IRB member will be provided access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting.

The minutes of IRB meetings will document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

- f. **Use of Primary and Secondary Reviewers with Convened Reviews.** In accordance with FDA and OHRP guidance, the NMRC IRB utilizes a “Primary and Secondary Reviewer System” to assist in the initial and continuing review of research by the convened IRB.

When utilized, the Primary and Secondary Reviewers are considered the lead reviewers for research proposals assigned to them. Primary and Secondary Reviewers are responsible for:

- Being thoroughly versed in all details of the research
 - Conducting an exhaustive review of the research using the IRB Reviewer Checklists
 - Contacting individual investigators for clarification as needed prior to the convened meeting
 - Leading the discussion of the research at the convened meeting.
- g. **Use of Subcommittees to Support IRB Activities.** The NMRC IRB may utilize subcommittees to support IRB review activities. At the discretion of the IRB Chair, subcommittees may be appointed to perform pre-reviews or fulfill the duties of Primary and/or Secondary reviewers. The IRB Chair may also appoint subcommittees on an *ad hoc* basis to perform additional functions as needed.

- h. Review More Often Than Annually.** The NMRC IRB recognizes that protecting the rights and welfare of subjects sometimes requires that research be reviewed more often than annually. The IRB will consider the following factors in determining which studies require more frequent review:
- The probability and magnitude of anticipated risks to subjects
 - The likely medical condition of the proposed subjects
 - The overall qualifications of the principal investigator and other members of the research team
 - The specific experience of the principal investigator and other members of the research team in conducting similar research
 - The nature and frequency of adverse events observed in similar research at this and other institutions
 - Any other factors that the IRB deems relevant

In specifying an approval period of less than one year, **the IRB may define the period with either a time interval or a maximum number of subjects.**

- i. Expedited Review of Research.** DoD regulations at 32 CFR 219.110 and FDA regulations permit the IRB to review research through an expedited procedure if:
- The research constitutes a minor change in previously approved research during the period for which approval is authorized, *or*
 - The research is not classified, not greater than minimal risk and falls within the categories on the November 9, 1998 DHHS/FDA list of research eligible for expedited IRB review.

Under an expedited review procedure, the IRB Chair or Vice Chair may review the research on behalf of the IRB, request additional information, or forward the application to the fully convened IRB. The IRB Chair or Commanding Officer (relying on the recommendations of the Vice Chair) may approve research on behalf of the IRB. The expedited reviewer may not disapprove any research activity. The research activity may be disapproved only after review by the fully convened IRB.

For initial or continuing reviews conducted by expedited review, the IRB reviewer should receive all of the documentation listed in the relevant sections above. The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review.

Documentation for expedited reviews will be maintained in IRB records and will include the category and circumstances that justify using expedited procedures.

The IRB Administrator will keep all IRB members advised of research that has been approved under expedited procedures by listing the research in the agenda

and minutes of the next IRB meeting (32 CFR 219.110(c)). At the request of any NMRC IRB member, the fully convened IRB may re-review any research that has been approved using expedited review procedures. The re-review will be conducted in accordance with the IRB's usual non-expedited procedures.

1. **Expedited Review of Minor Changes in Previously Approved Research.** The NMRC IRB may utilize expedited procedures to review a proposed change to previously approved research if it represents a minor change to be implemented during the previously authorized approval period. NMRC defines a minor change to be one that makes no substantial alteration in any of the following:

- The probability or magnitude of risks to subjects
- The research design or methodology
- The number of subjects enrolled in the research
- The qualifications of the research team
- The facilities available to support safe conduct of the research
- The likelihood of subjects' willingness to participate
- Any factor that might warrant convened review

2. **Expedited Review of Research in Specified Categories.** The NMRC IRB may utilize expedited procedures for the initial or continuing review of research that is no greater than minimal risk and falls within the FDA/DHHS specified expedited review categories (63 FR 60353-60356 and 60364-60367, November 9, 1998). These categories do NOT apply to research involving prisoners.

Expedited Category #1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met:

- Research on **drugs** for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
- Research on medical **devices** for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

Expedited Category #2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

- **From 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 collection may not occur more frequently than 2 times per week; or
- **From other adults and children**, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

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

- Hair and nail clippings in a nondisfiguring manner
- Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction
- Permanent teeth if routine patient care indicates a need for extraction
- Excreta and external secretions (including sweat)
- 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
- Placenta removed at delivery
- Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
- 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;
- Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; and
- Sputum collected after saline mist nebulization.

Expedited Category #4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-ray s or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (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:

- Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy
- Weighing or testing sensory acuity
- Magnetic resonance imaging
- Electrocardiography, electroencephalography, thermography, detection of naturally occurring Radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography
- Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

Expedited 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). *Note: Some research in this category may be exempt from the DoD regulations for the protection of human subjects 32 CFR 219.101(b)(4). This listing refers only to research that is not exempt.*

The intent of the drafters was to define two categories here, each appropriate for expedited review.

- Non-exempt research involving materials that have already been collected (for any previous research or non-research purpose) at the time when the research is proposed.
- Non-exempt research involving materials that will be collected in the future (i.e., prospectively) for a non-research purpose (see below).

Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research.

Prospective studies using materials (data, documents, records or specimens) that will “exist” in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do **not** qualify for **exemption** under DoD regulations at 32 CFR 219.101(b)(4) because the materials in these studies are not in existence at the time the study is proposed and initiated.

However, the IRB may utilize **expedited procedures** to review research that proposes to use materials (i.e., data, documents, records, or specimens) that will be collected in the future (i.e., after the research has been proposed and

initiated) for non-research purposes (e.g., clinical observations, medical treatment, or diagnosis occurring in a non-research context).

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

Expedited 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 group, program evaluation, human factors evaluation, or quality assurance methodologies. *Note: Some research in this category may be exempt from the DoD regulations for the protection of human subjects (32 CFR 219.101(b)(2) and (b)(3)). This listing refers only to research that is not exempt.*

Expedited Category #8. Continuing review of research previously approved by the convened IRB as follows:

- Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; **or**
- Where no subjects have been enrolled and no additional risks have been identified; **or**
- Where the remaining research activities are limited to data analysis.

Expedited Category #9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

- j. Protocol Revisions, Modifications, and Amendments.** Revisions, modifications, or amendments to a research protocol must be summarized on the Request for Amendment to IRB Approved Research (see IRB Form 2) and must be incorporated into the written protocol. This practice ensures that there is only one complete protocol with the revision dates noted on each revised page and the first page of the protocol itself. This procedure is consistent with the procedure used for revised and approved informed consent documents, which then supersede the previous one.
- k. Investigators' Duty to Report to the IRB.** DoD regulations at 32 CFR 219.103(b)(5) and FDA regulations at 21 CFR 56.108(b) require that investigators report promptly to the IRB (i) any unanticipated problems in research involving risks to subjects or others; and (ii) any serious or continuing non-compliance with the human subject regulations or the determinations of the IRB.

These same regulations require that the NMRC Institutional Official report promptly to BUMED, to any Federal Agency supporting the research, and/or to the FDA (i) any unanticipated problems in research involving risks to subjects or others; (ii) any serious or continuing non-compliance with the human subject regulations or the determinations of the IRB; and (iii) any suspension or termination of IRB approval of research.

FDA regulations at 21 CFR 812.150 require that investigators report unanticipated device effects to the IRB, and NMRC requires that investigators report adverse drug effects to the IRB.

- 1. Investigators' Duty to Report Unanticipated Problems.** Investigators are required to report to the IRB (using IRB Form 2, "Reporting Adverse Events or Unanticipated Problems") **any unanticipated problems involving risks to subjects or others** that occur in research conducted at NMRC or NMRC facilities or by NMRC or NMRC employees or agents.

Note that under DoD and DHHS regulations, "unanticipated problem" means any research-related event involving risk to anyone associated with the research in any way (including investigators and research assistants) that is not included in the protocol and informed consent document. It includes not only unanticipated adverse events, but other unanticipated problems (e.g., breeches of confidentiality, equipment malfunctions that may injure the investigator, loss of data that results in the need to enroll additional subjects, thus exposing additional subjects to the risks of the research).

- 2. Investigators' Duty to Report Serious Adverse Events.** Investigators are required to report to the IRB (using the Adverse Event /Unanticipated Problem Reporting Form contained in Appendix II) **any serious adverse event** that occurs in research conducted at NMRC facilities or by NMRC's employees or agents.

A **serious adverse event** is defined as any adverse experience occurring that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect (21 CFR 312.32(a); 21 CFR 812.3(s)).

- 3. Investigators' Duty to Report Other Adverse Events.** Investigators are required to report to the IRB (using IRB Form 2, "Reporting Adverse Events or Unanticipated Problems") any adverse event occurring in research conducted at NMRC or NMRC facilities or by NMRC or NMRC employees or agent **that is reported to the research sponsor or the FDA.**
- 4. Investigators' Duty to Forward Correspondence or Reports of Monitoring or Auditing.** Investigators are required to forward reports or correspondence concerning the monitoring or auditing of their research activities or research sites by sponsors, cooperative research groups, federal agencies, or other external entities to the IRB within 5 working days of receipt.

5. **Investigators' Duty to Forward Sponsor Safety Reports.** Investigators are required to forward safety reports (or other information concerning adverse events) issued by sponsors to the IRB within 5 working days of receipt. Each report should be accompanied by the completed IRB Form 2, "Reporting Adverse Events or Unanticipated Problems".
6. **Investigators' Duty to Forward Data and Safety Monitoring Board (DSMB) Reports.** Investigators are required to forward DSMB reports to the IRB within 5 working days of receipt. When DSMBs are employed, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to make its continuing review substantive and meaningful.
7. **Investigators' Duty to Notify the IRB of Serious or Continuing Non-Compliance.** Whether involved in the research or not, all employees and agents of NMRC or NMRCO are required to notify the IRB if they become aware of any serious or continuing non-compliance with human subject regulatory requirements or with the determinations of the IRB.

Serious non-compliance is defined as non-compliance that involves greater than minimal risk of harm or discomfort to subjects or others involved in the research. **Continuing** non-compliance is defined as violation of regulatory requirements or determinations of the IRB that occurs over an extended period.

8. Reporting Timelines.

- **Notification within 24 hours.** The NMRC IRB Chair must be **notified** of any unanticipated problem involving subjects or others or serious adverse event within 24 hours of learning of the event or problem.
 - **Reporting within 5 working days.** The NMRC IRB should receive the completed using IRB Form 2, "Reporting Adverse Events or Unanticipated Problems", Safety Report, DSMB Report, or other report from the investigator promptly, *i.e.*, within 5 working days of the investigator becoming aware of the event or report.
1. **Review of Reports of Unanticipated Problems or Adverse Events.** Investigators are required to notify the IRB Chair within 24 hours of any unanticipated problems involving risks to subjects or others that occur in research conducted under the purview of the NMRC IRB. Investigators are also required to notify the IRB Chair within 24 hours to the IRB any adverse event that is reported to the FDA or the sponsor in accordance with FDA requirements. Notification to the IRB Chair may be via e-mail, telephone or facsimile.

The NMRC IRB should receive the completed Adverse Event or Unanticipated Problem report form (see IRB Form 3) from the investigator within 5 working days of knowledge of the event. (See also item “1” below.)

1. **IRB Chair Review.** All of the materials and reports described above are reviewed by the IRB Chair or Vice Chair. If the situation or event is determined not to be related to the research or not serious, and if the situation or event does not require a change in the informed consent document, the reviewer documents this determination in writing. The material and/or report with documentation of the reviewer’s determination is placed in the IRB protocol file and listed in the minutes of the next IRB meeting.
2. **Referral for Convened IRB Review.** If, in the judgment of the IRB reviewer, the situation or event (i) is serious **and** related to the research, or (ii) may warrant more than a minor change in the protocol or informed consent process, the Chair will refer the situation or event to the convened IRB for review. In the interim, the IRB Chair may require modification or suspension of research activities, as he/she deems necessary to eliminate apparent immediate hazards to subjects.

During the convened review, the IRB determines whether the research will be permitted to continue as previously approved or whether changes are required. If the research will continue, the IRB also determines whether a consent form revision is required and to what extent re-consenting and/or subject notification about new information is warranted. The IRB has the authority to suspend or terminate its approval of the research if it has significant safety or other concerns.

3. **Notice of IRB Determination(s).** Regardless of the type of review (expedited or convened), the investigator is notified in writing of the IRB’s determinations, even if no further action is necessary on the part of the investigator. In the case where no further action is necessary, this communication will be satisfied by returning the report with the completed IRB Chair/Vice Chair determination section indicating no further action is required.

It is the responsibility of the IRB Chair in collaboration with the ORA Director to provide prompt written notification to the NMRC Institutional Official of (i) any unanticipated problems in research involving serious risks to subjects or others and of the resolution of those problems or issues; (ii) any serious or continuing non-compliance with human subject regulatory requirements or with the determinations of the IRB and of the resolution of that non-compliance; and (iii) and suspension or termination of IRB approval of research.

4. **Notice of IRB Determination(s) to Agencies.** It is the responsibility of the IRB Chair in collaboration with the ORA Director and the Commanding Officer to provide prompt written notification to relevant Federal Agencies, including BUMED, OHRP (for DHHS-supported research) and FDA (for FDA-regulated research) of any unanticipated problems involving risks to

- subjects or others, and of the resolution of those problems. (See also item “r” below).
- m. **Review of Sponsor Adverse Event or Safety Reports.** The IRB review and notifications of such reports is handled in the same manner as internal reports of unanticipated problems or adverse events. Each report should be accompanied by the completed IRB Form 3, “Reporting Adverse Events or Unanticipated Problems”.
 - n. **Review of Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) Reports.** Investigators are required to forward DSMB or DMC reports to the IRB within 5 working days of receipt. The review of DSMB or DMC reports is handled in the same manner as internal reports of unanticipated problems or adverse events.

When DSMBs or DMCs are employed and the IRB is conducting continuing review of research, the IRB may rely on a current statement from the DSMB or DMC indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to make its continuing review substantive and meaningful.

- o. **Outcomes of IRB Review.** The NMRC IRB will notify investigators in writing of its determinations. All IRB actions must be communicated in writing.

IRB actions for initial or continuing review of research include the following:

1. **Recommended for approval as submitted.** Approved as submitted, with no changes (or no additional changes). The research may proceed.
2. **Recommended for approval with minor changes.** Approved with minor changes to be reviewed by a designated IRB member. Such minor changes must be clearly delineated by the IRB so the investigator may simply concur with the IRB’s stipulations. The research may proceed after the required changes are verified and the protocol approved by the designated IRB member-reviewer. IRB staff and so-called non-voting members of the IRB may not approve these changes. Such changes require the approval of a voting IRB member.
3. **Recommended for approval with substantive changes.** Approved with substantive changes to be reviewed by the convened IRB. The research may proceed only after the convened IRB has reviewed and approved the required changes to the research.
4. **Deferred.** Deferred pending receipt of additional substantive information. The IRB determines that it lacks sufficient information about the research to proceed with its review. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.

- 5. Disapproved.** The IRB has determined that the research cannot be conducted at NMRC or by employees or agents of NMRC.

The communication to the investigator will include, at minimum, the following information (where appropriate): investigator's name, title of study, IRB number, level of risk as determined by the IRB, approval date, approval expiration date.

- p. Expiration of Approval Period.** DoD regulations at 32 CFR 219.109(e) state that the NMRC IRB is required to conduct substantive and meaningful continuing review of research not less than once per year. Thus, the IRB approval period for research may extend no more than 365 days after the convened meeting at which the research was last approved (i.e., approved as submitted or approved with minor changes).

The regulations permit no grace period and no exceptions to this one-year requirement. Research that continues after the approval period expires is research conducted without IRB approval.

Consequently, the IRB will automatically suspend the enrollment of new subjects in any ongoing research that does not receive continuing review and approval prior to the end of the stipulated approval period. Previously enrolled subjects may continue their involvement in suspended research only where the IRB determines that continued involvement is in the best interest of the subjects.

- q. Suspension or Termination of IRB Approval.** The IRB may vote to suspend or terminate approval of research that is not being conducted in accordance with IRB or regulatory requirements or that has been associated with serious unexpected problems or serious harm to subjects.

When the IRB Chair determines that such action is necessary to protect the rights and welfare of subjects, he/she may require an immediate, temporary suspension of enrollment of new subjects, or of continued participation of previously enrolled subjects, pending review of the situation by the convened IRB.

- 1. Notification of Determinations to Investigator.** The IRB will notify the principal investigator orally and in writing of such suspensions or terminations and will include a statement of the reasons for the IRB's actions. The investigator will be provided with an opportunity to respond in person or in writing.
- 2. Notification of Determinations to NMRC Officials and Federal Agencies.** It is the responsibility of the IRB Chair to provide prompt (within 5 business days) written notification of any for-cause suspensions or terminations of IRB approval to the NMRC Institutional Official, the ORA Director and other relevant officials of NMRC or NMRCO, as well as relevant Federal agencies, including BUMED, OHRP (for DHHS-supported research) and FDA (for FDA-regulated research).

Note: The term “suspension or termination of IRB approval” does not include the permanent or temporary suspension of subject enrollment or participation in research that results solely from the expiration of the IRB approval period for the research.

- r. **NMRC Reports to Federal Agencies.** As indicated in above, DoD regulations at 32 CFR 219.103(b)(5), DHHS regulations at 45 CFR 46.103(b)(5) and FDA regulations at 21 CFR 56.108(b) require that the NMRC Institutional Official, report the following events promptly and in writing to BUMED, OHRP (for DHHS-supported research), to any Federal Agency supporting the research, and/or to the FDA (for FDA-regulated research):

1. **Unanticipated Problems Involving Subjects or Others.** DoD regulations at 32 CFR 219.103 (b)(5) require “prompt” reporting of unanticipated problems involving subject or others to the BUMED and if the research is DHHS-supported or FDA-regulated to OHRP, respectively.

Under DoD and DHHS regulations, “unanticipated problems are means any research-related event involving risk to anyone associated with the research in any way (including investigators and research assistants) that is not included in the protocol and informed consent document. It includes not only unanticipated adverse events, but other unanticipated problems (e.g., breaches of confidentiality, equipment malfunctions that may injure the investigator, loss of data that results in the need to enroll additional subjects, thus exposing additional subjects to the risks of the research).

2. **Serious or continuing non-compliance.** DoD regulations at 32 CFR 219.103 (b)(5) require “prompt” reporting of investigations of allegations of serious or continuing non-compliance with the governing regulations to the BUMED. NMRC policy requires that such allegations be reported within ten (10) working days using HRPP Form 2, Human Research Report.

NMRC to report serious or continuing non-compliance in DHHS-supported research promptly to OHRP. Copies of these reports should be simultaneously submitted to BUMED. If there is an Investigational New Drug (IND) or an Investigational Device (IDE) involved in the research, the FDA may need to be notified as well.

NMRC should also consider whether the funding agency might also need to be informed of serious non-compliance related to research supported under a federal contract or grant. For example, the National Institutes of Health (NIH) expects to be informed when research that it supports is the subject of a serious allegation of non-compliance or other problem that warrants investigation.

Within NMRC, allegations of non-compliance must be reported to the IRB Chair and the ORA Director. (See, Chapter 19 “Managing Allegations of Serious or Continuing Non-Compliance”).

3. **Serious Adverse Events (SAEs).** When an adverse event (or imminent threat of an adverse event) results in a **substantive IRB action**, then the IRB's determination to take such action must be promptly reported to BUMED. **Substantive IRB actions** materially alter the substance and meaning of a protocol, informed consent process or document, investigator status, including but not limited to restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the adverse event. Investigators must notify the IRB Chair within 24 hours of learning of the SAE. Investigators are then required to submit a SAE report within five (5) working days using HRPP Form 2, Reporting Unanticipated Problems & Adverse Events.
4. **Suspension or Termination of IRB Approval.** DoD policy requires that for-cause suspensions and terminations be promptly reported to BUMED (32 CFR 219.113). Pursuant to the terms of NMRC's FWA, if the research is DHHS-supported, then the for-cause suspensions and terminations must also be promptly reported to OHRP. NMRC policy requires that such actions be reported within ten (10) working days.
5. **Research Misconduct.** DoD Directive 3216.2 and DoD Directive 3210.7 requires NMRC to initiate and carry through on any actions that are necessary to ensure resolution of scientific misconduct findings. Research misconduct includes fabrication, falsification, or plagiarism in proposing, performing or reviewing research, or in reporting results. All findings of confirmed research misconduct must be reported to the Navy Surgeon General. (See NMRC's "*Scientific Misconduct: Policies and Procedures for Managing the Responsible Conduct of Human Subject Research*").

In developing and forwarding such reports, the NMRC Institutional Official will consult as appropriate with the ORA Director and IRB Chair.

- s. **Research Activities in Emergency Situations.** DoD regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity, except as required under FDA regulations.

The IRB must be notified in writing within 5 working days of any activities involving the Emergency Use of a Test Article under an FDA Exemption or Exception (see Chapter 13). The IRB will acknowledge such notification in writing but, in accordance with FDA guidance, will not issue any "approval" of the activity.

FDA regulations at 21 CFR 50.24 include special provisions for IRB review and approval of planned emergency research with waiver of the usual informed consent requirements. Planned emergency research must be approved by the Assistant Secretary of the Navy, Research, Development and Acquisition (ASN(RDA)).

- t. **International Research.** All human subject research in which NMRC or NMRCO investigators are involved must comply with all applicable federal regulations for the protection of human subjects in all material respects. This includes research conducted by NMRC and NMRCO investigators in foreign countries.

DoD regulations at 32 CFR 219.101(h) recognize that “the procedures normally followed in the foreign countries may differ from those set forth in this policy.” Research may be approved, therefore, if “the procedures prescribed by the [foreign] institution afford protections that are at least equivalent to those provided in this policy.” The foreign country's procedures may then be substituted for the procedures required by the federal regulations. Approval of the substitution is to be given by the relevant federal department or agency head after review of the foreign procedures; notice of actions taken on such reviews are to be published in the Federal Register (or elsewhere, as provided for in department or agency procedures). *Note: FDA has not adopted this provision for research that it regulates. All FDA-funded research, however, must comply with both DoD and FDA regulations.*

When reviewing international research, the IRB should obtain the following to ensure that the proposed research is ethical and appropriate given the host country's population and cultural norms. If necessary, the IRB may rely on continuing consultants with knowledge of the host country's cultural norms or rely on other experts with such knowledge on an ad hoc basis. The IRB may also rely on the determinations of the host country's local ethics review and determinations. For example, breach of confidentiality should receive especially careful IRB review relative to research conducted in a foreign country where disclosure may entail risks to employment and financial status that differ from the kinds of risks to which we are accustomed in the U.S.

Investigators should submit the following additional documentation:

- adequate documentation of prospective host-country government approval.
- adequate documentation of prospective host-country ethical review.
- approval period issued by such host-country entities.
- information relating to the training of the individuals in the host countries regarding their understanding of ethics concerns and the involvement of human subjects in research.
- information relating to the manner of recruiting subjects.

The IRB should also confirm that the informed consent documents for use in other countries provide adequate contact persons in the host county in addition to contacts in the United States.

- u. **Collaborative Research.** Under the DoD regulations at 32 CFR 219.103 and DHHS regulations at 45 CFR 46.103, every institution engaged in human

subjects research that is funded or conducted by DoD or DHHS, respectively must obtain an Assurance. Both "awardee" institutions **and** collaborating "performance site" institutions must file Assurances.

NMRC investigators who are conducting research with human subjects that is DoD-supported or DHHS-supported and who are engaged in research at sites that are *not* NMRC sites, should ask collaborating institutions to provide a FWA number in the case of DHHS-supported research or either a FWA or DoD Assurance number in case of DoD-supported research. If an institution does not have an approved FWA, investigators should ask the institution to apply for an FWA or DoD Navy Assurance. In the alternative, the collaborating investigator may enter into an "Individual Investigator Agreement."

The following describes some of the available mechanisms in collaborative research efforts:

1. **Individual Investigator Agreements.** The Individual Investigator Agreement (see HRPP Form 3, NMRC's Individual Investigator Agreement) may be used by an assured institution, such as NMRC, to extend, for one or more research protocols, the applicability of its FWA to cover either:
 - **collaborating independent investigators** (i.e., not an NMRC or NMRCDC employee or agent; conducting collaborative research activities outside the facilities of the assured institution; and not acting as an employee of any institution with respect to his or her involvement in the research being conducted by the assured institution); or
 - **collaborating institutional investigators** (i.e., not an NMRC or NMRCDC employee or agent; conducting collaborative research activities outside the facilities of the assured institution; acting as an employee or agent of a non-assured institution with respect to his or her involvement in the research being conducted by the assured institution; and employed by, or acting as an agent of, a non-assured institution that does not routinely conduct human subjects research)

The extension of NMRC's FWA through the Individual Investigator Agreement is only permissible when the following conditions are satisfied:

- The NMRC or NMRCDC investigator directs and appropriately supervises **all** of the collaborative research activities to be performed by the collaborating individual investigator outside of NMRC or NMRCDC.
- NMRC will maintain a copy of the Individual Investigator Agreement.
- For collaborating institutional investigators, the appropriate authorities at the non-assured institution state in writing that the conduct of the research is permitted at their institution.
- NMRC and the NMRC IRB approve the extension of the assurance through either the Individual Investigator Agreement;

- The following documents are made available to the collaborating individual investigator: (i) *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* or other internationally recognized equivalent; (ii) the DoD and DHHS regulations for the protection of human subjects or other procedural standards designated by a non-U.S. institution under its FWA; (iii) the terms of NMRC's DoD Navy Assurance and FWA; and (iv) the NMRC policies and procedures for the protection of human subjects of the assured institution.
- The collaborating individual investigator understands and accepts the responsibility to comply with the standards and requirements stipulated in the documents referenced in the preceding paragraph and to protect the rights and welfare of human subjects involved in the covered research.
- The collaborating individual investigator agrees to comply with all other applicable federal, international, state, and local laws, regulations, and policies that may provide additional protections for human subjects participating in covered research.
- The collaborating individual investigator agrees to abide by all determinations of the NMRC IRB and agrees to accept the final authority and decisions of the NMRC IRB, including but not limited to directives to terminate participation in designated research activities conducted under the Individual Investigator Agreement.
- The collaborating individual investigator agrees to complete any NMRC required educational training prior to initiating the covered research.
- The collaborating individual investigator agrees not to enroll subjects in the covered research prior to the research being reviewed by the NMRC IRB and approved.
- The collaborating individual investigator agrees to report promptly to the NMRC IRB any proposed changes in the research and will not initiate changes in the covered research without prior NMRC review and approval, except where necessary to eliminate apparent immediate hazards to subjects.
- The collaborating individual investigator agrees to report immediately to the NMRC IRB any unanticipated problems involving risks to subjects or others in the covered research.
- The collaborating individual investigator, when responsible for enrolling subjects, agrees to obtain, document, and maintain records of informed consent for each such subject or each subject's legally authorized representative as required under DoD and DHHS regulations and stipulated by the NMRC IRB.
- The collaborating individual investigator acknowledges and agrees to cooperate with the NMRC IRB in its initial and continuing review, record

keeping, reporting, and certification for the covered research. The collaborating institutional investigator agrees to provide all information requested by the NMRC IRB in a timely fashion.

2. **Written Research Review Agreements.** When necessary, an appropriate written agreement shall be established between the collaborators that includes a Statement of Work (SOW) and specific assignment of responsibilities. The agreement should briefly describe the research, specific roles and responsibilities of each institution, responsibility for scientific and IRB review, recruitment of subjects, and procedures for obtaining informed consent. The agreement also should describe provisions for oversight and on-going monitoring, reporting requirements, documentation retention, and compliance for the entire research project. All collaborators must ensure compliance with all relevant human subject protection regulations at their sites.
 - a) **Relying on Another Institution's IRB.** In limited circumstances to avoid duplication of effort, NMRC may rely on the collaborating institutions' IRBs (or vice versa) for the review and ongoing continuing oversight of the research. In such circumstances, each institution must ensure that such reliance does not compromise any standards or requirements.

A written research review agreement must be executed prior to relying on another IRB's review. Investigators should note that if the primary site of the conduct of research is at one institution, and the Principal Investigator is an employee of another institution, both institutions' IRBs will review the research protocol. Investigators should contact ORA prior to submission for additional guidance on whether reliance on another institution's IRB is appropriate.

All such agreements will be maintained in ORA and will be submitted to BUMED for headquarters-level administrative review.

- b) **Collaborations with WRAIR.** Occasionally, the NMRC IRB will review research that is also regulated by the Army. For example, NMRC research may involve Army funding, resources or may involve Army investigators. When the PI is a NMRC or NMRC investigator, or the research is supported by DoN funding, the research must be reviewed by the NMRC IRB. If the PI is a WRAIR investigator and the Army funds the research, NMRC may choose to rely on the WRAIR IRB under the terms of the WRAIR/NMRC Memorandum of Agreement.
 - c) **Relying on the Army's Human Subject Research Review Board (HSRRB):** In limited circumstances, NMRC may also rely on the HSRRB for review and continuing oversight of Army funded research when there is an appropriate research review agreement between NMRC and US Army Medical Research and Materiel Command (USAMRMC). However, as mentioned above, if the research is also DoN-funded, or the Principal Investigator is NMRC employee, then NMRC IRB review will be required.

Chapter 11

Criteria for IRB Approval

DoD regulations at 32 CFR 219.111, FDA regulations at 21 CFR 56.111, and the Federal Policy (Common Rule at Section 111) delineate specific criteria for the approval of research. The NMRC IRB will determine that all of the required criteria are satisfied before approving proposed research.

- a. Risks are Minimized.** The IRB must consider the overall level of risk to subjects in evaluating proposed research. In general, the regulations require that the IRB distinguish research that is “greater than minimal risk ” from research that is “no greater than minimal risk.” Under specific circumstances, research that is no greater than minimal risk may be eligible for expedited review, waiver or alteration of informed consent requirements, or waiver of the requirement to obtain written documentation of consent.

Under DoD regulations at 32 CFR 219.102(i) and the Common Rule, “minimal risk means that the probability and magnitude of harm or discomfort in the research are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

In order to approve research, the IRB must determine that risks are minimized by using procedures that are consistent with sound research design and do not expose subjects to unnecessary risks (32 CFR 219.111(a)(1)). Whenever appropriate, the research should utilize procedures already being performed on the subjects for diagnostic or treatment purposes.

The IRB is expected to consider the research plan, including the research design and methodology, to determine that there are no flaws that would place subjects at unnecessary risk. When the research design presents unnecessary or unacceptable risks to subjects without commensurate benefits to the subjects or to others, the research cannot ethically proceed and cannot be approved by the IRB.

In order to ascertain whether the research project is adequately designed and thus subjects protected, the IRB reserves the authority to seek opinions from consultants on proposed research and its design. The IRB may determine that the proposed research must be re-designed to enhance subject autonomy, maximize benefits, reduce risks, select subjects equitably, minimize undue influence or coercion, or otherwise protect the rights and welfare of human subjects.

The IRB will also consider the qualifications of the research team. Clinicians are expected to maintain appropriate professional credentials and licensing privileges. Overall, the research team must possess the professional and educational qualifications, as well as the resources, to conduct the research project and to protect the rights and welfare of subjects.

When evaluating research, the NMRC carefully examines not only the risk of **physical harm** but also the risk of **psychological and social harms**. For example, the IRB considers:

- The potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm.
- The risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, reputation; stigmatization; and damage to social relationships.
- Whether information is being collected on other living individuals in addition to the primary “target” subjects. The IRB will consider the risk of harm to those “non-target” individuals, as well. Collecting any identifiable, private information about any living individual constitutes human subject research. The IRB may require additional protections, study redesign, or the informed consent of “non-target” individuals (unless the requirement for informed consent can be waived).

In order to mitigate such harms, the NMRC IRB reviews proposed research for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in the research.

- b. Risks Are Reasonable Relative to Anticipated Benefits.** In order to approve research, the IRB must determine that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects and/or to the importance of the knowledge that may reasonably be expected to result (32 CFR 219.111(a)(2)).

The IRB develops its risk/benefit analysis by evaluating the most current information about the risks and benefits of the interventions involved in the research, in addition to information about the reliability of this information. The IRB will consider only those risks that result from the research, and will not consider long range effects (e.g., public policy implications) of applying the knowledge gained in the research.

- c. Selection of Subjects is Equitable.** In order to approve research, the IRB must determine that the selection of subjects is equitable (32 CFR 219.111(a)(3)). To this end, NMRC investigators must provide details of the proposed involvement of humans in research, including the characteristics of the subject population, anticipated numbers, age ranges, and health status. The proposed research should specify the gender and racial/ethnic composition of the subject population, as well as criteria for inclusion or exclusion of any subpopulation.

If ethnic, racial, and gender estimates are not provided as background information for initial review, and enrollment statistics are not provided for continuing review, the investigators must provide a clear rationale for exclusion of this information.

In making the determination that subject selection is equitable, the IRB will evaluate the purposes of the research and the research setting, and will be especially cognizant of issues involving potentially vulnerable subject populations, which may include children, pregnant women, prisoners, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB will carefully examine inclusion-exclusion criteria and recruitment procedures in order to determine that the burdens and benefits of the research are being distributed equitably.

1. **Inclusion of Females and Minorities.** It is the policy of NMRC that females and members of minority groups and their sub-populations should be included in all research projects involving human subjects, **unless** compelling scientific justification is provided that inclusion is inappropriate with respect to health of the subjects or the purpose of the research.

The IRB will remain mindful of the desirability of including both males and females as research subjects and will not permit the **arbitrary** exclusion of persons of reproductive age. Exclusion of such persons must be fully justified and based on sound scientific rationale.

2. **Inclusion of Non-English Speaking Participants.** Non-English speaking participants should not be systematically excluded because of inconvenience in translating informed consent documents (see also, item “e” below).
3. **Inclusion of Children.** In June 1996, the American Academy of Pediatrics and the NIH held a joint workshop concerning the participation of children in clinical research. There is valid concern that treatment modalities developed based on research conducted on adults, without adequate data from children, are being used to treat children for many diseases or disorders. Participants at the workshop concluded that there is a sound scientific rationale for including children in research.

- d. **Informed Consent Will Be Obtained.** In order to approve research involving adults as subjects, the IRB must determine that legally effective informed consent will be sought and obtained from each prospective subject or the subject's legally authorized representative (32 CFR 219.111(a)(4)), unless informed consent requirements can be waived or altered under Federal regulations. Any such waiver or alteration must be consistent with applicable Federal and State laws and regulations.

Where consistent with state law, the following are recognized as legally authorized representatives (1) persons appointed as health care agents under a Durable Powers of Attorney for Health Care; (2) court appointed guardians; (3) next of kin in the following order: spouse, adult child, parent, and adult sibling.

1. **Considerations for Reviewing Informed Consent Process:**

- Informed consent may only be sought under circumstances that minimize the possibility of coercion or undue influence and that provide the subject or legally authorized representative with sufficient opportunity to consider whether or not the subject will participate.
 - Information for informed consent must be presented in language that is understandable to the subject or legally authorized representative.
 - No informed consent process may include any exculpatory language (i) through which the subject is made to waive, or appear to waive, any of his/her legal rights; or (ii) through which the investigator, the sponsor, NMRC, NMRC D or NMRC/NMRC D employees or agents are released from liability for negligence, or appear to be so released.
 - Although it is appropriate for consent documents to state that certain specimens or information may be used for future research purposes, using the word “donation” to characterize the future use of specimens or information for research purposes implies abandonment of rights to the “property” donated and will not be approved by the NMRC IRB. Whether or not such wording is contained in “the actual informed consent document” is immaterial. All study-related documents must be submitted to the IRB for review. Any separate “donation” agreement for future research use of specimens is regarded to be part of the informed consent documentation and must be in compliance with regulatory requirements.
 - Informed consent must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research.
 - Alternatives to obtaining and documenting informed consent **immediately** before the start of the research include obtaining and documenting consent during a reasonable interval prior to the start of the research that permits the individual sufficient time to make an informed choice about the requested participation. When such alternatives are proposed, the IRB must determine that the alternative is appropriate under Federal and State law and regulation in the jurisdiction in which the subject will be enrolled and participate. These instances will be handled on a case-by-case basis. In some cases, the IRB may **require** that such alternatives be employed (see below).
2. **Waiting Periods.** In considering the adequacy of informed consent, permission, and assent procedures, the IRB may require that investigators include a “waiting period” within the process, or employ devices such as audiovisual aids or tests of comprehension. For example, the IRB might determine that obtaining research consent from a surgery subject should be obtained during the usual pre-surgery medical conferences that take place prior to the day of surgery, rather than moments before the surgery begins.
3. **Consent Monitoring.** In considering the adequacy of informed consent procedures, the NMRC IRB may require special monitoring of the process by

an impartial observer (consent monitor) in order to reduce the possibility of coercion and undue influence.

Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

- 4. Advertisements and Recruitment Incentives.** The NMRC IRB will review advertisements and recruitment incentives associated with the research that it oversees. Advertisements and incentives are directly related to the informed consent process and must be consistent with prohibitions on coercion and undue influence.

Any advertisement to recruit subjects should be limited to the information the prospective subjects, legally authorized representatives, parents, or guardians need to determine eligibility and interest. When appropriately worded, the following items may be included:

- The name and address of the investigator and/or research institution.
- The condition under study and/or the purpose of the research.
- In summary form, the criteria that will be used to determine eligibility for the study.
- A brief list of participation benefits, if any.
- The time or other commitments required of the subjects.
- The location of the research and the person or office to contact for further information.

Recruitment procedures must be designed so that informed consent, permission, and assent are given freely and coercion and undue influence are avoided. In order to evaluate this, the IRB must know who the subjects will be, what incentives are being offered, and the conditions under which the offer will be made.

- 5. Payments for Research Participation.** The NMRC IRB will review any proposed payments to research subjects (or their legally authorized representatives) associated with the research that it oversees. Payments may not be of such an amount as to result in coercion or undue influence on the decision to participate or continue participation. Payments may not be provided on a schedule that results in coercion or undue influence on the decision to participate or continue participation.

Generally, subjects should not be paid participate in research when the research is an integral part of a subject's medical care and when it makes no special demands on the subject beyond those of medical care. However,

payment may be permitted, with prior approval of the IRB, in the following circumstances:

- *No direct subject benefit.* When the study to be performed is not intended to directly enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated, non-DoD institutions is to pay patients in this situation.
- *Others being paid.* In multi-institution studies, where subjects at a collaborating non-DoD institution are to be paid for the same participation in the same study at the same proposed rate.
- *Comparable situations.* In other comparable situations in which, in the opinion of the IRB, payment of volunteers is appropriate.
- *Transportation expenses.* When the subject incurs transportation expenses that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism.

Investigators who wish to pay research subjects must indicate in their proposal the justification for such payment with reference to the criteria listed and, in addition, must:

- Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;
- State the terms of the subject participation agreement and the amount of payment in the informed consent form; and
- Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure on the veteran patient to volunteer for the research study.

The IRB shall review all proposals involving the payment of subjects (in excess of reimbursement for travel) in the light of these guidelines. The research office must ensure that such payments to subjects are made from appropriate funds.

6. **Compensation for Research Related Injuries.** Due to the possibility of injuries arising from participation in human subject research every, project, especially those involving more than minimal risk, shall include an arrangement for emergency treatment and necessary follow-up of any research related injury.
 7. **Indemnity and Liability Provisions.** Subjects in NMRC research may not be asked to waive, or appear to waive, any of their legal rights.
- e. **Informed Consent Will Be Documented.** In order to approve research, the IRB must determine that informed consent will be documented in writing, unless documentation can be waived under DoD regulations, FDA regulations or the

Common Rule.

DoD regulations at 32 CFR 219.117, DHHS regulations at 45 CFR 46.117 and FDA regulations at 21 CFR 50.27 provide two methods for documenting informed consent:

1. ***Long Form (General Informed Consent Document)***. Consent may be documented through use of a written document that embodies all of the required elements of informed consent (these elements will be discussed in detail in Chapter 12). The subject (or the subject's legally authorized representative in compliance with all regulatory requirements) must initial each page and sign the document and a copy must be given to the person signing the document. ***Note:*** *FDA regulations require that the signature be dated* and
2. ***Short Form (Oral Script)***. Consent or permission may also be documented through use of a short form document which states that the elements of informed consent have been presented orally to the subject (or legally authorized representative in compliance with all regulatory requirements). When this method is used:
 - there must be a witness to the oral presentation;
 - the IRB must approve a written summary of what is to be presented orally;
 - only the short form must be signed by the subject, representative, parent(s), or guardian(s);
 - the witness must sign both the short form and the summary;
 - the person actually obtaining consent must sign the summary; and
 - a copy of the summary and the short form will be given to the subject or the legally authorized representative.

FDA regulations require that when a short form is used, both the short form and the written summary must be in the language understandable to the subject.

The IRB should also consider the following when evaluating the documentation for informed consent:

1. **Illiterate Subjects.** Illiterate persons may have informed consent or permission information read to them and may "make their mark" in a manner consistent with the laws of the State in which the research is conducted to document their understanding. In this situation, the oral presentation and informed consent process should be witnessed, preferably by an individual not otherwise involved in the research. Both the witness and the person obtaining consent should also sign the informed consent document.

2. **Blind Subjects.** Blind persons may have informed consent or permission information read to them and may “make their mark” in a manner consistent with the laws of the State in which the research is conducted to document their understanding. In this situation, the oral presentation and informed consent process should be witnessed, preferably by an individual not otherwise involved in the research. Both the witness and the person obtaining consent should also sign the informed consent document.
3. **Non-English Speakers.** When conducted research in another country where the language of the subjects is not English, the informed consent documents must be translated into a language understandable to the subjects. The investigators must also provide a certified back-translation of the informed consent document into English for review by the IRB.

In other cases, the NMRC IRB may require that informed consent conferences include a reliable translator when the prospective subject does not understand the language of the person who is obtaining consent.

- a) When a full-length form embodying all required elements is required by the IRB to document consent, that form must be written in a language understandable to the subject. IRBs shall require that appropriately translated consent documents be submitted to the IRB for review and approval prior to their use in enrolling subjects. The IRB may utilize expedited review procedures in approving such documents if the English language consent document has already been approved, and the investigator attests in writing to the accuracy of the translation.
 - b) When a short-form consent document is used, the short form itself must be written in a language understandable to the subject, although the summary may be in English. The translator who took part in the informed consent conference may serve as the witness.
4. **Witness Signature.** The requirement of a witness name and signature signifies that the witness has observed the subject signing the consent form. The witness must be someone other than the person who obtains informed consent or someone who is not involved in the day-to-day operations of the research study.
 5. **Date Stamp Required.** All informed consent documents will have a date stamp indicating the beginning and end of the approval period during which the document may be used to obtain consent. Only the IRB-approved informed consent or permission document can be used for the informed consent or permission process. The investigator is responsible for storing signed informed consent and permission documents for at least three years following the completion of the research or forwarding them to ORA for storage, after which time ORA will ship the documents to the Federal Records Center.
- f. **Safety Monitoring Is Adequate.** In order to approve research, the IRB must determine that, where appropriate, the research plan makes adequate provision

for monitoring the data to protect the safety of subjects. For research in which risks are substantial, a detailed description of the data and safety monitoring plan should be submitted to the IRB as part of the proposal. This plan should contain procedures for reporting adverse events.

For research that is greater than minimal risk, a single appropriately qualified monitor must be designated by name. This individual must be independent from the research team (i.e., cannot be a member of the investigative team). The IRB should review information regarding the medical monitor procedures (e.g., information regarding the specific role, review materials, frequency of reports, etc.) to ensure that the medical monitor's role is appropriate for the research. Where the research protocol identifies more than one medical monitor, the IRB should also review information regarding the relationship between the medical monitors and how disagreements will be resolved. The NMRC IRB has authority to require a medical monitor in research it deems minimal risk where it determines that such monitoring is needed.

In general, it is desirable for a Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) to be established for research that is blinded, involves multiple sites, targets vulnerable subjects, or employs high-risk interventions. The NMRC IRB has the authority to require a DSMB/DMC as a condition for approval of research where it determines that such monitoring is needed.

In lieu of requiring that safety monitoring information be submitted directly to the NMRC IRB, the IRB may rely on a current statement from a duly constituted DSMB/DMC indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, and has determined that continuation of the research is justified.

- g. Privacy and Confidentiality Provisions Are Adequate.** In order to approve research, the NMRC IRB must determine that, where appropriate, there are adequate provisions to protect the privacy of subjects and the confidentiality of data.

It is important to be sure that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individual. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research.

NMRC or NMRC D personnel may obtain and use medical, technical, and administrative records from this or other DoD facilities or DoD databases for research purposes when in compliance with all DoD regulations and Privacy Rules as well as the institution's additional requirements.

It also is important to protect individually identifiable private information once it has been collected in order to prevent a breach of confidentiality that potentially could harm subjects. When information linked to individuals will be

recorded as part of the research design, the NMRC IRB requires that adequate precautions be taken to safeguard the confidentiality of the information.

Among the available methods for safeguarding confidentiality are coding of records, statistical techniques, and physical or computerized methods for maintaining the security of stored data.

In reviewing confidentiality protections, the IRB will consider the nature, probability, and magnitude of harms that likely would result from a disclosure of collected information outside the research. It will evaluate the effectiveness of proposed anonymizing techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

- 1. Certificates of Confidentiality.** Where research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes.

In such situations, the NMRC IRB may require that an investigator obtain a DHHS Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, State, or local civil, criminal, administrative, legislative, or other legal proceedings.

The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to DoD, DHHS or FDA for audit purposes. Consequently, the NMRC IRB will require that these conditions for release be stated clearly and explicitly in the informed consent document.

Information concerning Certificates of Confidentiality can be obtained from any of the following websites:

<http://www.nimh.nih.gov/research/confident.cfm>
<http://www.niaaa.nih.gov/extramural/confidential.htm>
<http://www.nida.nih.gov/funding/confidentialityfaq.html>
<http://www.hrsa.gov/quality/certconf.htm>
<http://www.cancer.gov/clinicaltrials/conducting/certificates-of-confidentiality>
<http://www.nhlbi.nih.gov/funding/policies/certsinfo.htm>

- h. Additional Safeguards for Vulnerable Subjects Are Appropriate.** In order to approve research, DoD regulations at 32 CFR 219.111(a)(3) and DoD Directive 3216.2 require the IRB determine that, where appropriate, additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as children (45 CFR 46 Subpart D), prisoners (45 CFR 46 Subpart C), pregnant women, fetuses and neonates (45 CFR 46 Subpart B), persons with mental disabilities, or economically or educationally disadvantaged persons. Details about protections

for vulnerable subjects are provided in Chapter 17.

US active military human subjects may be particularly vulnerable to unintended, coercive or undue influences relative to participation in research. Likewise, persons who primarily look to the DoD for treatment of their medical problems may not fully understand the implications of research participation, especially when it is offered by someone they consider a provider of clinical care.

Should the NMRC IRB find that they regularly review research involving such vulnerable subjects, the IRB will include among its reviewers persons who are knowledgeable about and experienced in working with these vulnerable subjects (32 CFR 219.107(a)). For example, a pediatrician when the IRB regularly reviews research involving children, or an active or retired marine when the IRB regularly reviews research involving U.S. Marines, etc.

- i. **Criteria for Requiring Review More Often Than Annually.** The NMRC IRB recognizes that protecting the rights and welfare of subjects sometimes requires that research be reviewed more often than annually. For example, when a new intervention is being tested, the risks may not be completely known. The IRB shall monitor the research project closely, and require more frequent review.

The IRB shall consider the following factors in determining the criteria for which studies require more frequent review and what the timeframes generally will be:

- Probability and magnitude of anticipated risks to subjects.
- Likely medical condition of the proposed subjects.
- Overall qualifications of the principal investigator and other members of the research team.
- Specific experience of the principal investigator and other members of the research team in conducting similar research.
- Nature and frequency of adverse events observed in similar research at this and other facilities.
- Vulnerability of the population being studied.
- Other factors that the IRB deems relevant.

In specifying an approval period of less than 1 year, the IRB may define the period with either a time interval or a maximum number of subjects, i.e., after 3 months or after three subjects). The minutes should clearly reflect these determinations regarding risk and approval period.

- j. **Criteria for Requiring Independent Verification From Sources Other than the Investigator.** The NMRC IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator, that no material changes or other problematic events have occurred during the IRB-designated approval period.

The IRB will consider the following factors in determining which studies require such independent verification:

- The probability and magnitude of anticipated risks to subjects
- The likely medical condition of the proposed subjects
- The probable nature and frequency of changes that may ordinarily be expected in type of research proposed
- Prior experience with the principal investigator and research team
- Any other factors that the IRB deems relevant

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review.

Chapter 12

Required Elements of Informed Consent

One overarching requirement of research involving human subjects is that investigators must obtain the informed consent of prospective subjects before they can be included in research. Informed consent presumes two simultaneous concepts: informed decision-making and voluntary participation. Prospective subjects must be given sufficient information about the research and its risks and benefits to reach an **informed decision** as to whether they will **voluntarily participate**.

To ensure an effective informed consent process, Department of Defense (DoD) regulations at 32 CFR 219.116(a), the Common Rule, and Food and Drug Administration (FDA) regulations mandate the **inclusion of eight basic informed consent elements**. Six additional elements may be required, depending on the nature of the research (32 CFR 219.116(b)). The IRB may require any or all of the six additional elements depending on the nature of the research.

a. **Research Statement (Required Element #1).** Informed consent information must include the following:

- A statement that the study involves research.
- An explanation of the purposes of the research.
- An explanation of the expected duration of subjects' participation.
- A description of what procedures will be followed.
- Identification of any procedures that are experimental.

If the treating physician is also the research investigator, some subjects may not realize they are participating in research, but believe they are just being treated for their condition. By specifying the purpose of the research and describing experimental procedures, it is intended that subjects will be able to recognize the difference between research and treatment.

b. **Reasonably Foreseeable Risks or Discomforts (Required Element #2).** Informed consent information must describe any reasonably foreseeable risks or discomforts associated with the research. Risks should be listed in descending order of probability and magnitude (risk of death (even if remote) before risks associated with blood draw, for example).

c. **Reasonably Expected Benefits to Subjects or Others (Required Element #3).** Informed consent information must describe any benefits to subjects or to others that may reasonably be expected from the research. However, care must be taken not to overstate the benefits and create an undue influence on subjects. Payment for subject's participation in a research project is not to be considered as a benefit of the research.

- d. **Appropriate Alternatives (Required Element #4).** Informed consent information must include a disclosure of any appropriate alternative procedures or courses of treatment that may be advantageous to the subject. Enough detail must be presented so that the subject can understand and appreciate the nature of any alternatives. It is not sufficient simply to state, “the doctor will discuss alternatives to participating.”
- e. **Extent of Confidentiality (Required Element #5).** Informed consent information must describe the extent to which confidentiality of records identifying the subject will be maintained (or not maintained). Research often poses the risk of loss of confidentiality to subjects who participate. Many persons who would not otherwise have access to identifiable, private information about the subject may be involved in the research process. Consent information should describe any procedures that the research team will use to protect subjects’ private records. In some research, loss of privacy may be the greatest risk of participation.

The following statement is required for FDA -regulated research:

Because this research involves articles regulated by the Food and Drug Administration (FDA), the FDA may choose to inspect and copy medical or research records that identify individual research subjects.

A comparable statement is recommended for any research that is subject to audit or inspection by any funding agency or sponsor.

- f. **Compensation or Treatment for Injury (Required Element #6).** Informed consent information for research involving more than minimal risk must include explanations regarding:
- Whether any compensation is available if injury occurs.
 - In accordance with DoD policy, a statement that subjects shall receive emergency treatment and necessary follow-up for injuries suffered as a result of participating in a Navy research program should be included.
 - A description of any such compensation or treatments or where more information about them is available.
 - A description of any applicable state law.
- g. **Contact Information (Required Element #7).** Informed consent information must include details, including telephone numbers, about whom to contact for three specific situations:
- *For answers to questions about the research.* The principal investigator and other members of the research team are appropriate contacts for this information.

- *For answers to questions about subjects' rights.* The IRB Chair or in the case of research conducted outside the US, a host-country ethics committee member are appropriate contacts for this information.
 - *In the event of a research-related injury occurs.* Depending upon the nature of the research, a research team member generally serves as appropriate contacts for this information.
- h. Voluntary Participation Statement (Required Element #8).** It is particularly important in the DoD and host country context for subjects and prospective subjects to understand and have complete confidence that failure to participate will not jeopardize their DoD or other usual health care. Informed consent information must contain clear statements of the following:
- Participation in the research is voluntary.
 - Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.
 - The subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- i. Additional Elements Where Appropriate.** Where appropriate, the regulations require that one or more of the following six additional elements are included in the informed consent information:
- 1. Unforeseeable Risks to Subjects, Embryos, or Fetuses.** Some research involves particular procedures or interventions that may result in unforeseeable risks to subjects, to the embryo, or the fetus (if the subject is or may become pregnant). For research of such a nature, the informed consent information must warn subjects that some risks are currently not known or not foreseeable.
 - 2. Investigator-Initiated Termination of Participation.** There may be instances that would require investigators to terminate the participation of particular subjects (e.g., subject non-compliance with research, subject not benefiting from research). The informed consent information must specify these circumstances.
 - 3. Additional Costs.** If subjects must bear any additional costs (transportation, time away from work, health costs, etc.), these must be disclosed in the informed consent information.
 - 4. Early Withdrawal /Procedures for Termination.** Subjects have the right to withdraw from the research. However, some studies involve medications or procedures that would be dangerous for subjects to discontinue abruptly. For studies of this nature, the informed consent information must provide subjects with knowledge of the consequences affecting a decision to withdraw. In addition, if there are procedures regarding how to withdraw safely from the research, these must also be described. It is not appropriate for research staff to administer any additional research-oriented questionnaires or

interventions that do not affect the safety of subjects who have decided to withdraw.

5. Significant New Findings. During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the informed consent information must detail the procedures for contacting subjects regarding this new information and for affirming their continued participation.

6. Approximate Number of Subjects. For certain types of research, the informed consent information should disclose the approximate number of subjects to be enrolled.

j. Waiver or Alteration of Informed Consent Requirements: State or Local Public Benefit Programs. DoD regulations at 32 CFR 219.116(c) and the Common Rule permit an IRB to approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. In order to approve such a waiver or alteration, the IRB must find and document that:

- The activity constitutes a research or demonstration project that is to be conducted by, or subject to the approval of, State or local government officials, and is designed to study, evaluate, or otherwise examine: (a) public benefit or service programs; (b) procedures for obtaining benefits or services under those programs; (c) possible changes in or alternatives to those programs or procedures; or (d) possible changes in methods or levels of payment for benefits or services under those programs; *and*
- The research could not practicably be carried out without the waiver or alteration.

These findings and their justifications will be clearly documented in IRB minutes when the NMRC IRB exercises this waiver provision. **This waiver provision is not applicable to research governed by FDA regulations**, and the NMRC IRB will not approve such alterations or waivers for FDA-regulated research.

k. Waiver or Alteration of Informed Consent Requirements: Minimal Risk Research. DoD regulations at 32 CFR 219.116(d) and the Common Rule permit an IRB to approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. In order to approve such a waiver or alteration, the IRB must find and document that:

- The research involves no more than minimal risk to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;

- The research could not practically be carried out without the waiver or alteration; *and*
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

These findings and their justifications will be clearly documented in IRB minutes when the NMRC IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the NMRC IRB will not approve such alterations or waivers for FDA-regulated research.

1. Waiver of Documentation of Consent. DoD regulations at 32 CFR 219.117(c) and the Common Rule permit an IRB to waive the requirement to obtain written documentation of informed consent. In order to approve such a waiver, the IRB must find and document either of the following conditions:

- The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. In this case, each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; *or*
- The research presents no more than minimal risk of harm to subjects and involves procedures or activities for which written consent is not normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the Principal Investigator to provide subjects with a written statement regarding the research.

These findings and their justifications will be clearly documented in IRB minutes when the NMRC IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the NMRC IRB will not approve such alterations or waivers for FDA-regulated research.

Chapter 13

FDA Regulated Research: Research Involving Drugs, Devices or Biologics

The Food and Drug Administration (FDA) is a component of the U.S. Department of Health and Human Services (DHHS). The FDA's mission is to promote and protect the public health by helping safe and effective products reach the market, and then monitoring these products for continued safety after they are in use.

The FDA regulates clinical investigations (research) conducted on drugs, biologics, devices, diagnostics, and, in some cases, dietary supplements and food additives, hereinafter referred to as "FDA regulated test articles." All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

When an FDA regulated test article is used in research being done at the DoD or funded by another federal agency, more than one set of regulations may apply. For example, clinical trials involving FDA regulated test articles that are supported by DHHS (e.g., the National Institutes of Health) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). To the extent that the research is also conducted by NMRC employees or agents, such trials must comply with the FDA and the DHHS human subject regulations, as well as DoD regulations. Where regulations differ, the NMRC IRB will apply the stricter one.

Given that the type of research in which NMRC investigators are becoming involved continues to expand, this chapter also includes information for IRB members on a variety of investigational new drug and device studies as well as information on available FDA exceptions and exemptions.

- a. FDA Requirements in Relation to the DoD and DHHS Requirements.** The human subject protection requirements found in FDA regulations are substantially the same as the DoD and DHHS requirements. However, there are important differences:
- FDA defines a "human subject" as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control; subject may be either a healthy individual or a patient. (Compare with DoD and DHHS definitions in Chapter 4.)
 - FDA defines a "clinical investigation (research)" as any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA, or need not meet the requirements for prior submission to the FDA, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit; the terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous. (Compare with DoD and DHHS definitions in Chapter 4.)

- FDA regulations contain no Assurance requirement.
- Conditions for exemption, exception, and waiver of IRB review and informed consent requirements differ.
- FDA regulations require specific determinations for the IRB review of device studies (see below).
- FDA regulations include specific requirements for reporting adverse events that are not found in DoD regulations, or the Common Rule.
- DoD Directive 3216.2 requires the inclusion of the specific DHHS additional protections for pregnant women, fetuses, and human in vitro fertilization (Subpart B); prisoners (Subpart C); and children (Subpart D) that are not contained in Common Rule requirements. In April 2001, FDA issued regulations to protect children in research (21 CFR Part 50 Subpart D).
- DoD Directive 3216.2 deems the use of investigational new drugs, biological products or devices **for purposes of Force Health Protection** as non-research activities. Such activities are governed by DoD Directive 6200.2

In addition to regulations governing human subject protection, the FDA also has regulations governing the use of investigational drugs and biological drugs (21 CFR Part 312) and devices (21 CFR Part 812).

- b. **INDs and IDEs.** New medical products that have not yet been approved for marketing by the FDA require a special status so they can be legally shipped for the purpose of conducting clinical investigations to establish safety and efficacy. New Applications are submitted to FDA for approval of research involving an investigational drug, device, or biologic as follows:
1. **An Investigational New Drug (IND)** application is submitted so that an investigation can be conducted in support of a potential New Drug Application. An investigational new drug (or investigational drug) means a new drug or biological drug used in a clinical investigation. An investigational drug must have an IND number before it can be shipped.
 2. **An Investigational Device Exemption (IDE)** supports research to be conducted for a Pre-Market Approval application. Devices that are substantially equivalent to other devices that are legally on the market are called 510(k) devices and can be marketed without clinical testing. Not all investigational devices need an IDE.
 3. **A Biologics License Application** is submitted to the FDA to receive approval for research on biological products that would support a Biologics License. Biologics include any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of human diseases or injuries.

With only a few exceptions, most clinical research being done on FDA regulated test articles with either an IND or IDE will need initial review at a convened IRB meeting.

c. Investigator Responsibilities. Under FDA regulations, the investigator in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study. Each clinical investigator must accept specific responsibilities that include the following:

- Obtaining IRB approval;
- Getting informed consent from each subject;
- Following the investigational plan;
- Complying fully with the regulations;
- Protecting the rights, welfare and safety of the subjects;
- Supervising the use and disposition of the test article;
- Maintaining accurate, current and complete records; and
- Disclosing relevant financial information.

1. Investigators' Requirements for Reporting to the Sponsor. FDA IND regulations require that the investigator report promptly to the Sponsor any "adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" (21 CFR 312.64(b)). FDA IDE regulations require that the investigator notify the sponsor of any unanticipated adverse device effect within 10 days (21 CFR 812.150(a)(1)).

2. Investigator Reporting to the IRB.

- **IRB Chair Notification within 24 hours.** The NMRC IRB Chair must be **notified** of any unanticipated problem involving subjects or others or serious adverse event within 24 hours of learning of the event or problem.
- **Reporting to the IRB Chair within 5 working days.** The NMRC IRB should receive the completed using IRB Form 3, "Reporting Adverse Events or Unanticipated Problems", Safety Report, DSMB Report, or other report from the investigator promptly, *i.e.*, within 5 working days of the investigator becoming aware of the event or report.

3. Investigators' Duty to Report Unanticipated Problems. Investigators are required to report to the IRB **any unanticipated problems involving risks to subjects or others** that occur in research conducted at NMRC facilities or by NMRC employees or agents.

Note: Under DoD and DHHS regulations, "unanticipated problem" means

any research-related event involving risk to anyone associated with the research in any way (including investigators and research assistants) that is not included in the protocol and informed consent document. It includes not only unanticipated adverse events, but other unanticipated problems (e.g., breeches of confidentiality, equipment malfunctions that may injure the investigator, loss of data that results in the need to enroll additional subjects, thus exposing additional subjects to the risks of the research).

- 4. Investigators' Duty to Report Serious Adverse Events.** Investigators are required to report to the IRB **any serious adverse event** that occurs in research conducted at NMRC facilities or by NMRC's employees or agents.

A **serious adverse event** is defined as any adverse experience occurring that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect (21 CFR 312.32(a); 21 CFR 812.3(s)).

- 5. Investigators' Duty to Report Other Adverse Events.** Investigators are required to report to the IRB any adverse event occurring in research conducted at NMRC or NMRC facilities or by NMRC or NMRC employees or agent **that is reported to the research sponsor or the FDA.**
- 6. Investigators' Duty to Forward Correspondence or Reports of Monitoring or Auditing.** Investigators are required to forward reports or correspondence concerning the monitoring or auditing of their research activities or research sites by sponsors, cooperative research groups, federal agencies, or other external entities to the IRB within 5 working days of receipt.
- 7. Investigators' Duty to Forward Sponsor Safety Reports.** Investigators are required to forward safety reports (or other information concerning adverse events) issued by sponsors to the IRB within 5 working days of receipt.
- 8. Investigators' Duty to Forward Data and Safety Monitoring Board (DSMB) Reports.** Investigators are required to forward DSMB reports to the IRB within 5 working days of receipt. When DSMBs are employed, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to make its continuing review substantive and meaningful.
- 9. Investigators' Duty to Notify the IRB of Serious or Continuing Non-Compliance.** Whether involved in the research or not, all employees and agents of NMRC or NMRC are required to notify the IRB if they become aware of any serious or continuing non-compliance with human subject regulatory requirements or with the determinations of the IRB.

Serious non-compliance is defined as non-compliance that involves greater than minimal risk of harm or discomfort to subjects or others involved in the research. **Continuing** non-compliance is defined as violation of regulatory requirements or determinations of the IRB that occurs over an extended period.

- d. **Sponsor Responsibilities.** The sponsor of a clinical investigation initiates and holds the IND or IDE for a clinical investigation, but may not actually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals can also be considered a sponsor for an investigation. An investigator is referred to as the sponsor-investigator when the individual investigator is also the initiator of the clinical investigation.

The responsibilities of sponsors and sponsor-investigators include the following:

- Maintaining the IND, IDE, or Biologics License
 - Obtaining qualified investigators and monitors
 - Providing necessary information and training for Investigators
 - Monitoring the investigation
 - Controlling the investigational agent
 - Reporting significant adverse events to FDA /Investigators
 - Maintaining and retaining accurate records
1. **Sponsor Reports to FDA and Investigators (INDs).** FDA IND regulations require that the Sponsor notify the FDA and all participating investigators of any adverse experience associated with the use of a drug or biologic that is both serious and unexpected as soon as possible but in no event later than 15 calendar days after the sponsor determines it to be reportable. The FDA should be notified by telephone, facsimile, or in writing as soon as possible but in no event later than seven calendar days of the sponsor's receipt of the information of any unexpected fatal or life-threatening experience.
- “Serious adverse drug experience” is defined as “any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect” (21 CFR 312.32(a)).
2. **Sponsor to Report to FDA, Investigator, and IRB (IDEs).** FDA IDE regulations require that the Sponsor is required to evaluate the event and report serious, unexpected adverse device effects to the FDA, to all

participating investigators, and to the IRB within 10 working days of the sponsor's receipt of the information.

e. IRB Review of Medical Devices.

1. Significant Risk vs. Non-Significant Risk Determination. In accordance with FDA requirements, it is the policy of NMRC that a determination of Significant Risk (SR) or Non-Significant Risk (NSR) for a medical device is made prior to consideration of approval of the medical device study. The Significant Risk vs Non-Significant Risk determination must be made by the convened IRB. The criteria for approval of device studies are the same as for any FDA-regulated study.

a) A Significant Risk (SR) Device study presents a potential for serious risk to the health, safety, or welfare of a subject and (i) is intended as an implant, or (ii) is used in supporting or sustaining human life, or (iii) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health. The FDA considers studies of all SR devices to present more than minimal risk; therefore, full IRB review for all studies involving SR devices is necessary. All devices with an IDE number require full Board approval. Note: It is very important to note that the terms "non-significant risk" and "minimal risk" are defined separately, and are not synonymous.

If the IRB determines, or concurs with the assessment of the sponsor that a device study involves a SR, then it would be governed by the IDE regulations at 21 CFR Part 812. The determination of the risk status of the device should be based on the proposed use of the device in the investigation. The IRB may review any of the following materials:

- A description of the device;
- Reports of prior investigations conducted with the device;
- The proposed investigational plan;
- A description of subject selection criteria;
- Monitoring procedures; and
- The sponsor risk assessment and the rationale used to make the sponsor's risk determination;
- The IRB may also request additional information if necessary from the sponsor or investigator or ask the FDA to provide a risk assessment;

b) A Nonsignificant Risk (NSR) Device study is one that does not meet the definition of a SR study. A device study that is deemed to involve a NSR may begin immediately following IRB approval since it would not require the submission of an application to the FDA.

2. **510(k) Devices.** A 510(k) Device is a new device that the FDA agrees is substantially equivalent to a device already on the market. 510(k) devices can be marketed without clinical testing. However, if clinical data are necessary to demonstrate equivalence, any clinical studies must be conducted in compliance with the requirements of the IDE, IRB review and informed consent regulations. Because 510(k) devices under clinical investigation fall under the IDE regulations, reporting of adverse or unanticipated 510(k) device effects follow the same requirements (see below).
3. **Radiology Devices and Radioactive Materials.** FDA is responsible for regulating radiology devices and radioactive materials used in healthcare and research. Oversight in this area is handled by the WRAMC Radiation Safety Chair.
- f. **“Off-label” (Unapproved) Use of FDA-Regulated Products in Medical Practice vs. Research.** The FDA approves the sale, use, and labeling of a product for specific indications (the reason the product is being used – a disease, condition, as a diagnostic tool, etc.). “Off-label” or unapproved use is when the product is used in a way or on a population different from that for which it was approved. The IND regulations do not apply to the use of marketed drugs for unlabeled indications in the practice of medicine (21 CFR 312.2(d)).

Good medical practice and the best interests of the patient require that physicians use legally available, marketed drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not included in the approved labeling (i.e., off-label), they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects.

The FDA definition of research in the IND regulations is as follows: “Clinical investigation” means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice (21 CFR 312.3(a)). Thus, under the FDA IND regulations, it is possible for one drug given to one person to be considered research.

The off-label use of a marketed drug or biologic in research does require IRB review, informed consent and, under some circumstances, may require an IND. To be exempt from the requirements of the IND regulations, all the following must apply (note that includes the requirement of IRB review and informed consent):

- The investigation is not intended to support a new indication for use nor any other significant change in the labeling for the drug;
- The investigation is not intended to support a significant change in the advertising for the product;

- 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 risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- The investigation is conducted in compliance with the requirements for IRB review and informed consent; and
- The investigation is conducted in compliance with the FDA regulations on promoting and charging for investigational drugs (21 CFR 312.7).

Use of an off-label marketed product in research intended to support **a new indication for use, change in labeling or advertising** requires IRB review, informed consent and submission of an IND.

Using an off-label marketed product in research involving a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with its use requires IRB review, informed consent and may also require submission of an IND.

g. Expanded Access to Investigational Drugs. Investigational products are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an investigational new drug (IND) used for these purposes reflect the recognition by the FDA that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval (21 CFR 312.34, 312.35, and 312.83).

1. Treatment IND. The treatment IND (21 CFR 312.34 and 312.35) is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug. Treatment IND studies require prospective IRB review and informed consent. Four requirements must be satisfied before a treatment IND can be issued:

- The drug must be intended to treat a serious or immediately life threatening disease;
- There must be no satisfactory alternative treatment available;
- The drug must already be under investigation or the drug trials must have been completed; *and*

- The trial sponsor must be actively pursuing marketing approval.
2. **Single Patient Treatment IND.** The Single-Patient Treatment IND is not described in regulations yet, but was added to the law under the FDA Modernization Act (FDAMA) in 1997. From an operational standpoint, the Single-Patient IND must meet the same requirements as a standard IND, and requires IRB review and approval and informed consent.
 3. **Group C Treatment IND.** Group C drugs are Phase III study drugs that have shown evidence of efficacy in a specific tumor type. Group C drugs are distributed by the National Cancer Institute (NCI) with a Guideline Protocol and an informed consent document. Informed consent is required, and although FDA and NCI permit the use of Group C drugs without local IRB review, NMRC policy normally requires review and approval by the NMRC IRB. Investigators who are considering use of Group C drugs should contact the IRB Chair for guidance.
 4. **Orphan Drugs.** The term "orphan drug" refers to a product that treats a rare disease affecting fewer than 200,000 Americans. The treatment use of orphan drugs requires prospective IRB review and approval and informed consent (21 CFR 316.40 and 312.34).
 5. **Parallel Track Studies.** FDA also permits wider access to promising new drugs for HIV/AIDS related diseases under a "separate access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. These so-called "parallel track" studies require prospective IRB review and informed consent.
 6. **Open Label Protocol or Open Protocol IND.** These are usually uncontrolled studies, carried out to obtain additional safety data (Phase III studies). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB review and informed consent.
- h. **Expanded Access to Investigational Devices.** According to statute and FDA regulations, an unapproved medical device may normally only be used in human subjects when the device is under clinical investigation and when used by investigators participating in the clinical trial. FDA recognizes, however, that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient, to prevent irreversible morbidity or to help a patient suffering from a serious disease or condition for which there exists no alternative therapy. Four main mechanisms are utilized by FDA to make unapproved devices available to patients/physicians faced with circumstances such as those described above. These mechanisms are consistent with the Expanded Access provisions of the FDA Modernization Act of 1997 (Section 561 of the Federal Food, Drug, and Cosmetic Act). The sponsor must agree and FDA must approve the use. Under most circumstances such studies require IRB review and informed consent.

1. **Treatment Use/IDE (21 CFR 812.36).** Treatment use of an investigational device facilitates the availability of promising new devices to desperately ill patients as early as possible before general marketing begins. Such use permits wide access to the device dependent upon patient need. IRB review and approval and informed consent are required. Such use may occur when:
 - the patient has a serious or immediate life-threatening condition;
 - there is no comparable or satisfactory alternative available;
 - the device is under investigation in a controlled trial for the same use (or such trials have been complete);
 - the Sponsor is pursuing marketing approval/clearance;
 - the Sponsor has submitted and the FDA has approved an IDE under 21 CFR 812.36.
2. **Single Patient/Small Group Access to Investigational Devices.** Allows access to a device where patient is not eligible for an ongoing clinical trial. The subject must have a serious condition/disease, with no alternative intervention available. Under some conditions, FDA may grant permission even if there is no pre-existing IDE.
3. **Continued Access to Investigational Devices.** Allows access to a device while a marketing application is being prepared and reviewed, and can be used to collect additional evidence of safety and effectiveness, as well as to address new questions regarding the investigational device, such as labeling claims. There must be a public health need for the device, as well as preliminary evidence that the device is effective.
4. **Access under a formal protocol.** Access in a controlled rate of enrollment and with no significant safety concerns identified for the proposed indication.
- i. **Gene Transfer Research.** Gene transfer involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by the both the FDA and the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA).

FDA regulations require the submission of an IND for human gene transfer research through the FDA Center for Biologics.

DHHS regulations specify that no individual may be enrolled in human gene transfer research until review has been completed by the NIH Recombinant DNA Advisory Committee (RAC), local Institutional Biosafety Committee approval has been obtained, local IRB approval has been obtained, and the investigator has obtained all other necessary regulatory authorizations from the subject.

While the RAC is advisory to the Director of the NIH, compliance with its

guidelines is mandatory for all investigators at institutions that receive NIH funds for research involving recombinant DNA.

j. Emergency Use of a Test Article Without IRB Review. An exemption under FDA regulations at 21 CFR 56.104(c) permits the emergency use of an investigational drug, device, or biologic on a one-time basis per institution without IRB review and approval.

1. Emergency Use of Drugs. Emergency use of an investigational new drug occurs when the emergency situation does not allow time for submission of an IND. Use of the drug requires a request to FDA to authorize shipment of the drug for the emergency use. Such authorization is conditioned on the sponsor making an appropriate IND submission as soon as practicable (21 CFR 312.36). The emergency use of an investigational new drug may take place without IRB review and approval, provided that the use is reported to the IRB within 5 working days. Informed consent is required unless the situation is life-threatening, the criteria at 21 CFR 50.23(a) or 50.23(b) have been met, and the IRB is notified within 5 working days.

2. Emergency Use of Devices. Emergency use of an unapproved device may occur in an emergency situation when (i) an IDE for the device does not exist, (ii) a physician wants to use a device in a way not approved under an existing IDE, or (iii) when a physician is not an investigator under the existing IDE. The device may be used if (i) the patient has a life-threatening condition that needs immediate treatment, (ii) there is no generally acceptable alternative treatment, and (iii) there is no time to obtain FDA approval. Such uses require as many of the following patient protections as possible (FDA Center for Devices and Radiological Health Guidance on IDE Policies and Procedures, January 20, 1998): (i) informed consent; (ii) clearance from the institution; (iii) concurrence of the IRB Chair (this concurrence does not constitute IRB approval); (iv) an independent assessment of an uninvolved physician; and (v) authorization from the IDE sponsor (if an IDE exists). Follow-up reports should be provided to the Sponsor if an IDE exists, or to FDA if no IDE exists. Such use is limited to a few patients.

If at all possible, investigators should consult the IRB Chair for guidance when considering the emergency use of drugs or medical devices.

The following conditions must be met for this type of emergency use:

- A human subject is in a life-threatening situation
- No standard acceptable treatment is available
- There is insufficient time to obtain IRB approval
- The emergency use must be reported to the IRB within 5 working days. This reporting must not be construed as an approval for the emergency use by the IRB

- Ordinarily, the investigator must obtain the informed consent of the subject for such an emergency use, except as described below

k. Emergency Use of a Test Article Without Informed Consent. An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

- The subject is confronted by a life-threatening situation necessitating the use of the test article
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject
- Time is not sufficient to obtain consent from the subject's legally authorized representative
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life

If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within 5 working days. The emergency use must be reported to the IRB within 5 working days. This reporting must not be construed as an approval for the emergency use by the IRB. *Note: This use without prospective IRB approval is not research, but medical treatment, and cannot be counted as research data.*

l. "Compassionate" or "Humanitarian" Use of a Test Article. "Compassionate Use" is not a term that appears in the FDA or DoD regulations or the Common Rule.

For studies involving investigational drugs "Compassionate Use" is often meant to refer to the emergency use situations discussed above. The term does not appear in FDA guidance relating to investigational drugs.

For studies involving investigational devices, compassionate use may occur when a device that is being tested in a clinical trial is the only option available for a patient with a serious condition who does not qualify for the trial. Such uses require prior FDA approval of a protocol deviation under 21 CFR 812.35(a). Prior FDA approval for compassionate use should be obtained before the device is used.

On occasion, compassionate use may occur even if there is no IDE for the device. Under this situation, the physician would submit the compassionate use request directly to FDA.

Compassionate use of an unapproved device also requires as many of the

following protections as possible: (i) informed consent; (ii) clearance from the institution; (iii) concurrence of the IRB Chair (which does not constitute IRB approval); (iv) an independent assessment of an uninvolved physician; and (v) authorization of the IDE sponsor. Follow-up reports should be provided to the Sponsor. Such use may involve an individual patient or a small group of patients.

If at all possible, investigators should consult the IRB Chair for guidance when considering such “compassionate use.”

Note: The above “Compassionate Use” situations should not be confused with the Humanitarian Use Device (HUD) Exemption (see below).

- m. Humanitarian Device Exemptions.** A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. FDA developed this regulation to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations. The regulation provides for the submission of a humanitarian device exemption (HDE) application. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use. The labeling for an HUD must state that the device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.

An approved HDE authorizes marketing of the HUD. However, a HUD may only be used after approval of the convened (full) IRB has been obtained for use of the device at the institution for the FDA approved indication (21 CFR 814.124(a)). After granting initial approval, the IRB may use expedited procedures for conducting continuing review. Informed consent of patients is not required because an HDE provides for marketing approval, so use of the HUD does not constitute research.

- n. Planned Emergency Research.** An exception under FDA regulations at 21 CFR 50.24 permits planned research in an emergency setting without the informed consent of the subjects. The requirements for planned emergency are extremely complex and require much consultation within NMRC, within the community in which the research will be conducted, and within FDA, DHHS, or other Common Rule Agency. Investigators should contact the IRB Chair well in advance if they wish to conduct planned emergency research.

Planned emergency research must be approved by the Assistant Secretary of the Navy, Research, Development and Acquisition (ASN(RDA)).

Chapter 14

Social and Behavioral Research

Social and behavioral research often involves surveys, observational studies, personal interviews, or experimental designs involving exposure to some type of stimulus or intervention. This chapter discusses when exemption and expedited review are appropriate for this type of research.

- a. Social and Psychological Harms.** When evaluating behavioral and social science research, the NMRC IRB carefully examines the research to determine the probability of risk of harm to subjects. The IRB should consider the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm. The IRB should also consider the risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, or reputation; stigmatization; and damage to social or family relationships.

If information is being collected on living individuals other than the primary “target” subjects, the IRB should consider the risk of harm to those “non-target” individuals, as well. The IRB may require additional protections, study redesign, or the informed consent of “non-target” individuals (unless the requirement for informed consent can be waived). (See also, Chapter 6)

To mitigate such risks, the NMRC IRB reviews the proposal for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in or affected by the research.

- b. Privacy and Confidentiality Concerns.** The use of confidential information is an essential element of much social and behavioral research. It is important to ensure that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individuals. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research. However, there are circumstances that are exempt from the regulations, and circumstances in which the IRB may approve a waiver of the usual informed consent requirements. These have been discussed previously in Chapters 9 and 11, and will also be discussed briefly in following sections of this chapter.

It is also important to ensure that adequate measures are taken to protect individually identifiable private information once it has been collected to prevent a breach of confidentiality that could lead to a loss of privacy and potentially harm subjects.

- c. Safeguarding Confidentiality.** When information linked to individuals will be recorded as part of the research design, the NMRC IRB ensures that adequate

precautions shall be taken to safeguard the confidentiality of the information. The more sensitive the data being collected, the more important it is for the researcher and the IRB to be familiar with techniques for protecting confidentiality.

IRBs that review research in which the confidentiality of data is a serious issue should have at least one member (or consultant) familiar with the strengths and weaknesses of the different mechanisms available to protect subjects' confidentiality.

When reviewing survey and interview research, the IRB will be aware of the regulatory provision at 32 CFR 219.117(c)(1) for waiving documentation of consent when a signed consent form constitutes the only link between the research and the subjects and would itself be a risk to the subjects (Chapter 11).

Among the available methods for ensuring confidentiality are coding of records, statistical techniques, and physical or computerized methods for maintaining the security of stored data.

DoD regulations at 32 CFR 219.116(a)(5) and the Common Rule require that subjects be informed of the extent to which confidentiality of research records will be maintained.

Federal officials have the right to inspect and copy research records, including consent forms and individual medical records, to ensure compliance with the rules and standards of their programs. Identifiable information obtained by Federal officials during such inspections is protected by the provisions of the Privacy Act of 1974.

The NMRC IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings. CoCs are discussed in Chapter 11.

- d. **Exempt Research.** Some social and behavioral research is exempt from the requirements of the DoD regulations (32 CFR 219.101(b)) and the Common Rule. However, appropriate application of these exemptions requires a relatively sophisticated level of expertise and should not be left to individual investigators. NMRC IRB policy requires that the IRB Chair or Vice Chair review all requests for exemption from IRB review and must have sufficient information from the investigator to ascertain whether the claimed exemption really applies.

The following exemptions are particularly applicable to social and behavioral research.

1. **Exempt Research in Educational Settings.** Research conducted in established or commonly accepted educational settings that involves normal educational practices is exempt from DoD regulations and the Common Rule in accordance with 32 CFR 219.101(b)(1) and 45 CFR 46.101(b)(1).

This exemption does not apply if the setting is not commonly recognized as an educational one, or if other than normal educational practices are employed. Even if the research is exempt, the investigator has an ethical obligation to ensure that students' rights and welfare are respected.

When educational institutions become engaged in the actual conduct of research, they are required to file an Assurance in accordance with DoD regulations at 32 CFR 219.103(a) and the Common Rule.

- 2. Exempt Research Using Educational Tests (Cognitive, Diagnostic, Aptitude, and Achievement Tests), Survey Procedures, Interview Procedures, or the Observation of Public Behavior.** Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is ordinarily exempt under Federal regulations at 32 CFR 219.101(b)(2).

When the subjects are adults, this exemption applies **unless**: (a) information is recorded in an identifiable manner (either directly or indirectly using codes or other identifying links); **and** (b) disclosure of the information would place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation. *Note: The research is exempt unless both (a) and (b) apply; i.e., the research is exempt unless the information collected is both identifiable and sensitive, except in the case of children as follows.*

This exemption applies to research involving children, **except** that: (a) research involving survey or interview procedures with children is **not exempt**; and (b) research involving observation of the public behavior of children is **not exempt** if the investigator participates in the actions being observed.

If not exempt under the conditions described above, research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is exempt where: (a) the subjects are elected or appointed public officials or candidates for public office; or (b) federal statutes require confidentiality without exception. *Note: Condition (b) regarding federal statutes rarely applies. The IRB should consult with BUMED if it receives an exemption request based on absolute confidentiality under a federal statute.*

If not exempt under the conditions described above, the IRB may often utilize expedited procedures for review and approval of research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior.

- 3. Exempt Research Using Existing Data and Documents.** Social and behavioral research often relies on analysis of existing data or documents. Such research, which is often exempt, was discussed in Chapter 9 and will be discussed further in Chapter 14.

- e. **Expedited Review.** Expedited review of behavioral and social science research that presents no greater than minimal risk to subjects and fits one (or more) of the nine categories specified in the November 9, 1998, Federal Register FR 60364-60367 may be reviewed by the IRB utilizing expedited procedures (see Chapter 10).

The categories discussed below are particularly applicable to social and behavioral research, and include research involving children as well as adult subjects.

1. **Expedited Review of Research Involving Existing Data and Documents (Expedited Category #5).** Minimal risk research involving materials, (including data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes, may be reviewed using expedited procedures. The intent is to define two categories here, each appropriate for expedited review.
 - Non-exempt research involving materials that have already been collected (for any previous research or non-research purpose) at the time when the research is proposed.
 - Non-exempt research involving materials that will be collected in the future for a non-research purpose.
2. **Expedited Review of Research Involving Data from Voice, Video, Digital, or Image Recordings Made for Research Purposes (Expedited Category #6).** The NMRC IRB may utilize expedited procedures to review research that involves the collection of data from voice, video, digital, or image recordings made for research purposes.
3. **Expedited Review of Research Involving Individual or Group Characteristics or Behavior or Research Employing Survey, Interview, Oral History, Focus Group, Program Evaluation, Human Factors Evaluation, or Quality Assurance Methodologies (Expedited Category #7).** The NMRC IRB may utilize expedited procedures to review the following:
 - Research on individual or group characteristics or behavior, or
 - Research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

This category covers a wide range of non-exempt social and behavioral research activities when they present no greater than minimal risk to subjects. Examples include, but are not limited to, research on perception, cognition, motivation, identification, language, communication, cultural beliefs or practices.

- f. **Research Involving Deception or Withholding of Information.** IRBs reviewing research involving incomplete disclosure or outright deception must apply both common sense and sensitivity to the review. Deception research involves

psychology research in which the subject is not told, or is misled, about the true purpose of the research, such as in certain studies of group processes, contextual influences on cognition, etc.

Where deception is involved, the NMRC IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects shall be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a corresponding benefit.) The NMRC IRB should also make sure that the proposed subject population is suitable.

Deception can only be permitted where the IRB documents that a waiver of the usual informed consent requirements is justified under the criteria present in DoD regulations at 32 CFR 219.116(d). Specifically, the NMRC IRB must find and document that all four of the following criteria have been satisfied:

- The research presents no more than minimal risk to subjects.
- The waiver or alteration shall not adversely affect the rights and welfare of the subjects.
- The research could not practicably be carried out without the waiver or alteration.
- Where appropriate, the subjects shall be provided with additional pertinent information after participation.

In making the determination to approve the use of deception under a waiver of informed consent, the IRB should consider each criterion in turn, and document specifically (in the minutes of its meeting and/or in the IRB protocol file) how the proposed research satisfies that criterion. **Note:** *The regulations make no provision for the use of deception in research that poses greater than minimal risks to subjects.*

Chapter 15

Research Combining Biomedical and Social & Behavioral Elements

Many studies combine characteristics of behavior and social research with characteristics of biomedical research. There are many interdisciplinary combinations of behavioral and medical research. They often use or create tissue, specimen, or data repositories (banks).

- a. Prospective Use of Existing Materials.** Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research.

Prospective studies using materials (data, documents, records or specimens) that will “exist” in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do **not** qualify for exemption under DoD regulations at 32 CFR 219.101(b)(4) and the Common Rule because the materials in these studies are not in existence at the time the study is proposed and initiated.

However, IRBs may utilize expedited procedures (under expedited category #5, see Chapters 10 and 14) to review research that proposes to use materials (i.e., data, documents, records, or specimens) that will be collected in the future (i.e., after the research has been proposed and initiated) for non-research purposes (e.g., clinical observations, medical treatment, or diagnosis occurring in a non-research context).

- b. Retrospective Use of Existing Materials.** Retrospective studies involve research conducted by reviewing materials (data, documents, records, or specimens) collected in the past (e.g., medical records, school records, or employment records) and existing at the time the research is proposed and initiated.

Such research may be exempt under DoD regulations at 32 CFR 219.101(b)(4) if the information is publicly available or if the information is recorded in such a manner that subjects cannot be identified, either directly or through identifiers linked to the subjects (Chapter 9).

If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects (see Chapter 10).

However, retrospective studies using existing materials occasionally entail significant, greater than minimal risks and require review by the convened IRB (e.g., where the research reveals previously undisclosed illegal drug use and the expedited review had concerns about invasion of subjects’ privacy and/or the adequacy of confidentiality protections proposed by the investigators).

- c. Research Utilizing Large Existing Data Sets.** Biosocial and bio-behavioral research often involves the use of large, existing data sets.

When the data sets are publicly available (i.e., available to the general public, with or without charge), their use is exempt, even if they contain sensitive, identifiable information (see Chapter 9). Of course, use of data from publicly available data sets would still be exempt if the information is not sensitive or not identifiable.

The use of large, existing data sets requires IRB review when they contain identifiable private information about living individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

In making this determination, the IRB should first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent.

If this is not the case, then the IRB should consider whether it is permissible to waive the usual informed consent requirements in accordance with 32 CFR 219.116(d). Many times, a waiver of consent will be appropriate.

In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses “anonymized” data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a manner that neither the investigator nor the source maintaining the data set can re-establish subjects’ identities.

An alternative to anonymizing data is to maintain the data set as a data repository under the guidelines established by the Office for Human Research Protections (OHRP).

- d. Research Using Data or Tissue Banks (also called Repositories).** Human data repositories collect, store, and distribute identifiable information about individual persons for research purposes. Human tissue repositories collect, store, and distribute identifiable human tissue materials for research purposes.

Tissue Bank activities involve three components: (a) the collectors of data or tissue samples; (b) the bank/repository storage and data management center; and (c) the recipient investigators. Under a repository arrangement, an IRB formally oversees all elements of repository activity, setting the conditions for collection, secure storage, maintenance, and appropriate sharing of the data and/or tissues with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is, or is not, required.

Typically, these parameters involve formal, written agreements stipulating conditions as follows:

- The repository shall not release any identifiers to the investigator.
- The investigator shall not attempt to recreate identifiers, identify subjects, or contact subjects.
- The investigator shall use the data only for the purposes and research specified.

The investigator shall comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects. Additional information about the operation of data repositories can be found in the list of references.

Chapter 16

IRB Considerations Regarding Study Design

- a. **Research Involving Data Sets and Repositories.** When the data sets are publicly available (i.e., available to the general public, with or without charge), their use is exempt, even if they contain sensitive, identifiable information. Of course, use of data from publicly available data sets would still be exempt if the information is not sensitive or not identifiable.

The use of existing data sets requires IRB review when they contain identifiable private information about living individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

In making this determination, the NMRC IRB will first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent. If this is not the case, then the IRB will consider whether it is permissible to waive the usual informed consent requirements in accordance with 32 CFR 219.116(d). Many times, a waiver of consent will be appropriate.

In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses “anonymized” data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a manner that neither the investigator nor the source maintaining the data set can re-establish subjects’ identities. An alternative to anonymizing data (or making data anonymous) is to maintain the data set as a data repository under the guidelines established by OHRP (see below and refer to Guidance on this topic on the OHRP Website).

Repository activities involve three components: (i) the **collectors** of data or tissue samples; (ii) the **repository** storage and data management center; and (iii) the **recipient** investigators.

Under a repository arrangement, the IRB formally oversees all elements of repository activity, setting the conditions for collection, storage, secure maintenance, and sharing of the data and/or tissues with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is not required.

Typically, these parameters involve formal, written agreements stipulating these conditions:

- The repository will not release any identifiers to the investigator;
- The investigator will not attempt to recreate identifiers, identify subjects, or contact subjects;

- The investigator will use the data only for the purposes and research specified; and
 - The investigator will comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects.
- b. Epidemiological Research.** Epidemiological research often makes use of sensitive, individually identifiable, private information (usually obtained from medical or other private records), and links this information with additional information obtained from other public or private records, such as employment, insurance, or police records. Epidemiological research may also combine historical research with survey and interview research.

Epidemiological studies often present significant problems regarding both privacy and confidentiality.

The IRB must first consider privacy issues, and must satisfy itself that the research does not constitute an unwarranted invasion of the subjects' privacy. In doing so, the IRB shall seek to establish that the investigator has legitimate access to any identifiable information that is to be utilized. For example, if State disease registry information is to be utilized, the IRB will need to examine State law relative to the legitimate release of such information for research.

Once the IRB's privacy concerns have been resolved, the IRB will examine mechanisms for maintaining the confidentiality of data collected. The IRB shall seek to establish that confidentiality protections are appropriate to the nature and sensitivity of the information that has been obtained.

Because epidemiological research typically requires large numbers of subjects, investigators should consider requesting that the IRB waive the usual requirements for informed consent. To approve such a waiver in epidemiological research, the IRB must find and document that the criteria for a waiver of informed consent have been met (32 CFR 219.116(d); specifically that (a) the research presents no more than minimal risk to subjects; (b) the waiver will not adversely affect the rights and welfare of the subjects; (c) the research could not practicably be carried out without the waiver, and (d) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

- c. Issues in Genetic Research.** Information obtained through genetic research may have serious repercussions for the subject or the subject's family members. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. Those genetic studies limited to the collection of family history information and blood drawing should not automatically be classified as "minimal risk" studies qualifying for expedited IRB review. The addition of the genetic analysis can radically alter the level of risk.

The protection of private information gathered for and resulting from genetic research is a major concern. The IRB should expect the investigator to describe in detail how individual privacy will be protected and how the confidentiality of obtained information will be maintained.

Those genetic studies limited to the collection of family history information and blood drawing should not automatically be classified as "minimal risk " studies qualifying for expedited IRB review. Because this is a developing field, there are some issues for which no clear guidance can be given at this point, either because not enough is known about the risks presented by the research, or because no consensus on the appropriate resolution of the problem yet exists.

"Third parties," about whom identifiable and private information is collected in the course of research, are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. IRB's can consider if informed consent from third parties can be waived in accordance with 32 CFR 219.116 and if so, document the specific criteria to waive informed consent in the IRB minutes.

- d. **Family History Research.** Family history research is a common technique used in bio-social and bio-behavioral research. Family history research typically involves obtaining information from one family member (called a proband) about other family members (third parties).

It is important to recognize the DoD regulations at 32 CFR 219.102 (f)(2) and the Common Rule include in the definition of human subject a living individual about whom an investigator obtains "identifiable private information."

Thus, the family members identified and described by the proband may be human subjects under the regulations if the investigators obtain identifiable private information about them.

IRBs must determine whether family members (third parties) are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived under the conditions specified at 32 CFR 219.116(d). There is not total consensus in the available guidance on this issue. OHRP representatives have advised that "third parties" about whom identifiable and private information is collected in the course of research are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. IRB 's can consider if informed consent from third parties can be waived in accordance with 32 CFR 219.116 and if so, document that in the IRB minutes. In most cases waiver of consent may be appropriate.

- e. **Issues in Testing for Seropositivity.** Seropositivity is a term for a positive serum reaction. This is typically used in reference to testing for the presence of antibodies in a blood sample. There may be additional factors that the IRB should consider when reviewing such research, especially where a positive test for an infectious agent or organism would have clinical significance for the subject.

1. **HIV Testing.** BUMED Instruction 3600.6B provides the following considerations for research involving testing of research subjects for infection with HIV, and whose test results can be associated with personal identifiers, i.e., are not anonymous:
 - Research subjects must be told in advance they will be tested for infection with HIV, and that this information will be reported to them and to the appropriate military or civilian authorities if required by law or regulation. These statements are to be incorporated into the informed consent process.
 - Research subjects must be told the investigators are obligated to make test results available to the individual research subject. If a research participant does not want to know his or her result, his or her only recourse is not to participate in the study.
 - If a research subject is informed that he or she has tested positive for infection with the HIV, the investigators are obligated to ensure the research subject is provided with the opportunity for appropriate counselling about the disease and infectivity.
 - If the human research subjects are foreign nationals and research is conducted under the auspices of a host government, it remains the responsibility of naval investigators to ensure the research subjects are informed of their positive test result and provided the opportunity to receive appropriate counselling. Delegation of either of these responsibilities to host country officials is prohibited without such participation by naval investigators that they could verify that the ethical and legal responsibilities have been properly executed. This policy does not require naval investigators to personally and exclusively inform and counsel research subjects, nor does it preclude appropriate delegation of these responsibilities. This policy does require the naval investigator participate in the process to the extent that they can verify their research subjects are being appropriately informed and counselled.
 - One of the greatest potentials for harm to a research subject involves disclosure of the confidential information regarding the research subject's HIV positive status. Considerations for protection of data and confidentiality are of particular importance in research involving research subjects with HIV infection. These considerations and safeguards must be fully disclosed in the research protocol and consent document.
2. **Testing for Other Organisms or Infectious Agents.** When testing for other infectious agents or organisms (such as HTLV-1, Hepatitis B or C), investigators and IRB members should consider tailoring the above safeguards to best meet the welfare and protections of participating subjects. For example, if testing for malaria exposure, a referral to a treating physician instead a counsellor would be appropriate.

- f. Research Involving Potentially Addictive Substances.** Research involving potentially addictive substances often involves the use of what may be termed “abuse-labile” substances. Abuse-labile substances are pharmacological substances that have the potential for creating abusive dependency. Abuse-labile substances can include both legal and illicit drugs. The following are among the issues that the IRB should consider when reviewing research involving potentially addictive substances:
- When this type of research is proposed, the IRB must consider the subjects’ capacity to provide continuous informed consent, ensuring that subjects are competent and are not coerced.
 - If such research involves subjects that are institutionalized, the subjects’ ability to exercise autonomy could be impaired.
 - The IRB must also consider the requirements for equitable selection of subjects and protections for maintaining confidentiality, as such a population may be at risk for being discriminated against, or over-selected.
 - The IRB must be sensitive to the ethical context of the research, in that there may be moral dilemmas associated with the use of placebos, or in cases where addicts are presented with alcohol and/or drugs.
 - It is critical that the IRB focus on the considerations of risk and benefit of such research.

Chapter 17

Potentially Vulnerable Subject Groups

Department of Defense (DoD) regulations at 32 CFR 219.111(b), Food and Drug Administration (FDA) regulations, and the Common Rule require IRBs to give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB is also required to ensure that it has adequate representation on the Board to consider specific kinds of research involving these vulnerable populations in a satisfactory manner.

a. Elements to Consider in Reviewing Research Involving Vulnerable Subjects.

IRBs must pay special attention to specific elements of the research plan when reviewing research involving vulnerable subjects.

- Strategic issues include inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.
- The IRB should carefully consider group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects.
- Investigators should not be permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available “captive” population.
- IRBs must be knowledgeable about applicable state or local laws that bear on the decision-making abilities of potentially vulnerable populations. State statutes often address issues related to competency to consent for research, emancipated minors, legally authorized representatives, the age of majority for research consent, and the waiver of parental permission for research.
- Just as in providing medical care, research studies that plan to involve any potentially vulnerable populations must have adequate procedures in place for assessing and ensuring subjects’ capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable subjects, the IRB shall look to see that such procedures are a part of the research plan. In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages

the subjects understand, and reading the consent form to subjects slowly and ensuring their understanding paragraph by paragraph.

- The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that the investigator submit each signed informed consent form to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

- b. Research Involving Pregnant Women, Human Fetuses and Neonates.** DHHS regulations at 45 CFR Part 46, Subpart B detail special protections for research involving pregnant women, human fetuses, and neonates. Under these regulations, IRBs are required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent. In general, Subpart B requires that research involving pregnant women and fetuses should involve the least possible risk.

On the other hand, unilateral exclusion of non-pregnant women of reproductive potential from research, in order to avoid a risk, should not be permitted by the IRB. Exclusion requires compelling scientific justification. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

The regulations set out specific categories, each with their own requirements and IRB determinations, for research involving pregnant women, human fetuses and neonates. Table 17.1 summarizes these requirements.

IRB determinations regarding the applicable category and protocol-specific findings relative to the specific requirements of the relevant category will be clearly documented in IRB meeting minutes and/or other IRB records.

Table 17.1 Summary of Requirements for Research Involving Pregnant Women, Fetuses and Neonates	
Regulatory Category	Requirements
<ul style="list-style-type: none"> ▪ Pregnant Women or Fetuses 	<ul style="list-style-type: none"> ▪ Where appropriate, preclinical data identify potential risks ▪ Direct benefit for pregnant woman or fetus , or risk to fetus not greater than minimal ▪ Any risk is least possible for achieving research objectives ▪ Persons consenting are fully informed ▪ Consent of pregnant woman if direct benefit to her, or risk to fetus not greater than minimal ▪ Consent of pregnant woman and father (if reasonably available) if research holds offers direct benefit solely to fetus ▪ For pregnant children, assent and permission per Subpart D ▪ No inducements to terminate a pregnancy ▪ Researchers have no part in decisions to terminate pregnancy ▪ Researchers have no part in determining viability
<ul style="list-style-type: none"> ▪ Neonates of Uncertain Viability 	<ul style="list-style-type: none"> ▪ Where appropriate, preclinical data identify potential risks ▪ Persons consenting are fully informed ▪ Researchers have no part in determining viability ▪ Enhance probability of survival and risk is least possible or no added risk to neonate and important medical knowledge will result ▪ Informed consent of one parent or legally authorized representative
<ul style="list-style-type: none"> ▪ Nonviable Neonates 	<ul style="list-style-type: none"> ▪ Where appropriate, preclinical data identify potential risks ▪ Persons consenting are fully informed ▪ Researchers have no part in determining viability ▪ Vital functions not artificially maintained ▪ No termination of heartbeat or respiration ▪ No added risk to neonate ▪ Important medical knowledge will result ▪ Informed consent of both parents, unless one unable ▪ No legally authorized representatives
<ul style="list-style-type: none"> ▪ Viable Neonates 	<ul style="list-style-type: none"> ▪ Refer to DHHS Subpart D for research involving children
<ul style="list-style-type: none"> ▪ Placenta, Dead Fetus, Fetal Material 	<ul style="list-style-type: none"> ▪ Refer to applicable Federal, State of Ohio, or local law
<ul style="list-style-type: none"> ▪ Not Otherwise Approvable 	<ul style="list-style-type: none"> ▪ IRB finds reasonable opportunity to advance health or welfare ▪ Approval of HHS Secretary after expert and public consultation

- c. **Research Involving Prisoners of War is Prohibited.** DoD policy prohibits the involvement of prisoners of war as human subjects of research (DoD Directive 3216.2 4.4.2). For purposes of ethical review of research only, NMRC considers “detainees” to be individuals in a similar position as prisoners of war. Accordingly, NMRC will not approve research involving prisoners of war or detainees.
- d. **Research Involving Prisoners.** DoD Directive 3216.2 requires the inclusion of additional safeguards set forth in DHHS regulations at 45 CFR Part 46, Subpart C when research involves prisoners. These regulations detail special protections for research involving prisoners who, due to their incarceration, may have a limited ability to make truly voluntary and uncoerced decisions about whether or not to participate as subjects in research.

A prisoner is defined as any individual involuntarily confined or detained in a penal institution. In order to consider research involving prisoners, the IRB must:

- Have a majority of its members not otherwise associated with the prison.
- Include a prisoner or a prisoner advocate, who can adequately represent the interests of the prisoners, unless the research has already been reviewed by an IRB that included a prisoner advocate.

The regulations set out specific categories and IRB determinations for research involving prisoners. Table 17.2 summarizes these requirements.

The IRB must forward its recommendations to the Assistant Secretary for the Navy, Research, Development and Acquisition (ASN(RDA)) for approval.

If the research is DHHS-supported, the IRB must certify its findings and forward them to OHRP for concurrence on behalf of the Secretary of HHS. Certification to OHRP is not required for research not supported by DHHS. However, the NMRC IRB will apply the standards of Subpart C to all prisoner research, regardless of its source of funding or support as directed by DoD policy. Should non-DHHS research fall outside the category stipulations under 45 CFR 46.306, the IRB will consult with appropriate experts before approving the research.

Table 17.2 Summary of Requirements for Research Involving Prisoners	
Permissible Categories	Additional Required Findings, Regardless of Category
A. Studies (involving no more than minimal risk or inconvenience) of the possible causes, effects, and processes of incarceration and criminal behavior	<ul style="list-style-type: none"> ▪ Any possible advantages to the prisoner, when compared with general living conditions, medical care, quality of food, amenities, and opportunity for earnings are not of such a magnitude that ability to weigh risks in the limited choice environment of the prison is impaired ▪ Risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers ▪ Procedures for selecting subjects are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners ▪ Unless the investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project ▪ Information is presented in language that is understandable to the subject population ▪ Adequate assurance exists that parole boards will not take into account a prisoner 's participation in the research in making decisions regarding parole ▪ Each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole ▪ Where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoner' s sentences, and for informing participants of this fact.
B. Studies (involving no more than minimal risk or inconvenience) of prisons as institutional structures or of prisoners as incarcerated persons	
C. Research on particular conditions affecting prisoners as a class (providing the Secretary of DHHS has consulted with appropriate experts and published the intent to support such research in the Federal Register)	
D. Research that has reasonable probability of benefiting the prisoner subject. If the research involves a control group that may not benefit from the research, the HHS must approve/disapprove after consulting experts	

- e. **Research Involving Children.** DoD Directive 3216.2 requires the inclusion of additional safeguards set forth in DHHS regulations at 45 CFR Part 46, Subpart D when research involves children. Under the regulations, children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable jurisdiction in which the research will be conducted. ORA maintains a growing reference binder with applicable country and state laws and will make this information available to IRB members. However, investigators are required to provide such information, especially in the case of research conducted outside the U.S. This information may be obtained from the host country Ministry of Health or other government agency that has access to such information.

There are three main issues to consider when reviewing research involving children:

1. Risk-Benefit Analysis. IRBs must make certain findings and determinations when reviewing research involving children. IRB records must reflect the IRB's understanding and justification for the risks and benefits posed by approved research involving children. Proposed research must fall within one of the following four categories:

- Research not involving greater than minimal risk.
- Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.
- Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Each category stipulates specific conditions that must be met before the proposed research can be approved. These conditions are summarized in Table 17.3.

2. Parental Permission. Provisions must also be made to obtain the child's assent when the IRB has determined that the child is capable of giving assent. The IRB should consider the age, maturity, and psychological state of the child involved. Even if the child has capacity to consent, the IRB may determine that the assent of the child is not necessary if and only if all three of the following conditions are satisfied:

- The research offers the child the possibility of a direct benefit;
- The benefit is important to the health or well being of the child; *and*
- The benefit is available only in the context of the research.

3. Assent of the Child. The NMRC IRB should take great care in approving research where the child is suffering from a life-threatening illness with little real chance of therapeutic benefit from the research. IRBs should also be cautious in allowing the parents to overrule the child's dissent where experimental therapy has little or no reasonable expectation of benefit. The justification for exposing the child to extreme discomfort, with little possibility for benefit, may be tenuous at best.

If it is deemed appropriate that the child's assent should be solicited, the IRB should ensure that the assent form is tailored for the child, with respect to his or her level of understanding. For young children, especially, the assent form should be designed as a one-page document, with simple, age-appropriate language, and presented in an understandable manner.

As a general rule, the NMRC IRB will require documentation of assent for

subjects between 8-17 years of age using a separate assent form. Oral assent should be solicited from subjects between 5-7 years of age. Children under the age of 5 years are considered to not have capacity to assent.

- 4. Use of Consultants.** When reviewing research proposed to include children as subjects, the NMRC IRB may call in consultants, e.g., pediatricians, child psychologists/psychiatrists, etc. who may be able to provide important consultation regarding the proposed research and any consent or assent concerns.

Table 17.3 Summary of Requirements for Research Involving Children	
Regulatory Category	Requirements
<ul style="list-style-type: none"> ▪ No Greater Than Minimal Risk 	<ul style="list-style-type: none"> ▪ Assent of child and permission of at least one parent
<ul style="list-style-type: none"> ▪ Greater Than Minimal Risk and Prospect of Direct Benefit to the Individual Subjects 	<ul style="list-style-type: none"> ▪ Assent of child and permission of at least one parent ▪ Anticipated benefit justifies the risk ▪ Anticipated benefit is at least as favorable as that of alternative approaches
<ul style="list-style-type: none"> ▪ Greater Than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects 	<ul style="list-style-type: none"> ▪ Assent of child and permission of both parents ▪ Only a minor increase over minimal risk ▪ Likely to yield generalizable knowledge about the child's disorder or condition that is of vital importance for the understanding or amelioration of the disorder or condition ▪ The intervention or procedure presents experiences to the child that are reasonably commensurate with those in the child's actual or expected medical, dental, or expected medical, dental, psychological, social, or educational situations
<ul style="list-style-type: none"> ▪ Not Otherwise Approvable But Presenting an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting Children 	<ul style="list-style-type: none"> ▪ Assent of child and permission of both parents ▪ IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children ▪ The DHHS Secretary or the FDA Commissioner approves, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following public comment

- f. Research Involving Decisionally Impaired Subjects.** Decisionally impaired persons are individuals who have a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affects cognitive or emotional functions. Other individuals who may be considered decisionally impaired, with limited decision-making ability, are individuals under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps.

There are no regulations specific to research involving cognitively impaired

persons. In all cases, the NMRC IRB should take special care to consider issues such as the selection of subjects, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis. Decisions should be made with the utmost deference to the ethical principles underlying human subjects research as set forth in the Belmont Report. Capacity should be evaluated on an individual basis to avoid incorrect assumptions as to an individual's ability to make decisions. In cases where research involving cognitively impaired individuals is approved, IRBs should require additional safeguards (e.g., involvement of subject advocates, independent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect participants.

The National Bioethics Advisory Commission (NBAC) has issued 21 recommendations for IRBs, the research community, and Federal regulators to consider regarding the decision-making capacity of particularly vulnerable subjects. The complete report, "Research Involving Persons with Mental Disorders That May Affect Decision Making Capacity" (December 1998), can be found on-line at <http://bioethics.gov/capacity/TOC.htm>.

g. Research Involving Active Duty Military. Military personnel may participate as research subjects. However, the IRB must take care to consider matters unique to military subjects.

1. Coercion and Undue Influence. Avoiding any real or apparent coercion to participate as a research participant, especially in training contexts, or other situations associated with major career branch points.

DoD Directive 3216.2 requires that in greater than minimal risk research, officers and noncommissioned officers in the chain of command shall not be present at the time of recruitment, consent or enrolment of members of units under their command. During recruitment briefings to a unit where a percentage of the unit is being recruited to participate as a group, an ombudsman not connected in the any way with the proposed research or the unit shall be present to monitor that the voluntary nature of individual participants is adequately stressed and that the information provided about the research is adequate and accurate.

2. Command Permission.

- **Research Targeting Military Populations.** When recruiting directly from a military unit, investigators must provide the IRB with written permission obtained through the unit's appropriate chain of command. In some instances, the Command may have its own Assurance. Consequently, review by the Command's designated IRB may be required or a joint research review agreement may be appropriate.

Additionally, if the research involves a survey, Navy Survey Review and Approval may be required under OPNAVINST 5300.8B.

- **Military Personnel Involved in Research Not Targeting Military Populations.** If research populations include active military personnel,

but the research is not specifically targeting military units, the investigators should submit a copy of the form requesting permission from their supervisor.

- 3. Plan for Deployment.** Investigators should consider a plan for how to manage military who deploy and how such deployment will affect the research. The IRB will consider this plan as well as whether participation affects readiness and availability to perform military duties.
 - 4. Reimbursement.** Unless authorized by statute or regulation, reimbursement for participation, monetary or otherwise, is prohibited. Investigators and IRB members should consult with ORA or NMRC's legal counsel as necessary.
- h. Research Involving NMRC or NMRC D Personnel as Subjects.** NMRC and NMRC D personnel who participate in research should also be considered vulnerable subjects because of the potential for undue influence by investigators who enroll their personnel. Thus, the IRB should uphold the same standards in approving research involving these groups as other vulnerable subjects research.
 - i. Research Involving Other Potentially Vulnerable Adult Subjects.** The context of the research is an important consideration for IRBs to have in mind when reviewing research that involves other potentially vulnerable subjects. Research involving homeless persons, members of particular minority groups, or the economically or educationally disadvantaged pose significant challenges. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence certain types of subjects, and IRBs must take such considerations into account. Nevertheless, research involving these subjects is socially important for understanding and eventually improving adverse health in these populations.
 - j. Human Fetal Tissue Transplantation Research.** Public Law 103-43 governs human fetal tissue transplantation research supported by DHHS. In the event that such research comes before the NMRC IRB, members should refer to the governing public law which will be made available by ORA.
 - k. Research Involving Deceased Persons.** Research involving deceased persons is not covered by the DoD or FDA human subject regulations or the Common Rule. However, such research may be covered under applicable state or local law.

Chapter 18

Managing Conflicts of Interest

Research personnel, IRB members, IRB Chairs, the Institutional Official, and research sponsors may all have certain conflicts of interest. Such conflicts of interest may arise because of the intellectual property involved in many research discoveries or industry-academic partnerships, from financial incentives many pharmaceutical or biotech companies offer researchers or physicians for conducting trials or enrolling subjects, or due to particular role relationships within the governance structure of particular institutions.

The public, whose members will be recruited to volunteer to test new theories, interventions, and products, must be assured that their interests and welfare will be protected to the fullest extent possible. The principle of justice, as articulated in the Belmont Report, demands that the benefits and the burdens of research be distributed equitably.

NMRC endorses the principle that all research should be conducted with the highest degree of ethical conduct and integrity and should not be negatively impacted by financial or other conflicts of interest. This conflict of interest policy is intended to help investigators, IRB members, and institutional officials effectively reduce, eliminate, and manage any financial interests they may have in the research they conduct, review, or sponsor.

- a. **Regulatory Requirement to Manage Conflicts of Interest.** Federal regulations at 21 CFR Part 50 and 42 CFR Part 50 require the disclosure and management of financial conflicts of interest in research. Federal human subject protection regulations at 32 CFR 219.107(e) and 21 CFR 56.107(e) require IRB members to be free of any conflict.
- b. **Conflicts of Interest Defined.** Conflict of interest can be defined as any situation in which financial, professional, or personal obligations may compromise or present the appearance of compromising an individual's professional judgment in designing, conducting, analyzing, reporting or reviewing research. Financial incentives may negatively impact the recruitment of subjects; collection, analysis and interpretation of data; or scientific objectivity and integrity — all of which ultimately affect public trust in the research enterprise.
- c. **Financial Interest Defined.** It is NMRC's policy that all personnel are required to disclose any Financial Interest in any human subject research in whose conduct or support they are involved (e.g., study planning and design, conduct of the study, data analysis, subject recruitment, subject consent, authorship, etc.)

Financial Interest means (i) anything of monetary value that could reasonably appear to affect, or to be affected by, the research; or (ii) anything of monetary value in components whose interest could reasonably affect, or be affected by, the research. The latter includes membership in partnerships or group practices that could reasonably affect, or be affected by, the research.

Financial interest includes, but is not limited to, the following:

- Salary or other payments for services (e.g., consulting fees or honoraria);
- Payments of other sorts from the sponsor of the research (e.g., a grant to fund other ongoing or additional research, compensation in the form of equipment, retainer for on-going consultation, etc.);
- Equity interests (e.g., stocks, stock options or other ownership interests); and
- Proprietary interests or intellectual property rights (e.g., patents, copyrights and royalties from such rights).
- The investigator's proprietary interest in the studied product, including but not limited to a patent, trademark, copyright or licensing agreement.

However, financial interest does not include the following:

- Salary, royalties, or other remuneration for purposes unrelated to the research in question;
- Income from seminars, lectures, or teaching engagements sponsored by public or non-profit entities.
- Income from service on advisory committees or review panels for public or non-profit entities.

d. Research Personnel. For researchers, financial or other incentives may negatively impact the collection, analysis and interpretation of data, scientific objectivity and integrity, and ultimately the public trust in the research enterprise. In addition, if also the treating physician, a researcher may unwittingly exert coercion or undue influence on patients to participate in research.

1. Investigator Disclosure. As one method of preventing, monitoring, managing, and resolving conflicts of interest, this facility requires full disclosure of conflicts of interest by investigators. Full disclosure of conflicting information demonstrates good faith and protects the integrity of the research and the reputation of the institution. Investigators will disclose any significant financial conflicts of interest in the Initial Review Application (IRB Form 1) and in the Continuing Review Report (IRB Form 4).

2. Management Plan. Where appropriate, and as determined by the NMRC IRB or Institutional Official, disclosure to the human subjects involved in the research may be warranted via the informed consent document. Other examples of **conditions or restrictions** that might be imposed to manage conflicts of interest include, but are not limited to:

- Public disclosure of significant financial interests including any manuscripts or oral presentations based upon the research in question;
 - Monitoring of research by independent reviewers;
 - Modification of the research plan;
 - Disqualification from participation in all or a portion of the research funded;
 - Selection of another investigator or research staff person to perform the research or research-related function.
 - Divestiture of significant financial interests; and
 - Severance of relationships that create actual or potential conflicts.
- e. **IRB Chairs and Members.** DoD regulations at 32 CFR 219.107(e), the Common Rule, and FDA prohibit IRB members, chairs, or staff who have a conflicting interest from participating in the IRB's initial or continuing review of research. Such conflicts must be disclosed, and the IRB member, Chair, or staff member must not take part in the discussion or voting of such research, except to answer questions from the IRB. NMRC IRB Chairs and members may find themselves in any of the following conflicts of interest when reviewing research:
- Where the IRB Chair or member is listed as an investigator or member of the research team on the research.
 - Where the IRB Chair or member is reviewing a research protocol submitted by an immediate supervisor.
1. **Procedures for IRB Members.** The following procedures govern the management of conflicts of interest in the review of research by the IRB.
- If the IRB member believes that a conflicting interest might impact, or appear to impact, IRB deliberations or the protection of human subject, the member must declare the presence of the conflict to the IRB and absent himself or herself from any deliberative IRB discussion or vote on the research. There are no exceptions from this requirement.
 - In most cases, it is not necessary for the IRB member to disclose to the IRB the details of the conflict of interest for which the member voluntarily absents himself or herself from the IRB's deliberative discussion and vote, and limits himself or herself to answering questions posed by the IRB. However, there may be circumstances in which it is in the best interest of the individual, NMRC, and/or the human subjects involved for the member to make a complete disclosure to the IRB, IRB Chair, or the ORA Director. IRB members are expected to use their best judgment to ensure that all IRB deliberations take place without any appearance or possibility of conflict of interest.

- At the beginning of every meeting, the NMRC IRB Chair will review the agenda and request declaration of any possible conflicts of interest that have not already been identified to the IRB Chair or IRB staff.
 - Members found to have any (financial or non-financial) interest in the research under consideration will be recused from participation in or voting on review of the relevant protocol. The member may be present to answer questions posed by the IRB, but any other IRB Activity – including the final discussion in which a determination is made as to how the IRB will vote on the protocol – must be conducted without the presence or participation of the conflicted IRB member.
 - All recusals/absences of IRB members for conflict of interest must be noted as such in the official minutes. Recused members may not be counted toward the quorum for IRB action on the affected research. If the absent member has a designated alternate member who is present at the meeting, the alternate may be counted toward meeting quorum and will vote in the stead of the voting member with whom he/she is matched.
 - If the absence of the conflicted member and designated alternate results in a majority of the IRB members no longer being present at the meeting, no IRB actions or determination can take place until a majority of the IRB members have again joined the meeting.
 - If the absent conflicted member was the only non-scientist member present at the meeting, no IRB actions or determination can take place until an additional non-scientist member has joined the meeting.
- f. **Institutional Officials.** To avoid possible conflict of interest among institutional officials, such as the NMRC Commanding Officer, Research Services Director, ORA Director, etc. should not serve as IRB members. Available guidance explains that those who administer the research programs have access to wider knowledge, have the ability to influence programmatic and budgetary decisions, and are in a position to exert undue influence on the IRB.

Protocols will be referred to a higher research approval authority for review when the NMRC Commanding Officer is an investigator or member of the research team.

Chapter 19

Managing Allegations of Serious or Continuing Non-Compliance

All personnel involved in human subject research are required to comply with applicable human subject protection regulations and the reviewing IRB requirements. NMRC is required to maintain policies and procedures for managing allegations of serious or continuing non-compliance. This chapter meets this requirement.

- a. **IRB Responsibility to Review Allegations of Non-Compliance.** The NMRC IRB has responsibility to oversee the involvement of human subjects in research conducted at NMRC or by NMRC employees or agents in order to protect the safety and welfare of the research subjects. To exercise this authority, the IRB shall review all allegations of non-compliance with human subjects regulations and IRB requirements. The IRB will follow these policies and procedures for conducting an inquiry and investigation into allegations of non-compliance.
- b. **Definitions.**
1. **Non-Compliance** shall mean conducting research involving human subjects in a manner that disregards or violates federal regulations governing such research or policies established by the applicable IRB. This can include, but is not limited to:
 - failure to obtain IRB approval for research involving human subjects;
 - inadequate or non-existent procedures for informed consent;
 - inadequate supervision in research involving experimental drugs, devices or procedures;
 - failure to follow the approved version of the protocol;
 - failure to follow recommendations made by the IRB to insure the safety of subjects;
 - failure to report adverse events or proposed protocol changes to the IRB; and
 - continued failure to provide ongoing progress reports.
 2. **Director** shall mean the ORA Director. The Director has the responsibility of directing the case from the inquiry process through disposition of the case - in consultation at all times with the IRB Chair and/or Vice Chairs.

3. **Executive Committee** shall mean the NMRC IRB Chair and Vice Chairs, and the ORA Director.
4. **Inquiry Panel** shall mean the IRB Chair and an IRB member designated by the IRB Chair whose charge is to review the initial allegation, the response from the researcher and any other appropriate materials and to issue a recommendation to the Commanding Officer as to whether an investigation is warranted.
5. **Investigation Panel** shall mean an ad hoc subcommittee, appointed by the IRB Chair and consisting of at least three members of the IRB whose charge is to investigate the allegation of non-compliance. To assure continuity and avoid duplication of effort, the IRB Chair shall also be a member. The Investigation Panel will issue findings and recommendations to the IRB and Commanding Officer.
6. **Appeals Panel** shall mean an ad hoc subcommittee, appointed by the IRB Chair and consisting of at least three members of the IRB who have not served on the inquiry or investigation panels and whose charge is to review an appeal by the researcher and issue a recommendation to the Commanding Officer as to whether reconsideration of the decision is warranted.

c. Process for Handling Allegations of Non-Compliance.

1. **Submission of an Allegation.** There are several ways allegations of non-compliance may be submitted:
 - Any individual or organization may submit a written complaint or allegation of non-compliance to the IRB.
 - The IRB itself may initiate a complaint based on information available to the IRB (e.g., deficiencies noted in IRB files, media or scholarly reports of research activity subject to IRB jurisdiction).
 - Continuing monitoring programs such as the command publications clearance program may reveal information suggesting non-compliance.

All allegations of non-compliance should be promptly reported to the IRB Chair.

- d. Inquiry.** In the inquiry stage, factual information is gathered and expeditiously reviewed to determine if an investigation of the complaint is warranted. An inquiry is not a formal hearing or an in-depth analysis of the allegations; it is designed to separate allegations deserving further investigation from those that are frivolous, unjustified or related to minor infractions.

1. **Process.** Whenever an allegation or complaint of non-compliance is made, the Director will forward the allegation to the Executive Committee. The IRB Chair and one other IRB member will conduct the initial inquiry. The

Director will also send written notice of the allegations to the investigator and request a response from the investigator within 10 working days. If the Complaint raises issues of safety and welfare for research subjects that are apparent upon initial review, the Director also will give the investigator notice of an opportunity to address in his/her response the possible summary suspension of the researcher's project(s).

The Inquiry Panel will review the allegation of non-compliance, the response from the investigator and any other information necessary to determine whether an investigation is warranted. The Inquiry Panel may interview the researcher and others, but is not obligated to do so. It may be necessary to secure critical data or materials at the outset of an inquiry to protect the integrity of those data, materials or records. The IRB maintains the authority to secure such materials at any time during an inquiry or investigation.

2. Recommendations and Outcome. At the conclusion of the inquiry phase, the Inquiry Panel will make a recommendation to the Executive Committee. Possible recommendations include:

- Dismissal of the allegation or complaint as unjustified;
- Referral of the matter to another more appropriate official for resolution (e.g., Research Integrity Office if related to scientific misconduct);
- Resolution through corrective or educational measures where the violation of human subjects regulations is minor or inadvertent; or
- A formal IRB investigation where the allegation or complaint appears founded and is of a serious nature.

The report of the Inquiry Panel will initiate a report to the investigator regarding the outcome. This report will include a statement of the reasons for the decisions. Depending on the nature of the allegation and the extent of the review required, the inquiry phase is expected to be completed within 30 days. An extension of this time frame may be granted if warranted.

3. Reporting to Commanding Officer and BUMED. The Executive Committee will report the findings of the inquiry stage to the Commanding Officer. The initiation of an Investigation into serious or continuing non-compliance must be promptly reported to BUMED using HRPP Form 2 "Human Research Report," and to other regulatory agencies as applicable.

e. Investigation. The purpose of the investigation is to explore the allegations by assembling and examining relevant information. The Investigation Panel's charge is to generate a report that summarizes the information considered, conclusions regarding as to where there was non-compliance with regulations, and recommendations for action. During an investigation, additional information may emerge that justifies broadening the scope beyond the initial allegations.

The investigator shall be informed if new and different allegations are discovered during the course of the investigation.

1. **Process.** A subcommittee of 3 members of the NMRC IRB will conduct the investigation. These members will have areas of expertise suited to reviewing the matter. Depending on the nature and scope of the matter, the IRB members may be relieved of their regular IRB duties during the investigation.

The Investigation Panel may use any and all materials and reports gathered during the inquiry phase but are not limited to actions or conclusions of the Inquiry Panel. The Investigation Panel may obtain documents and other records relevant to the investigation (e.g. researcher's records, medical charts, grant applications, etc.). The Investigation Panel may interview any persons who may have information relevant to the complaint. The Investigation Panel may draw on the resources of the institution or external consultants to assist in the review of issues that require expertise beyond or in addition to that available on the Investigation Panel.

The investigator under investigation will be given an opportunity to submit written comments and to appear before the Investigation Panel on at least one occasion prior to the Investigation Panel issuing its report. The investigator may offer relevant information to the Investigation Panel and suggest other individuals to be interviewed.

At the conclusion of its investigation, the Investigation Panel will prepare a report summarizing the information it has considered and outlining its conclusion and recommended actions. A copy will be sent to the investigator who will be given 10 working days in which to submit comments. The Investigation Panel will review any such comments and decide whether to modify the preliminary report. When completed, the Investigation Panel will distribute its report as appropriate. The investigation phase is expected to be completed within 60 working days with an extension possible if warranted.

2. **Outcome.** The Executive Committee will base a decision on the report of the Investigation Panel. Appropriate actions to be taken include, but are not limited to:
 - Dismissal of the complaint as unjustified
 - Remediation or educational measures
 - Increased reporting by the investigator of human subject research activity
 - Restrictions on research practice such as limiting the privilege to minimal risk or supervised projects
 - Suspension of approval for one or more of the investigator's studies

- Termination of approval for one or more of the investigator's studies

The Executive Committee will issue the final investigative report and the Director will forward the report to the researcher. Its decision becomes final within 5 working days of release unless the investigator files a written statement of appeal within that time.

The Executive Committee will also report the determinations to the IRB and the Commanding Officer. A follow-up report to BUMED must be promptly submitted using HRPP Form 2 "Human Research Report".

- f. **Suspensions and Reporting.** At any time during the inquiry or investigation process, the IRB may determine the necessity to suspend accrual of research subjects or suspend approval of research project(s) to assure the protection of human subjects. The authority to suspend research rests with the IRB, IRB Chair and Vice Chairs and the Commanding Officer.

When a decision has been made to suspend approval of research by IRB or the IRB Chair/Vice Chair, the ORA Director will notify the Commanding Officer as well as the investigator's Department Head and Director. The Commanding Officer will send written notice to the following entities, as required under federal regulations:

- BUMED
- Office Federal Office of Human Research Protection (OHRP) in the case of DHHS-supported research
- Federal Food & Drug Administration (FDA) in the case of FDA-regulated research
- Other sponsors funding a study, which is placed under suspension.

Reports will be filed within 5 working days of suspension. Follow-up reports will be reported promptly.

- g. **Appeals Process.** The purpose of an appeal is to give the investigator an opportunity to request reconsideration of the decision reached by the Executive Committee. Grounds for appeal are limited to:

- new information not available during the investigation
- sanction exceeds the severity of the violations
- failure of the panels to follow these policies and procedures

An ad hoc subcommittee of the NMRC IRB, which includes members who have not served on either the Inquiry or Investigation Panels, will consider the appeal. The Appeals Panel will review the written statement of appeal and make a

recommendation as to whether there should be a reconsideration of any aspect of decisions made. In reaching this recommendation, the Appeals Panel may ask for a response from the Investigation Panel.

If the Appeals Panel denies the appeal, the Executive Committee's prior decision becomes final. If the Appeals Panel recommends reconsideration, the Executive Committee will reopen the case. When this is done, the Executive Committee may choose to reconvene the Investigation Panel or reconsider the matter on its own. Either the Executive Committee or the Investigation Panel will offer the investigator the opportunity to appear personally or via teleconference to present the appeal.

Upon reconsideration, the Executive Committee will determine whether to modify or uphold the original decision reached. This action is final. Consistent with the IRB's regulatory authority, no other entity within the Command may override such a decision.

The reconsideration phase is expected to be completed within 30 working days.

- h. Dissemination of Findings.** At the time when the Executive Committee's decision becomes final, the Committee will release its findings to the investigator and to appropriate institutional and governmental officials as required under federal regulations. The same guidelines as set forth for reporting suspensions will apply. The NMRC IRB will not initiate any public disclosure of findings.

The Executive Committee as well as the Inquiry, Investigation, and Appeals Panels shall have access to the necessary resources and staff to conduct a thorough and fair review of allegations. Internal and external consultants may be called to assist in the review.

- i. Conflicts of Interest.** To avoid conflicts of interest, only individuals not involved in the conduct of the research may serve as members of any panel.