

Required Education for Clinical Research Investigators

Attached are required educational materials regarding the principles and laws governing human subjects research:

1. **Basic Information for Prospective Investigators**
 - a. Assurance of compliance with policies for the protection of human subjects.
 - b. Definition of Human Subjects Research
 - c. Duties of the Principal Investigator
 - d. Collaboration in Research
2. **The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research**
3. **The Nuremberg Code**
4. **Code of Federal Regulations Title 32 Part 219- Protection of Human Subjects**
5. **Code of Federal Regulations Title 45 Part 46 -Protection of Human Subjects**
 - a. **Subpart B** - Additional protections pertaining to research, development, and related activities involving **Fetus, Pregnant Women, and Human In-Vitro Fertilization**
 - b. **Subpart D** - Additional protections for **Children** involved as subjects In Research
6. **DOD DIRECTIVE 3216.2 25 MAR 02** - Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research
7. **SECNAVINST 3900.39C** - Protection of Human Subjects

I have reviewed all of these documents and received a copy for my records:

Investigator - printed Name: _____

PI Signature

date

BASIC INFORMATION FOR PROSPECTIVE INVESTIGATORS

ASSURANCE OF COMPLIANCE WITH POLICIES FOR THE PROTECTION OF HUMAN SUBJECTS

Federal regulations for the protection of human subjects require each institution that conducts research involving human subjects to describe, in detail, the procedures it will use to protect the rights and welfare of the human subjects. Each institution prepares a document that describes these procedures. The document is called an "Assurance of Compliance," commonly referred to as an "Assurance".

The NMCS D Federal Wide Assurance (FWA) is a public declaration by NMCS D that commits all NMCS D employees to comply with policies for the protection of human subjects before beginning any research and to continue compliance until completion.

The NMCS D FWA sets standards that meet both ethical and legal requirements. Failure to comply with the NMCS D FWA may constitute unethical behavior and violation of the law. Failure to comply can delay research, harm subjects, and generate sanctions against an investigator, the research program, NMCS D or the Navy.

The NMCS D Assurance applies to all research activities involving human subjects conducted by NMCS D personnel or supported by NMCS D contracts or other agreements, and requires that all NMCS D research activities involving human subjects follow the ethical principles of The Belmont Report and the legal requirements of applicable Federal Regulations (e.g. 32 CFR 219 and 45 CFR 46).

THE PRINCIPLES OF THE BELMONT REPORT GOVERN ALL RESEARCH SUPPORTED BY THE U.S. GOVERNMENT.

These principles are:

1. **Respect for Persons:** This principle acknowledges the dignity and freedom of every person. It requires obtaining informed consent from research subjects (or their legally authorized representatives).
2. **Beneficence:** This principle requires that researchers maximize benefits and minimize harms associated with research. Research related risks must be reasonable in light of expected benefits.
3. **Justice:** This principle requires equitable selection and recruitment and fair treatment of research subjects.

DEFINITION OF HUMAN SUBJECTS RESEARCH

Federal regulations and the FWA apply to research involving human subjects.

A **human subject** is a living individual about whom an investigator obtains either (1) data through intervention or interaction with the individual; or (2) identifiable private information.

Research means a systematic investigation designed to produce generalizable knowledge. Research may involve direct interactions or interventions with subjects, such as obtaining data by taking medical histories, obtaining blood samples, urine sampling, diagnostic procedures, or treating patients at least in part for the purpose of gaining generalizable information. Research may also involve indirect activities such as the analysis of specimens or data from people. Participation in these kinds of indirect activities, particularly if you plan to publish the results (or be a co-author), constitutes human subjects research.

The intent to publish the results of an activity nearly always means that it is research.

DUTIES OF THE PRINCIPAL INVESTIGATOR

The Principal Investigator:

- Designs the research study.
- Writes the protocol.
- Submits the protocol to the NMCS D Institutional Review board (IRB) for initial review and approval.
- Complies with all IRB decisions and stipulations.
- Is responsible for the conduct of the protocol, including rigorous adherence to sound scientific procedures and sound ethical principles.
- Submits all required forms / information to the IRB for its continuing review of the protocol.
- Reports promptly to the appropriate NMCS D IRB and others any unanticipated problems involving risks to subjects or others, or unexpected serious harm to subjects.
- Submits to the IRB proposed amendments to previously approved research.
- Complies with all requirements of the Food and Drug Administration when using investigational drugs, investigational devices, biologics, or other regulated test articles.

COLLABORATION IN RESEARCH

Special provisions must be made if you intend to collaborate in research involving human subjects at sites other than the NMCS D. These provisions are required because when you collaborate, you accept some measure of responsibility for protecting the rights and welfare of the human subjects involved.

What constitutes "collaboration" on the part of an NMCS D investigator? Collaboration exists if the NMCS D participant expects "something in return" as a result of having participated in a research activity. "Something in return" could include data, authorship on a publication, samples, or even patent rights. NMCS D views authorship as evidence of collaboration.

Collaborative activities may include but are not limited to:

- Collection of specimens.
- Visits to institutions to perform research activities or clinical research.
- Exchange of information containing personal identifiers.
- Preliminary data-collection activities involving human subjects.
- Substantive intellectual contributions to research techniques, protocol design, or interpretation of data.

Collaboration with researchers in human subjects research activities at other institutions is subject to the requirements of the NMCS D's Assurance. For example, collaborative research activities in which subjects are enrolled at a non-NMCS D site must meet high ethical standards similar to those required at the NMCS D. Before you begin the research, both you and your IRB must have documentation that your collaborator's IRB has reviewed and approved the protocol.

BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH

Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Summary

On July 12, 1974, the National Research Act (Public Law 93348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects, and to develop guidelines, which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: (i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research, and (iv) the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center, supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects.

By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of institutional review boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists, who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 780013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.

Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.

Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.

*David W. Louisell, J. D., Professor of Law, University of California at Berkeley.

Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.

Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.

*Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.

* Deceased.

THE BELMONT REPORT

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg Code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This Code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied, so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred, partly because both often occur together (as in research designed to evaluate a therapy), and partly because notable departures from standard practice are often called "experimental", when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental" in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage, in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

Research and practice may be carried on together, when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is, that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence and justice.

Respect for Persons

Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy, and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals, and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices, while refraining from obstructing their actions, unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part, because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm, and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated, and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities, for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

Beneficence

Persons are treated in an ethical manner, not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm; and (2) maximize possible benefits, and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person, regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment". Learning what will in

fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge, and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined, justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children—even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that, on closer investigation, turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk, without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out, that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

Justice

Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved". An injustice occurs, when some benefit to which a person is entitled is denied without good reason, or when some burden is imposed unduly. Another way of conceiving the principle of justice is that, equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property, on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices, such as punishment, taxation and political representation. Until recently, these questions have not generally been associated with scientific research. However, they are foreshadowed, even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries, the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularlyagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected, simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic

devices and procedures, justice demands both that these not provide advantages only to those who can afford them, and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk / benefit assessment, and the selection of subjects of research.

Informed Consent

Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided, when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information

Most codes of research establish specific items for disclosure, intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate, since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient, since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be, that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk, and the voluntary nature of participation.

A special problem of consent arises, where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research, of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified, only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases, in which disclosure would destroy or invalidate the research, from cases in which disclosure would simply inconvenience the investigator.

Comprehension

The manner and context, in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for

consideration, or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made, when comprehension is severely limited --for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill, and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose, to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected, both by acknowledging their own wishes, and by the use of third parties to protect them from harm.

The third parties chosen should be those, who are most likely to understand the incompetent subject's situation, and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research, as it proceeds, in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness

An agreement to participate in research constitutes a valid consent, only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another, in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture, in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences, if the subject is especially vulnerable.

Unjustifiable pressures usually occur, when persons in positions of authority or commanding influence -- especially where possible sanctions are involved-- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely, where justifiable persuasion ends and undue influence begins. But undue influence would include actions, such as manipulating a person's choice through the controlling influence of a close relative, and threatening to withdraw health services to which an individual would otherwise be entitled.

Assessment of Risks and Benefits

The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits

The requirement that research be justified on the basis of a favorable risk / benefit assessment, bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons.

The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm, and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk", "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk / benefit assessments are concerned with the probabilities and magnitudes of possible harms, and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm, and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests, other than those of the subject, may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects, and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits

It is commonly said that benefits and risks must be "balanced", and shown to be "in a favorable ratio". The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished, with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject --or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

Selection of Subjects

Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk / benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients, who are in their favor, or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens, and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice, that there is an order of preference in the selection of classes of subjects (e.g., adults before children), and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators, and treated fairly in the course of research. Thus, injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if institutional review boards are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects, if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized, may continually be sought as research subjects, owing to their ready availability in settings, where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

Directives for Human Experimentation

NUREMBERG CODE

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Reprinted from *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181-182.* Washington, D.C.: U.S. Government Printing Office, 1949.

**TITLE 32--NATIONAL DEFENSE
PART 219--PROTECTION OF HUMAN SUBJECTS**

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Sec. 219.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in Sec. 219.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in Sec. 219.102(e) must be reviewed and approved, in compliance with Sec. 219.101, Sec. 219.102, and Sec. 219.107 through Sec. 219.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

(ii) Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or

(ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) 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:

(i) Public benefit or service programs;

- (ii) Procedures for obtaining benefits or services under those programs;
 - (iii) Possible changes in or alternatives to those programs or procedures; or
 - (iv) Possible changes in methods or levels of payment for benefits or services under those programs.
- (6) Taste and food quality evaluation and consumer acceptance studies,
- (i) If wholesome foods without additives are consumed or
 - (ii) If 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 or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.
- (c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.
- (d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.
- (e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.
- (f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.
- (g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.
- (h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. (An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.) In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the Federal Register or will be otherwise published as provided in department or agency procedures.
- (i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, Department of Health and Human Services (HHS), and shall also publish them in the Federal Register or in such other manner as provided in department or agency procedures. Institutions with HHS-approved assurances on file will abide by provisions of title 45 CFR part 46 subparts A-D. Some of the other Departments and Agencies have incorporated all provisions of title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, subparts B and C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Sec. 219.102 Definitions.

(a) Department or agency head means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

(b) Institution means any public or private entity or agency (including federal, state, and other agencies).

(c) Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) Research subject to regulation, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) Human subject means 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.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) IRB means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) IRB approval means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) Minimal risk means 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.

(j) Certification means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

Sec. 219.103 Assuring compliance with this policy--research conducted or supported by any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, HHS, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Protection from Research Risks, HHS.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under Sec. 219.101 (b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head, unless in accord with Sec. 219.103(a) of this policy, the existence of an HHS- approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, HHS.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject. (5) Written procedures for ensuring prompt reporting to the IRB,

appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under Sec. 219.101 (b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by Sec. 219.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by Sec. 219.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

Sec. 219.104-106 Reserved

Sec. 219.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member 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.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

Sec. 219.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in Sec. 219.103(b)(4) and, to the extent required by, Sec. 219.103(b)(5).

(b) Except when an expedited review procedure is used (see Sec. 219.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

Sec. 219.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with Sec. 219.116. The IRB may require that information, in addition to that specifically mentioned in Sec. 219.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with Sec. 219.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

Sec. 219.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the Federal Register. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, HHS, Bethesda, Maryland 20892.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in Sec. 219.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

Sec. 219.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized:

(i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

(ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by Sec. 219.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by Sec. 219.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects 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, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Sec. 219.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

Sec. 219.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

Sec. 219.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

Sec. 219.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. (3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in Sec. 219.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in Sec. 219.103(b)(4) and Sec. 219.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by Sec. 219.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

Sec. 219.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- (2) A description of any reasonably foreseeable risks or discomforts to the subject;
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
- (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

- (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
- (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- (3) Any additional costs to the subject that may result from participation in the research;
- (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project 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:

(i) Public benefit of service programs;

(ii) Procedures for obtaining benefits or services under those programs;

(iii) Possible changes in or alternatives to those programs or procedures; or

(iv) Possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the 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.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

Sec. 219.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by Sec. 219.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by Sec. 219.116 have been presented orally to the subject or the subject's legally authorized representative. When

this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That 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. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

Sec. 219.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under Sec. 219.101 (b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

Sec. 219.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

Sec. 219.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

Sec. 219.121 [Reserved]

Sec. 219.122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

Sec. 219.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has have directed the scientific and technical aspects of an activity has have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

Sec. 219.124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

TITLE 45--PUBLIC WELFARE AND HUMAN SERVICES PART 46--PROTECTION OF HUMAN SUBJECTS--Table of Contents Subpart B--Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

Sec. 46.201 Applicability. Source: 40 FR 33528, Aug. 8, 1975, unless otherwise noted. (a) The regulations in this subpart are applicable to all Department of Health and Human Services grants and contracts supporting research, development, and related activities involving: (1) The fetus, (2) pregnant women, and (3) human in vitro fertilization. (b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart. (c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

Sec. 46.202 Purpose. It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

Sec. 46.203 Definitions. As used in this subpart: (a) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated. (b) Pregnancy encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus. (c) Fetus means the product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable. (d) Viable as it pertains to the fetus means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a fetus is viable for purposes of this subpart. If a fetus is viable after delivery, it is a premature infant. (e) Nonviable fetus means a fetus ex utero which, although living, is not viable. (f) Dead fetus means a fetus ex utero which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached). (g) In vitro fertilization means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means. [40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978]

Sec. 46.204 Ethical Advisory Boards. (a) One or more Ethical Advisory Boards shall be established by the Secretary. Members of these board(s) shall be so selected that the board(s) will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research scientists, physicians, psychologists, sociologists, educators, lawyers, and ethicists, as well as representatives of the general public. No board member may be a regular, full-time employee of the Department of Health and Human Services. (b) At the request of the Secretary, the Ethical Advisory Board shall render advice consistent with the policies and requirements of this part as to ethical issues, involving activities covered by this subpart, raised by individual applications or proposals. In addition, upon request by the Secretary, the Board shall render advice as to classes of applications or proposals and general policies, guidelines, and procedures. (c) A Board may establish, with the approval of the Secretary, classes of applications or proposals which: (1) Must be submitted to the Board, or (2) need not be submitted to the Board. Where the Board so establishes a class of applications or proposals which must be submitted, no application or proposal within the class may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Board and the Board has rendered advice as to its acceptability from an ethical standpoint. [40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978; 59 FR 28276, June 1, 1994]

Sec. 46.205 Additional duties of the Institutional Review Boards in connection with activities involving fetuses, pregnant women, or human in vitro fertilization. (a) In addition to the responsibilities prescribed for Institutional Review Boards under Subpart A of this part, the applicant's or offeror's Board shall, with

respect to activities covered by this subpart, carry out the following additional duties: (1) Determine that all aspects of the activity meet the requirements of this subpart; (2) Determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made by the applicant or offeror for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the Institutional Review Board or subject advocates in: (i) Overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen); (3) Carry out such other responsibilities as may be assigned by the Secretary. (b) No award may be issued until the applicant or offeror has certified to the Secretary that the Institutional Review Board has made the determinations required under paragraph (a) of this section and the Secretary has approved these determinations, as provided in Sec. 46.120 of Subpart A of this part. (c) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been established under Subpart A of this part. [40 FR 33528, Aug. 8, 1975, as amended at 46 FR 8386, Jan. 26, 1981]

Sec. 46.206 General limitations. (a) No activity to which this subpart is applicable may be undertaken unless: (1) Appropriate studies on animals and nonpregnant individuals have been completed; (2) Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity. (3) Individuals engaged in the activity will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and (4) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity. (b) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity. [40 FR 33528, Aug. 8, 1975, as amended at 40 FR 51638, Nov. 6, 1975]

Sec. 46.207 Activities directed toward pregnant women as subjects. (a) No pregnant woman may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal. (b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if: (1) The purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

Sec. 46.208 Activities directed toward fetuses in utero as subjects. (a) No fetus in utero may be involved as a subject in any activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means. (b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

Sec. 46.209 Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects. (a) Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity covered by this subpart unless: (1) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or (2) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability. (b) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless: (1) Vital functions of the fetus will not be artificially

maintained, (2) Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and (3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means. (c) In the event the fetus ex utero is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part. (d) An activity permitted under paragraph (a) or (b) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape. [40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978]

Sec. 46.210 Activities involving the dead fetus, fetal material, or the placenta. Activities involving the dead fetus, macerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

Sec. 46.211 Modification or waiver of specific requirements. Upon the request of an applicant or offeror (with the approval of its Institutional Review Board), the Secretary may modify or waive specific requirements of this subpart, with the approval of the Ethical Advisory Board after such opportunity for public comment as the Ethical Advisory Board considers appropriate in the particular instance. In making such decisions, the Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modification or waiver and that such benefits cannot be gained except through a modification or waiver. Any such modifications or waivers will be published as notices in the Federal Register.

TITLE 45--PUBLIC WELFARE AND HUMAN SERVICES PART 46--PROTECTION OF HUMAN SUBJECTS--Table of Contents Subpart D--Additional Protections for Children Involved as Subjects in Research

Sec. 46.401 To what do these regulations apply? Source: 48 FR 9818, Mar. 8, 1983, unless otherwise noted. (a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services. (1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint. (2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of Sec. 46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type. (b) Exemptions at Sec. 46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at Sec. 46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at Sec. 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed. (c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of Sec. 46.101 of Subpart A are applicable to this subpart. [48 FR 9818, Mar. 8, 1983; 56 FR 28032, June 18, 1991; 56 FR 29757, June 28, 1991]

Sec. 46.402 Definitions. The definitions in Sec. 46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart: (a) Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. (b) Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. (c) Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research. (d) Parent means a child's biological or adoptive parent. (e) Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

Sec. 46.403 IRB duties. In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

Sec. 46.404 Research not involving greater than minimal risk. HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in Sec. 46.408.

Sec. 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that: (a) The risk is justified by the anticipated benefit to the subjects; (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in Sec. 46.408.

Sec. 46.406 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. HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that: (a) The risk represents a minor increase over minimal risk; (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder

or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and (d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in Sec. 46.408.

Sec. 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. HHS will conduct or fund research that the IRB does not believe meets the requirements of Sec. 46.404, Sec. 46.405, or Sec. 46.406 only if: (a) The 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; and (b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either: (1) That the research in fact satisfies the conditions of Sec. 46.404, Sec. 46.405, or Sec. 46.406, as applicable, or (2) The following: (i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) The research will be conducted in accordance with sound ethical principles; (iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in Sec. 46.408.

Sec. 46.408 Requirements for permission by parents or guardians and for assent by children. (a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with Sec. 46.116 of Subpart A. (b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by Sec. 46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under Sec. 46.404 or Sec. 46.405. Where research is covered by Secs. 46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. (c) In addition to the provisions for waiver contained in Sec. 46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, state or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition. (d) Permission by parents or guardians shall be documented in accordance with and to the extent required by Sec. 46.117 of Subpart A. (e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

Sec. 46.409 Wards. (a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under Sec. 46.406 or Sec. 46.407 only if such research is: (1) Related to their status as wards; or (2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. (b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way

(except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.



Department of Defense DIRECTIVE

NUMBER 3216.2

March 25, 2002

DDR&E

SUBJECT: Protection of Human Subjects and Adherence to Ethical Standards in
DoD-Supported Research

- References:
- (a) DoD Directive 3216.2, "Protection of Human Subjects in DoD-Supported Research, "January 7, 1983 (hereby canceled)
 - (b) Section 980 of title 10, United States Code
 - (c) Title 32, Code of Federal Regulations, Part 219, "Protection of Human Subjects," current edition
 - (d) DoD Directive 6200.2, "Use of Investigational New Drugs for Force Health Protection," August 1, 2000
 - (e) through (m), see enclosure 1

1. REISSUANCE AND PURPOSE

This Directive:

1.1. Reissues reference (a) to update policies for protecting the rights and welfare of humans as subjects of study in Department of Defense (DoD)-supported research, development, test and evaluation, and other related activities hereafter referred to as "research."

1.2. Implements 10 U.S.C. 980 (reference (b)).

1.3. Supports implementation of 32 CFR Part 219 (reference (c)), referred to as the "Common Rule."

1.4. Establishes other DoD policies for the ethical conduct of research.

2. APPLICABILITY AND SCOPE

This Directive:

2.1. Applies to the Office of the Secretary of Defense, the Military Departments, the Chairman of the Joint Chiefs of Staff, the Combatant Commands, the Office of the Inspector General of the Department of Defense, the Defense Agencies, the DoD Field Activities and all other organizational entities in the Department of Defense (hereafter referred to collectively as "the DoD Components").

2.2. Applies to research involving human subjects, as defined herein, 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.

2.3. Does not apply to the use of investigational new drugs, biological products, or devices for purposes of Force Health Protection. Such use is not research and is governed by DoD Directive 6200.2 (reference (d)).

2.4. Does not apply to accepted medical practice, including the use of investigational products in such practice, undertaken for purposes of treatment, not research. Such medical practice is not research and is not subject to this Directive.

3. DEFINITIONS

Terms used in this Directive are as defined in enclosure 2.

4. POLICY

It is the policy of the Department of Defense that:

4.1. Protection of Human Subjects in Research. The rights and welfare of human subjects in research supported or conducted by DoD Components shall be protected. This protection encompasses basic respect for persons, beneficence, and justice in the selection of subjects.

4.2. Informed Consent. In general, as required by reference (b), no DoD Component may conduct or use appropriated funds to support research involving a human being as an experimental subject without the prior informed consent of the subject.

4.2.1. In the case of research intended to be beneficial to the subject, if the subject lacks capacity, due to age, condition, or other reason, to make a decision regarding consent to participate in the research, prior consent may be provided by a legal representative of the subject. In any such case, the determination that research is intended to be beneficial to the subject must be made by an Institutional Review Board (IRB) under reference (c).

4.2.2. Consistent with 10 U.S.C. 980(b) (reference (b)), the requirement for prior informed consent under paragraphs 4.2. or 4.2.1. may be waived by the Head of a DoD Component with respect to a specific research project to advance the development of a medical product necessary to the Armed Forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws and regulations, including 21 CFR 50.24 (reference (j)).

4.3. Applicability of Federal Policy for Protection of Human Subjects in Research

4.3.1. The Department of Defense has joined with other Federal Agencies to adopt the "Common Rule" Federal policy for protection of human subjects in research. Reference (c) is the Department of Defense's implementation of the Common Rule. All DoD-supported and -conducted research shall comply with reference (c) and this Directive.

4.3.2. The IRBs of DoD Components established under reference (c) shall consist of members who are either Federal employees, individuals covered under the Intergovernmental Personnel Act (IPA), or consultants consistent with the requirements established by 5 U.S.C. 3109 (reference (e)).

4.3.3. All human subject research supported or conducted by the Department of Defense shall be conducted under an assurance of compliance acceptable to the funding agency. Research performed at DoD facilities and funded by the Department of Defense shall have a DoD assurance of compliance. The DoD Components conducting or supporting research must ensure that the investigators are familiar with the Nuremberg Code, the Belmont Report, 32 CFR Part 219 (reference (c)), this Directive, and any related requirements.

4.4. Additional Protections for Certain Categories of Research. In addition to the requirements of reference (c), the following requirements apply to research involving certain subjects or purposes.

4.4.1. Research supported or conducted by the Department of Defense that affects vulnerable classes of subjects shall meet the additional protections of 45 CFR

Part 46, Subparts B, C, and D (reference (f)) (e.g., fetuses, pregnant women, human in vitro fertilization, prisoners, or children). For purposes of this paragraph, actions authorizing or requiring any action by an official of the Department of Health and Human Services (HHS) with respect to any requirements of reference (f) shall be under the authority of the Director, Defense Research and Engineering.

4.4.2. The involvement of prisoners of war as human subjects of research is prohibited.

4.4.3. For research involving more than minimal risk (as defined in 32 CFR 219.102(i), reference (c)) to subjects, an independent medical monitor shall be appointed by name. Medical monitors shall be physicians, dentists, psychologists, nurses, or other healthcare providers capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. Medical monitors shall be independent of the investigative team and shall possess sufficient educational and professional experience to serve as the subject/patient advocate.

4.4.3.1. Depending on the nature of the study, the medical monitor may be assigned to assess one or more of the following phases of a research project: subject recruitment, subject enrollment, data collection, or data storage and analysis.

4.4.3.2. At the discretion of the IRB, the medical monitor may be assigned to discuss research progress with the principal investigator, interview subjects, consult on individual cases, or evaluate adverse event reports. Medical monitors shall promptly report discrepancies or problems to the IRB. They shall have the authority to stop a research study in progress, remove individual subjects from a study, and take whatever steps are necessary to protect the safety and well-being of research subjects until the IRB can assess the medical monitor's report.

4.4.4. For research involving more than minimal risk and also involving military personnel, unit officers and noncommissioned officers (NCOs) shall not influence the decisions of their subordinates to participate or not to participate as research subjects. Unit officers and senior NCOs in the chain of command shall not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session. 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 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.

4.4.5. Research involving use of human subjects for testing of chemical or biological agents is generally prohibited by 50 U.S.C. 1520a (reference (g)), subject to possible exceptions for research for prophylactic, protective, or other peaceful purposes. Any such research shall comply with reference (g).

4.5. Education and Training on Protection of Human Subjects in Research.

Awareness of human subjects protection requirements shall be established for all DoD personnel involved in the conduct, review, or approval of research covered by this Directive.

4.5.1. Awareness activities shall be commensurate with the duties and responsibilities of the participants in the process of protection of human subjects of research, and compatible with Office of Human Research Protections (OHRP) policies.

4.5.2. Research ethics training shall be incorporated into the continuing education program at all DoD Component activities that conduct research involving human subjects.

4.6. Inclusion of Women and Minorities in Clinical Research Projects. The selection of subjects reflecting gender and minority participation as appropriate shall comply with section 252 of Pub. L. 103-160 (reference (h)). The Head of the DoD Component concerned may exercise the waiver authority under this law.

4.7. Fetal Tissue Research. Fetal tissue research supported or conducted by the Department of Defense shall comply with 42 U.S.C. 289g - 289g-2 (reference (i)).

4.8. Research Misconduct. All DoD Components shall establish procedures to monitor and review the ethical conduct of research. The DoD Components that conduct or support research shall ensure that data and data collection are conducted in an ethical manner. In cases in which data are not collected in an appropriate manner, the DoD Component shall determine if the misconduct was intentional or reckless; was an isolated event or part of a pattern; had significant impact on the research record; or had significant impact on other researchers or institutions. The DoD Component shall initiate and carry through on any actions that are necessary to ensure resolution of misconduct findings. All findings of serious research misconduct under this section shall be reported to the Director, Defense Research and Engineering.

4.9. Relationship to Other Requirements. Some activities subject to this Directive may also be subject to regulations of other Federal Agencies, organizations,

and non-U.S. entities. Examples include: Food and Drug Administration policies regarding investigational drugs, vaccines, biological products, or devices; multi-agency research; and international research. Activities subject to this Directive and one or more of these other requirements shall comply with all applicable requirements (e.g., references (c) (32 CFR 219.101(g) and (h)), (j), (k), and (l)).

4.10. Non-compliance. Issues related to non-compliance with this Directive by any DoD Component, subordinate, or supported activity shall be referred initially to the next higher management echelon to take deliberate action to resolve. All findings of serious non-compliance under this section shall be reported to the Director, Defense Research and Engineering.

5. RESPONSIBILITIES

5.1. The Director, Defense Research and Engineering, under the Under Secretary of Defense (Acquisition, Technology and Logistics):

5.1.1. Shall be the single point of contact within the Department of Defense for all matters relating to the Department of Defense's compliance with the "Common Rule" and act as the principal DoD liaison with Agencies outside the Department of Defense on matters pertaining to protection of human subjects in research.

5.1.2. May initiate updates to reference (c) and issue any DoD Instructions or other guidance necessary to implement this Directive. With respect to matters affecting medical research, this shall be done in coordination with the Assistant Secretary of Defense (Health Affairs) (ASD(HA)).

5.1.3. Shall establish a committee to coordinate DoD Component activities in the protection of human subjects. The committee shall be composed of representatives from the DoD Components' human subject protection offices.

5.1.4. Shall exercise the authorities of the Secretary of Defense under reference (c), except for matters not delegable, reserved, or covered by another specific delegation.

5.1.5. Shall establish procedures and standards, consistent with the Federal Policy on Research Misconduct (reference (m)), for the prevention of research misconduct in the Department of Defense.

5.1.6. May grant exceptions to policy under this Directive if justified by special circumstances and consistent with law. Records shall be maintained on exceptions granted under this Directive.

5.2. The Assistant Secretary of Defense for Health Affairs, under the Under Secretary of Defense for Personnel and Readiness shall:

5.2.1. Advise the Director, Defense Research and Engineering on matters related to the involvement of human subjects in research, especially, regarding medical safety, ethics, and standards of professional care and conduct.

5.2.2. Serve as the DoD representative on matters relating to implementation of Food and Drug Administration regulatory requirements (references (j) and (k)).

5.3. The Heads of the DoD Components shall:

5.3.1. Develop, issue, and monitor implementing policies to ensure compliance with this Directive and with any implementing Instructions issued under the authority of this Directive. In research undertakings in which more than one DoD Component is involved, the Heads of the Components shall determine and jointly assign executive responsibility for compliance.

5.3.2. Maintain adequate documentation of DoD-supported or -conducted research involving human subjects and establish procedures for supporting DoD reporting requirements.

5.3.3. Delegate authorities and responsibilities under this Directive to levels of command or authority appropriate to ensure compliance. This shall include procedures for the investigation and resolution of allegations of non-compliance, and may include procedures for headquarters-level administrative review of research. A DoD Component may delegate headquarters-level research review responsibility to another DoD Component for purposes of efficiency and consolidation of functional offices.

5.3.4. With respect to research for which primary involvement is from the Department of Defense, establish the required administrative procedures to protect human subjects from medical expenses (not otherwise provided or reimbursed) that are the direct result of participation in a research project involving more than minimal risk. For this purpose the determination of primary involvement shall be based on consideration of the DoD portion of the total involvement (i.e., funding, personnel, facilities, and all other resources) in the research.

6. EFFECTIVE DATE

This Directive is effective immediately.



Paul Wolfowitz
Deputy Secretary of Defense

Enclosures - 2

1. References, continued
2. Definitions

E1. ENCLOSURE 1

REFERENCES, continued

- (e) Section 3109 of title 5, United States Code, "Employment of Experts and Consultants, Temporary or Intermittent"
- (f) Title 45, Code of Federal Regulations, Part 46, "Protection of Human Subjects," Subparts B, C and D
- (g) Section 1520a of title 50, United States Code, "War and National Defense"
- (h) Section 2358 note of title 10, United States Code, "National Defense Authorization Act for Fiscal Year 1994," (Public Law 103-160, Sec. 252)
- (i) Sections 289g - 289g-2 of title 42, United States Code, "Public Health and Welfare"
- (j) Title 21, Code of Federal Regulations, Subchapters A, D, F, and H, "Food and Drug Administration"
- (k) Memorandum of Understanding between the Food and Drug Administration and the Department of Defense, "Concerning Investigational Use of Drugs, Antibiotics, Biologicals, and Medical Devices by the Department of Defense," May 1, 1987
- (l) DoD Directive 6000.8, "Funding and Administration of Clinical Investigation Program," November 3, 1999
- (m) Federal Policy on Research Misconduct, Office of Science and Technology Policy, 65 Federal Register 76260-76264 (December 6, 2000)

E2. ENCLOSURE 2

DEFINITIONS

E2.1.1. Common Rule. The regulation adopted by multiple Federal Agencies for the protection of human subjects in research. The Department of Defense's implementation of the Common Rule is at 32 CFR 219, "Protection of Human Subjects" (reference (c)).

E2.1.2. Research. Any systematic investigation, including research, development, testing, and evaluation (RDT&E), designed to develop or contribute to generalizable knowledge.

E2.1.3. Research Involving a Human Being as an Experimental Subject. 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), reference (c)). Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject's environment, the withholding of an intervention that would have been undertaken if not for the research purpose. This does not include:

E2.1.3.1. Activities carried out for purposes of diagnosis, treatment, or prevention of injury and disease in members of the Armed Forces and other mission essential personnel under Force Health Protection programs of the Department of Defense.

E2.1.3.2. Authorized health and medical activities as part of the reasonable practice of medicine or other health professions.

E2.1.3.3. Monitoring for compliance of individuals and organizations with requirements applicable to military, civilian, or contractor personnel or to organizational units. This includes such activities as drug testing, occupational health and safety monitoring, and security clearance reviews.

E2.1.3.4. Activities exempt under 32 CFR Part 219 (reference (c)).

E2.1.4. Support. Unless otherwise clarified in a specific paragraph of this Directive, this term generally means the provision of funding, personnel, facilities, and all other resources.



DEPARTMENT OF THE NAVY
OFFICE OF THE SECRETARY
1000 NAVY PENTAGON
WASHINGTON, DC 20350-1000

SECNAVINST 3900.39C
ONR 34
25 February 2002

SECNAV INSTRUCTION 3900.39C

From: Secretary of the Navy
To: All Ships and Stations

Subj: PROTECTION OF HUMAN SUBJECTS

Ref: (a) 32 Code of Federal Regulations 219
(b) 45 Code of Federal Regulations 46
(c) DoD Directive 3216.2 of 7 Jan 83 (NOTAL)
(d) 5 United States Code 3109
(e) SECNAVINST 5212.5D, Navy and Marine Corps Records
Disposition Manual, Section 3900, Paragraph 5, Page III-
3-63 of 22 Apr 98
(f) 10 United States Code 980
(g) SECNAVINST 5211.5D, Department of the Navy Privacy Act
(PA) Program, 10(a) Page 12, 10(d) Page 13 of 17 July 92
(h) 21 Code of Federal Regulations 50 and 56

Encl: (1) Definitions

1. Purpose. To prescribe policy and assign responsibility concerning the use and protection of human subjects and assurance of their personal privacy rights in studies conducted by, within, or for the Department of the Navy (DON) per references (a) through (h).

2. Cancellation. SECNAVINST 3900.39B. This instruction has been extensively rewritten and should be read in its entirety.

3. Scope

a. This instruction applies to the use of human subjects:

(1) In all research conducted by naval activities or personnel, or supported by naval activities through any agreement (e.g., contract, grant, cooperative agreement, or other arrangement), regardless of the source of funding or site of performance.

(2) In the development, testing or evaluation of any item, system, vehicle, aircraft, piece of equipment or other materiel, even if a person is not the direct object of the research. Examples include training exercises associated with

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the testing of personal protective equipment when worn by a person and the study of a new clinical laboratory test requiring freshly drawn blood.

b. This instruction does not apply to:

(1) Efforts determined to be exempt per Section 101(b) of reference (a). For determination of exempt research, see paragraph 7g(1) of this instruction.

(2) Professionals who are specifically qualified by training and experience to perform some hazardous duty while they are acting within the scope of those duties, such as, but not limited to, test pilots or experimental divers. However, these professionals are not categorically exempt from this instruction. If these professionals are enrolled as subjects in studies that are not specifically included in their professional duties, regardless of whether such studies are collateral or entirely unrelated to their routine duties, this instruction applies.

(3) Provision of commercial services or other non-collaborative services that do not produce results that either merit professional recognition or publication.

c. This instruction shall not be suspended or waived:

(1) Due to operational contingency or

(2) During times of national emergency, except by explicit action of higher authority.

d. Nothing in this instruction is intended to supersede either the requirements for health or safety reviews required by other authority, or the authority of a health care practitioner to provide emergency medical care.

4. Background. The use of humans as research subjects has received considerable national and international attention in recent years. Many studies conducted during operational exercises considered appropriate during their time are now considered unethical. Nevertheless, research using human subjects remains mission essential in a wide variety of operational, medical, and research, development, testing and evaluation settings. Human use research encompasses a broad range of endeavors, some of which are not commonly recognized as research (see definition of Research). Support from all echelons is required to protect the rights and safety of the volunteer subject.

5. Definitions. Terms used in this instruction are defined by references (a), (b), (c), and (h), except as modified in enclosure (1).

6. Policy

a. Guiding Principles

(1) Protection of human subjects shall be viewed as an important command issue at all echelons, both ashore and afloat. Commanders, commanding officers, officers in charge, heads of activities, scientific and technical program managers, project directors and investigators must maintain concern for the safety and ethical use of volunteer subjects.

(2) Studies involving human subjects must have reasonable prospects of contributing to human benefit and of yielding important results that are not obtainable by other methods. Research involving human subjects shall be scientifically sound and designed to minimize risk. The anticipated benefit shall clearly justify the risk incurred by the subjects. The number of human subjects used shall be kept to the minimum necessary to test appropriately a question or hypothesis.

(3) When applicable, sufficient preliminary animal or laboratory experiments must be completed to minimize the risk of any proposed research involving human subjects.

(4) The rights, welfare, interests, privacy and safety of the human subject shall be held paramount at all times, and all projects must be conducted in a manner that avoids all unnecessary physical or mental discomfort, and economic, social or cultural harm.

(5) Due to the possibility of injuries arising from participation in human subject research, every project involving more than minimal risk shall include an arrangement for treatment and necessary follow-up of any research-related injury in addition to providing emergent treatment. Such arrangement may be that all subjects are eligible Department of Defense (DoD) healthcare beneficiaries, that they are granted secretarial designation as DoD healthcare beneficiaries, or that specific obligations for such treatment have otherwise been made.

(6) No human subject research shall be conducted until the organization performing the research meets all the provisions of this instruction.

(7) Studies involving protected classes of human subjects such as fetuses, pregnant women, human in vitro fertilization, prisoners, and children shall only be conducted following reference (b). Subjects enrolled in an approved study who are imprisoned for whatever reason shall be disenrolled from the study in the most expeditious manner commensurate with their safety.

(8) Voluntary informed consent is fundamental to ethical human use research. It is not simply a document. It is a process that begins with subject recruitment. Informed consent includes a full discussion of the nature of the study between scientifically competent persons and the prospective subjects and/or their legally authorized representatives and continues for at least the duration of the research. Depending on the nature, type and duration of the research, ongoing discussion with and education of subjects about the study may continue long after the original informed consent is obtained.

b. Review, Approval, and Performance of Human Use Research

(1) Reference (c) specifically separates Institutional Review Boards (IRB) review from protocol approval. DON IRBs shall not approve protocols but advise the Approval authority. However, the IRB Chair may be delegated Approval authority for expedited review as defined in Section 110 of reference (a).

(2) No study involving human subjects shall be initiated nor shall subjects be solicited or enrolled until the protocol has been favorably reviewed by an IRB and approved per reference (c). Second-level review shall be provided for all protocols, including studies categorized as exempt according to Section 101(b) of reference (a), following local review. It is unnecessary to wait for completion of the Second-level Review before initiating the study.

(3) All naval commands or activities shall hold an Institutional Assurance from a DON Assurance Issuing Authority before conducting or engaging in human use research. Non-naval activities engaged in human use research must hold either a DoD assurance or an assurance from the Office of Human Research Protection, Department of Health and Human Services (HHS), per Section 103 of reference (b).

(4) IRBs at DON activities perform a Government, and not merely an advisory, function in the approval process. Members shall be either Federal employees, or consultants consistent with the requirements established per reference (d).

(5) No person shall be involved in any review or approval of a protocol when there may be an apparent, actual, or potential conflict of interest, except to provide information requested by the IRB. Any project for which the commander, commanding officer, head of the DON activity, or Approving Official is also an investigator shall be approved at a higher echelon of command, with Approval authority.

(6) Safeguards or special conditions recommended by the IRB shall not be reduced by the Approving Official, nor shall a protocol be approved that has been recommended for disapproval by the IRB.

(7) In the case of studies intending to use investigational new drugs, biologicals or medical devices, IRB membership shall include at least one physician. The physician member may be either a regular or an ad hoc member.

(8) Investigators or research staff may install, familiarize themselves with, calibrate or exercise research equipment, in preparation for the research effort, prior to IRB review.

(9) Familiarization or training of persons who may become research subjects is considered part of the research and shall only be conducted after the protocol has been approved and the subject has provided informed consent.

(10) Investigators may act as subjects in their research only after approval of the protocol and provision of informed consent. Additionally, in the case of greater than minimal risk research, the specific concurrence of the IRB is required.

(11) A joint review agreement may be negotiated among participating activities with the intention of minimizing duplication and speeding approval without sacrificing any of the protections of human subjects in accordance with Sections 103 and 114 of reference (a). Each component of the study file should be managed in accordance with the respective institution's policy regarding the manner and duration of storage.

c. Informed Consent

(1) Informed consent must be obtained and documented following reference (f) and Sections 116 and 117 of reference (a) prior to the involvement of the subject in the research. The requirement to obtain a signed informed consent document may only be waived with a specific IRB determination consistent with Section 117(c) of reference (a).

(2) For research involving any person without the legal capacity to provide consent (that is, for all children and for any adult with compromised capability to give informed consent), participation in research is only authorized when the prospective subject is intended to benefit from the research per reference (f), and subpart D of reference (b) in the case of children.

(3) For research involving adults who may have compromised competence, the protocol shall specify the method for determining the intended subject's legal competence. When an incompetent subject regains competence, direct informed consent must be obtained from the subject for continued participation in the protocol or the subject must be disenrolled.

(4) An investigator shall provide the prospective subject or the subject's legal representative sufficient opportunity to consider whether or not to participate voluntarily, an adequate opportunity to understand the consent document, and enough time to have questions answered. All information provided to the prospective subject or the subject's legal representative shall be presented in language understandable to that individual.

(5) The informed consent document shall not include exculpatory language waiving or appearing to waive any of the subject's legal rights, or releasing or appearing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(6) The informed consent document shall include text that discusses the risks to the subject and any costs that may be incurred as a consequence of participation in the study.

(7) In all cases, the subject or the subject's legal representative shall be made aware of the provisions of reference (g), and an appropriate Privacy Act statement shall be included with the consent document.

(8) The informed consent document shall be signed and dated by the subject or subject's legal representative, the

individual(s) authorized by the IRB to obtain the consent, and the witness, if required.

(9) All signatures on informed consent documents shall be performed in the presence of a witness when the research involves greater than minimal risk or when oral consent is used in accordance with Section 117(b)(2) of reference (a). The witness shall not be involved in the study or related to the subject. The witness' signature is intended to attest that the information in the consent document and any other written information was explained to and apparently understood by the subject or the subject's legal representative, that questions and concerns were addressed, and that informed consent was freely given.

(10) In the case of exceptional circumstances, such as physical disability precluding signature by an otherwise competent subject, the IRB will determine appropriate means for documenting the consent process, following the policies of Section 117 of reference (a).

(11) DON IRB records and DON completed original signed informed consent documents (or records documenting oral consent per Section 117 of reference (a)) shall be considered "Project Case Files" and retained permanently following reference (e).

d. Studies Involving the Use of Investigational Agents. All studies involving the use of Investigational Agents shall follow the guidance of reference (h).

e. International Studies. When research is conducted outside the United States involving the use of human subjects, the laws, customs and practices of the country in which research is conducted, or those required by this instruction, whichever are more stringent, shall take precedence. The research shall meet the same standards of ethics and safety that apply to research conducted within the United States.

7. Responsibilities

a. The Assistant Secretary of the Navy (Research, Development and Acquisition) (ASN(RD&A)) shall:

(1) Ensure development of policies and programs for the safe and ethical use of human subjects in naval research in coordination with the Office of the Director, Marine Corps Staff.

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These policies and programs shall provide for the responsible conduct of research, including:

(a) Education and training of all personnel who review, approve, perform, and manage research involving human subjects,

(b) Ethical review, and

(c) Compliance.

(2) Endorse and forward to the Director, Defense Research and Engineering for approval of all studies involving actual exposure of human subjects to the effects of nuclear, biological, or chemical warfare agents or weapons.

(3) Serve as the Approving Official for any research involving:

(a) Severe or unusual intrusions, either physical or psychological, on the human subject (e.g., consciousness-altering drugs, mind-control techniques, abnormal environments involving extreme risk),

(b) Prisoners, or

(c) Potential political or public embarrassment to the DON.

(4) Ensure availability of ASN(RD&A) staff expertise in the protection of human subjects in research.

b. The Chief of Naval Operations (Surgeon General (SG) of the Navy (N093)) is:

(1) Delegated authority to issue DoD Institutional Assurances to all naval activities. The SG is also delegated authority to issue DoD Institutional Assurances to contractors conducting research using human subjects as described in paragraph 3a of this instruction, except as specifically assigned to the Chief of Naval Research (CNR). All studies using Navy or Marine Corps personnel or employees of the DON as subjects fall under the purview of the SG. This authority may be delegated but not further subdelegated.

(2) Designated the Approving Official for all naval research using human subjects except for research under the Approval authority of the CNR or research requiring approval by higher authority. The SG may further delegate Approval authority

to Navy Assurance Issuing Authorities. This Approval authority may be further delegated.

c. The CNR is:

(1) Delegated authority to issue DoD Institutional Assurances to all contractors conducting research using human subjects in studies that do not include Navy or Marine Corps personnel or employees of the DON as subjects, and that are funded or sponsored by the Office of Naval Research. This authority may be delegated but not further subdelegated.

(2) Designated the Approving Official for research using human subjects in studies specified in paragraph 7c(1). This Approval authority may be further delegated to offices responsible for Second-level Review.

d. Assurance Issuing Offices shall:

(1) Provide guidance and consultation regarding the implementation of this instruction.

(2) Negotiate and issue numbered DoD Institutional Assurances.

(3) Establish appropriate monitoring procedures to determine if institutions under their purview remain in compliance with the terms of their Institutional Assurance.

(4) Provide Second-level Review for all protocols from institutions under their purview, including studies categorized as exempt according to Section 101(b) of reference (a). Second-level Review shall be accomplished regardless of whether the research is performed under a DoD or HHS Assurance.

(5) Approve, before implementation, requests from performing institutions to enter into joint review arrangements.

(6) Not further subdelegate any of the above responsibilities.

(7) Delegate, as appropriate, to the commander, commanding officer, or head of a DON activity the authority to approve the use of human subjects in research. Recipients of delegated Approval authority from an Assurance Issuing office may

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not subdelegate this authority except to permit IRB chairs to approve research using expedited procedures.

e. Commanders/commanding officers/heads of naval activities whose involvement with a specific research protocol is limited to permitting outside investigators to recruit personnel as subjects onboard their command, shall require Certification(s) from the performing activity or activities before allowing participation of their personnel. This responsibility extends to commanders/commanding officers/heads of all naval activities, including vessels afloat, training commands and Marine units.

f. Commanders/commanding officers/heads of naval activities engaged in research shall:

(1) Establish an IRB following references (a) and (c) or negotiate a formal agreement with an external IRB at another institution that holds an appropriate assurance.

(2) Obtain an Institutional Assurance, appropriate for the research in question, from the activity's Assurance Issuing Authority or provide evidence of an appropriate HHS Assurance before conducting research using human subjects.

(3) Serve as their activity's Approving Official, contingent upon holding delegated Approval authority. Subdelegation is authorized only to the Chair of the IRB for expedited review as set forth in paragraph 7d(7) above.

(4) Issue Certifications to funding sponsors following Section 103(f) of reference (a).

(5) Provide the activity's Assurance Issuing Authority with documents for Second-level Review within 15 working days after approval.

(6) Maintain research records as "Project Case Files" following reference (e).

(7) Allocate adequate resources including but not limited to logistical, financial, and educational resources, to ensure compliance with the activity's Institutional Assurance and all applicable guidance.

(8) In cooperative/collaborative research projects, negotiate an agreement with the other participating institution(s) that includes at a minimum a statement of work and a specific assignment of responsibilities. This assignment must

include at least responsibility for IRB review, oversight, reporting, and compliance for the project as a whole, as well as record keeping, reporting, ongoing monitoring and compliance at each site of performance. In cases of proposed assignment of primary IRB responsibility to another institution, the commanding officer shall obtain the approval of the activity's Assurance Issuing Authority as set forth in paragraph 7d(5) of this instruction prior to finalizing the agreement. All cooperative research still requires specific DON approval and Second-level Review.

(9) Verify that a contractor applying for support holds a valid HHS or DoD Institutional Assurance and has submitted a Certification executed by an individual authorized to act for that organization.

g. Naval Approving Officials shall:

(1) Not approve a protocol that has been recommended for disapproval by the IRB.

(2) Not reduce the safeguards or conditions recommended by the IRB.

(3) Determine whether to approve or disapprove the protocol, require additional safeguards, or refer the protocol to a higher Approval authority. When determining whether to approve the proposed research, the Approving Official shall review and consider, at a minimum, the signed minutes of IRB meetings.

h. Naval IRBs shall:

(1) Determine the applicability of this instruction to all protocols presented for review, including determination of exempt research.

(2) Establish the level of risk involved in a particular protocol.

(3) Following reference (c), approve an appropriate health care provider to be the medical monitor for all research categorized as greater than minimal risk. IRBs will ensure that the role(s) of the monitor during subject selection, enrollment, participation, and/or follow-up have been specified in writing. The monitor shall not be an investigator on that research study.

(4) Ensure that safety-monitoring plans are implemented proportionate to risk following reference (c).

(5) Conduct continuing review of all approved studies at least once a year, or more often, as warranted by the level of risk.

(6) Provide timely notification to the Approving Official of all issues of safety or incidents of non-compliance with this instruction and other relevant guidance and directives.

(7) Ensure that the study shall be conducted only by investigators possessing the requisite human use training and relevant scientific qualifications.

i. Chairs of Naval IRBs shall:

(1) Have delegated authority from the Approving Official to suspend a previously approved research project when there is any significant deviation from the protocol, any serious adverse event, or for other reasonable cause.

(2) Ensure that the IRB is informed of all actions taken under expedited review authority.

j. Principal Investigators shall:

(1) Have primary responsibility for compliance with all provisions of this instruction and the protection of human subjects regulations.

(2) Submit all proposals that may involve research using human subjects, even those thought to be exempt under Section 101(b) of reference (a), to the IRB for determination of the applicability of this instruction.

(3) Provide a written Investigator's Assurance for compliance with all applicable laws, regulations, policies and directives for all designated investigators on a specific study.

(4) Submit all proposed changes to an approved study to the IRB for review and approval prior to implementation.

(5) In the case of research involving greater than minimal risk of physical harm, make provision in the protocol for the rapid medical evacuation of subjects to an adequate treatment facility in case of need.

(6) Notify an affected subject as soon as feasible of any serious adverse event.

(7) Notify the IRB Chair within 24 hours of any unanticipated serious adverse event.

(8) Notify the IRB Chair of any deviation from the approved protocol as soon as possible. Identify causes, and submit a protocol amendment to the IRB that addresses the problems that led to the deviation.

(9) Provide a summary of all adverse events to the IRB at each continuing review and at the conclusion of the research project.

(10) Provide subjects or their legally authorized representative with a copy of the completed informed consent document except for those studies qualifying for waiver of documentation of informed consent per Section 117 of reference (a). For greater than minimal risk research, in the case of a DoD beneficiary, a copy shall also be forwarded to the subject's medical records custodian, and for a non-DoD beneficiary, a second copy shall be provided to the individual subject for inclusion in the subject's personal medical records.

(11) Suspend a subject's participation at any time if there is reason to suspect that continuation is likely to result in harm, disability or death. This responsibility extends to every member of the investigative team.

k. Any specific situations not addressed in this instruction should be referred to the SG for clarification.

Gordon R. England
Secretary of the Navy

Distribution:
SNDL Parts 1 and 2
MARCORPS PCN 71000000000 and 71000000100

DEFINITIONS

1. Adverse Event. Any unfavorable and unintended occurrence associated with the conduct of a research project.
2. Approval. Specifically delegated authority to accept the recommendation of an IRB.
3. Approving Official. An individual with delegated Approval authority. Such individual may or may not also have authority to certify a research protocol.
4. Assurance Issuing Authority. An office authorized to issue Institutional Assurance numbers to DON activities and contractors performing human subjects research.
5. Certification. The formal written notification by the performing activity that a human subject research protocol has been properly reviewed and approved by an IRB specified in the activity's assurance, and that participation is within the bounds of the activity's assurance.
6. Contractor. Any individual or organization that is a party to a contract, grant, interagency transfer or other agreement with any Navy or Marine Corps activity. An organization includes any Federal, State, municipal or other Government activity, or any corporation, institution, foundation, agency, or other legal entity, whether foreign or domestic.
7. Engaged in Research. An activity becomes engaged in research when its personnel or agents either (a) intervene or interact with living individuals for research purposes; or (b) obtain individually identifiable private information for research purposes.
8. Institutional Assurance. A written document originated by the performing institution to be considered by the Assurance Issuing Authority which states that the performing institution will comply with the requirements of reference (a) for a specific project or category of research.
9. Investigational Agents. Drugs, biologicals, and devices as defined by reference (h).
10. Investigator's Assurance. A pledge signed by all investigators in which they acknowledge their responsibilities for the protection of human subjects.

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11. Joint Review Agreement. A written agreement coordinating action and responsibility between two or more activities working together on a research project to minimize duplication of effort while ensuring compliance with all requirements of this policy.
12. Naval Activities. Includes both Navy and Marine Corps components.
13. Principal Investigator. A qualified individual who initiates a protocol and conducts a research study based on the protocol after appropriate approval.
14. Prisoner. Any person who is involuntarily detained or held for the purposes of confinement or rehabilitation, relating to military, criminal or civil offenses, or for other purposes.
15. Protocol. The detailed written research plan.
16. Research. Any systematic investigation designed to develop or contribute to generalizable knowledge including but not limited to any project, task, test, pilot study, experiment, investigation, study, clinical study, evaluation, developmental effort or similar undertaking, whether or not conducted or supported under a program that is officially considered research. Any effort, even if not considered research for other purposes, is nonetheless considered research for purposes of this instruction if it meets this definition.
17. Risk. Any possibility of harm, discomfort, or injury -- physical, psychological, sociological, or other -- as a consequence of any act or omission.
18. Second-level Review. Administrative review of approved protocols by a Navy Assurance Issuing Authority to ascertain regulatory compliance following local approval.

Enclosure (1)

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