

**WILLS EYE HOSPITAL
INSTITUTIONAL REVIEW BOARD
IRB POLICY & PROCEDURES MANUAL**

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1. INTRODUCTION AND BACKGROUND

1.1. Welcome to the Wills Eye Hospital Institutional Review Board (IRB)

The IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated. Beginning in the early 1960's, there has been a continuing evolution in the system used to protect human research subjects. In 1974, the National Research Act required that institutions engaged in clinical research establish a committee, called the IRB, to protect research subjects. Somewhat later, in 1981, similar regulations were published by the Food and Drug Administration. The IRB has the authority to approve, require modifications in or disapprove all research activity that falls within its jurisdiction as specified by both federal regulations and local institutional policy.

The Wills Eye Hospital IRB is registered with the Office for Human Research Protection (OHRP) within the Department of Health and Human Services to review all research activities conducted under its auspices. The following institutions operate under their own Federal Wide Assurances (FWA). These FWA allow Wills Eye Hospital and its components to do research in human subjects under regulations promulgated by the FDA and other federal departments and agencies, i.e. NIH, NASA, Department of Energy, etc.

Wills Eye Hospital Institutional Review Board

IRB Registration: #290

Wills Eye Hospital, Philadelphia, PA
Cherry Hill ASC (NJ)
Plymouth Meeting ASC (PA)
Warminster ASC (PA)
Wilmington ASC (DE)

FWA: #1933
FWA: #26099
FWA: #8862
FWA: #7663
FWA: #20123

1.2. The History of the Institutional Review Board

In 1946, during World War II trials at Nuremberg, 23 Nazi physicians went on trial for crimes committed on prisoners of war and other persons at Dachau, Ravensbruck and other “camps” throughout Germany and occupied territories. This was known as “The Nazi Doctors Trial.” These doctors performed such medical experiments as placing victims in vacuum chambers without breathing devices to test the effects of high altitude exposure, immersing victims in ice-cold water to test the effects of cold exposure and purposefully producing infected wounds to test the effects of anti-infective drugs. Following this trial, during which most of the defendants were found guilty, there was developed the Nuremberg Code which set out a series of requirements to perform research in humans which were:

1. Voluntary consent is absolutely necessary.
2. The experiments should be sound and yield results for the good of society.
3. The experiment should be based on results of animal experiments and a knowledge of the natural history of the disease.
4. The experiment should avoid unnecessary physical and mental suffering and injury.
5. No experiment should be conducted if death or disabling injury will occur; unless where the experimental physician is also the subject.
6. The risk should not exceed the humanitarian importance of the problem to be solved.
7. Proper preparation and adequate facilities should be available to protect subjects against injury, disability or death.
8. The experiment should be conducted by properly qualified persons.
9. During the experiment, the subject should be free to end the experiment.
10. During the experiment, the scientist in charge should be prepared to terminate the experiment at any stage if it may cause injury, disability or death to the subject.

For those currently engaged in clinical research, it is clear that many of these requirements set down in 1947 remain important today.

Federal funding for clinical research began to expand in the 1960's and there was also an increased interest in protecting the rights of persons participating in clinical trials. This interest was intensified by the numerous reports of research studies conducted in human subjects without their knowledge or consent. Examples of these reports include the injections of live cancer cells into elderly, indigent patients at the Jewish Chronic Disease Hospital, Brooklyn, New York in 1963 and the research done at Willowbrook State School in New York in which retarded children were purposefully infected with a mild strain of infectious hepatitis.

In 1966, Henry Beecher, a highly respected physician-investigator from Boston, published a paper in the New England Journal of Medicine in which he outlined numerous examples of unethical or questionably ethical studies done in human subjects at many of the premier medical institutions in the United States.

The World Health Organization, in 1964, believed that guidelines broader than the Nuremberg Code were necessary, and the Declaration of Helsinki was adopted by the World Medical Society. These guidelines have been revised a number of times and suggestions for their

revision continue today. In the original document, the recommendation was made that “the design and performance of each experimental procedure...should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially supported committee independent of the investigator and sponsor....”

The NIH, in 1966, promoted the development of the first Public Health Service Policy on the Protection of Human Subjects which applied to extramural research only. Later, the policy was expanded to cover all human research conducted or supported by DHEW. It required prospective review of human subject research, taking into account the rights and welfare of the subjects involved, the appropriateness of the methods used to secure informed consent, and the risks and potential benefit of the research. The elements of informed consent included the requirement that consent be documented and signed by the subjects or their representatives.

In the 1970's, several events resulted in renewed and intense efforts to protect human research subjects. In 1972, the New York Times reported on a study, designed by the Center for Disease Control (CDC), to determine the need to establish a syphilis treatment program. The Tuskegee Institute, in Alabama, was selected as the study site and a major effort was made to recruit syphilitic black subjects to enroll by offering free examinations and medical care. The study, begun in 1932 was intended to be of short duration and no treatment was to be given because the intention was to determine what health effects had taken place during the study duration. A second phase of the study, begun in 1933, added a group of black control subjects, who, like the original participants, were not informed the nature of the study. Even after 1943, when penicillin was accepted as the treatment for syphilis, participants did not receive treatment.

The Senate Committee on Labor and Human Resources held hearings on this study and on other alleged abuses of children and prisoners. The outcomes of these hearings included the enactment of the National Research Act of 1974 requiring DHHS to codify its policy for protection of human subjects into Federal Regulations and which included formal requirements for the establishment of IRBs. Also, as a result of the National Research Act, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was formed. The Commission published in 1979 the “Ethical Principles and Guidelines for the Protection of Human Subjects of Research,” generally recognized as the Belmont Report. [Named after the Belmont Conference Center at the Smithsonian Institution where the Commission held their discussion]. Members of the Commission included Robert Cooke, M.D., President, Medical College of Pennsylvania and Eliot Stellar, Ph.D., Provost, University of Pennsylvania. The Belmont report provides guidance for distinguishing therapeutic medicine from research, identifies three fundamental ethical principles for the protection of human subjects, and illustrates how the ethical principles should be applied to the conduct of human research subjects.

In 1979, DHHS began the process of revising the 1974 regulation but it was not until 1981 that final Department approval was given to Title 45, Code of Federal Regulations, Part 46 [45 CFR, Part 46]. At first, these regulations were applicable only when research was conducted or supported by DHHS, but in 1991, all federal departments and agencies adopted as regulation, a common Federal Policy for the Protection of Human Subjects (The Common Rule). This policy applies to research involving human subjects conducted, supported or otherwise subject to regulation by any of sixteen federal departments and agencies and which are:

- Department of Agriculture
- Department of Energy
- NASA
- Department of Commerce
- Consumer Product Safety Commission
- International Development Cooperation Agency
- Agency for International Development
- Department of Housing and Urban Development
- Department of Justice
- Department of Defense
- Department of Education
- Department of Veteran Affairs
- Environmental Protection Agency
- Department of Health and Human Services
- National Science Foundation
- Department of Transportation

FDA regulations pertaining to research in human subjects are codified separately. All these regulations described in detail the role and importance of the IRB in the clinical research process.

1.3. The Nuremberg Code

From: <http://ohsr.od.nih.gov/guidelines/nuremberg.html>

Directives for Human Experimentation

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.

1.4 The Declaration of Helsinki

From: <http://ohsr.od.nih.gov/guidelines/helsinki.html>

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged

must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to

the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.¹
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.²

¹ **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki** The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

² **Note of clarification on paragraph 30 of the WMA Declaration of Helsinki** The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Revised: 09/10/2004

prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

1.5 The Belmont Report

From: <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>

The Belmont Report

Office of the Secretary

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

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

April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by 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) 78-0013 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.

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

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-

Ethical Principles & Guidelines for Research Involving Human Subjects

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 codes³ intended to assure that research involving human subjects would be carried out in an ethical manner.

³ Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare. Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

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.

Part A: Boundaries Between Practice & Research

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.⁴ 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.

⁴ Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as 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.⁵

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.

Part B: Basic Ethical Principles

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 of persons, beneficence and justice.

1. 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 consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The

⁵ Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

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.

2. 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.

3. 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 particularly flagrant 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.

Part C: Applications

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.

1. 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 provisions 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 disable 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.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful array 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 harm 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.

3. 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 IRBs 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.

1.6. Recruiting Research Subjects

Recruiting research subjects is the beginning of the informed consent process. The methods and materials investigators use to recruit subjects must be reviewed and approved by the IRB and should be submitted to the IRB with the study protocol and informed consent form.

A. Media Advertising

Direct advertising for research subjects, i.e., advertising that is intended to be seen or heard by prospective subjects to solicit their participation in a study, is acceptable practice. Direct advertising includes, but is not necessarily limited to: newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects. Not included are: 1) communication intended to be seen or heard by health professionals, such as “dear doctor” letters and doctor-to-doctor letters, 2) news stories and 3) publicly intended for other audiences, such as financial page advertisements directed toward potential investors.

IRB review and approval of listings of clinical trials on the internet is not required when the system format limits information provided to basic trial information such as: the title, purpose of the study, protocol summary, basic eligibility criteria, study site location(s), and how to contact the site for further information. Examples of such clinical trials listing services include the National Cancer Institute’s cancer trial listing (PDQ) and the government sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information to the listing service is not precluded by the data base system, IRB review and approval is required.

FDA and the IRB considers direct advertising for study subject to be part of the informed consent and subject selection process. Advertisements must be reviewed and approved by the IRB as part of the package for initial review. If the investigator decides at a later date to advertise for subjects, the advertising will be considered an amendment to the study. When this advertisement can be easily compared to the approved consent document and protocol, expedited review and approval can be done. If there are doubts about the advertisement or other complicating issues are involved, full IRB review and approval are required.

When direct advertising is to be used, the IRB must review the information contained in the advertisement and the mode of communication, to determine that the procedure is not coercive and does not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and protocol. The IRB must review the final copy of printed advertisements to evaluate the relative size of type used and other visual effect. When advertisements are to be taped for broadcast, the IRB must review the final audio/video tape. No claim should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purpose under investigation, or that the test article is known to be equivalent or superior to any other drugs, biologics or device. This is a violation of FDA regulations concerning promotion of investigational drugs or devices advertisements should not use terms such as “new treatment,” “new medication,” or “new drug” without explaining the test article is investigational. A phrase such as “receive new treatment” leads study subjects to believe they will be receiving newly improved products which are approved by the FDA and of proven worth. Advertisements should not promise “free medical treatment” when the intent is only to say subjects will not be charged for taking part in this study. Advertisements may state subjects will

be paid but should not emphasize the payment or the amount to be paid by such means as larger or bold type. The FDA recommends and the IRB requires the following items to be included in the advertisement:

1. the name and address of the investigator and/or research facility;
2. the condition under study and/or the purpose of the study;
3. in summary form, the criteria that will be used to determine eligibility for the study;
4. a brief list of participation benefits, if any (e.g., no cost health examination);
5. the time or other commitment required of the subjects;
6. the location of the research and the person or office to contact for further information.

B. Research/Office Nurse - Receptionist Scripts

The first contact prospective study subjects make is often with a nurse or receptionist who uses a list of questions to determine eligibility and a “script” to describe the research study. In this sense, the IRB must determine that the procedures followed adequately protect the rights and welfare of prospective subjects. In some cases, personal and sensitive information is gathered about the person. The IRB must have assurance that the information will be appropriately handled. A simple statement such as “confidentiality will be maintained” may not adequately inform the IRB of the procedures to be used. Examples of issues that are appropriate for IRB review are:

1. What happens to personal information if the caller ends the interview or simply hangs up?
2. Are names of non-eligible individuals maintained in case they would qualify for another study?
3. Are paper copies of records shredded or are readable copies put out as trash?

Clearly, the acceptability of the procedures is dependent on the sensitivity of the data gathered, including personal, medical and financial.

C. Other

Researchers ordinarily use information that subjects have disclosed or provided voluntarily for research purposes (e.g., with their informed consent). Under these circumstances, there is little reason for concern about privacy, other than to assure that appropriate confidentiality of data is maintained. Where privacy issues do arise is in regard to information obtained for research purposes without the consent of subjects. When patients give information about themselves to a doctor or hospital for the purpose of facilitating diagnosis or treatment of disease, they do so in a relationship of trust. This information becomes part of the patient’s medical record.

Patients generally expect that the information will be shared only as necessary for their health care or reimbursement by their insurance company or other third party payer: patients

would not expect information that identifies them to be passed onto clinical researchers. However, confidences are not absolute. Patient records are commonly used for a variety of purposes other than care of a particular patient, for example, for the management of the organization through quality assurance programs and for utilization review.

Clearly, some important research cannot be conducted unless an investigator gains access to patient records. It is not possible to specify precisely when an institution should honor a researcher's request to examine records or when an IRB should approve this potential invasion of privacy. In 1977, the Privacy Protection Study Commission concluded that medical records can legitimately be used for biomedical or epidemiological research without the individual's explicit permission, provided that the "medical care provider" maintaining the record determines, among other things:

1. that the use or disclosure in individually identifiable form is necessary to accomplish the research;
2. that the importance of the research is such as to warrant the risk to the individual;
3. that adequate safeguards are present to protect from unauthorized disclosure, including a program for removal or destruction of identifiers;
4. that written consent be obtained before further use or re-disclosure of the record identifying the patient is permitted.

The National Commission endorsed this recommendation and concluded that in studies of documents, records or pathological specimens where subjects are identified, informed consent can be waived if the IRB determines that the subjects entered are adequately protected and the importance and value of the research justifies the invasion of privacy.

In any case, use of patients' medical records for research purposes and to identify patients for research studies is an extremely sensitive issue. Researchers wishing to use medical records for research purposes should provide the IRB with a detailed plan as to how the records will be used and how patient confidentiality will be protected. It is advisable that researchers contact the IRB for guidance.

1.7. Selecting Research Subjects

“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.” 45 CFR 46.111(a)(3).

Selecting subjects for a research project involves many factors: requirements for scientific design, susceptibility to risk, likelihood of benefit, practicability, and consideration of fairness. IRBs are required to make a specific determination that the selection of subjects is equitable.

The requirement for an equitable selection of subjects helps ensure that the burdens and benefits of the research will be fairly distributed. When the National Commission for the Protection of Human Subjects recommended that IRBs be required to make this determination they noted that in the 19th and early 20th centuries, the burdens of research fell largely upon poor patients in hospital wards, while the benefits flowed primarily to private patients. This inequity was dramatically revealed in the Tuskegee syphilis study in which disadvantaged blacks in the rural south were recruited for studies of the untreated course of a disease that was by no means confined to that population. The National Commission recommended that selection of research subjects be scrutinized to determine whether “some classes” (e.g. welfare patients, racial or 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.

Easy availability, compromised position and susceptibility to manipulation often overlap. For example, psychology students are readily available for psychology research, medical students are readily available for medical research and employees of drug manufacturing companies are readily available for drug research. Subjects selected from these populations are also compromised to the extent that their jobs, promotions, grades, evaluations, etc. are dependent upon those who might be recruiting them for research. This circumstance makes them susceptible to manipulation.

Prisoners and patients in mental institutions are confined under the strict control of people whom they must please and to whom they must appear cooperative and rational if they are to earn their release. These potential subjects may believe, probably as a result of their dependent situation, that agreeing to participate in research will be viewed positively by their wardens, psychiatrists or social worker. At least in the past, mental patients and prisoners have accepted the risks of research in disproportionate numbers, while the benefits of the research in which they participated went to all segments of society. This led the National Commission to suggest that investigators be required to justify any proposed involvement of hospital patients, other institutionalized persons, disproportionate number of racial or ethnic minorities, or persons of lower socioeconomic scale.

Patients may also be susceptible to real or imaginary pressure to participate. If an investigator also serves as a patient’s primary physician, he or she may feel obliged to participate in the research out of a desire to please, gratitude or fear that failure to do so will result in

hostility or abandonment. Patients who are dependent on a particular facility for their care may feel that they will be treated less well or with less favor if they refuse to participate in research.

The National Commission recommended, as a matter of social justice, there should be an order of preference in the selection of classes of subjects: adults before children, competent individuals before incompetent individuals, and non-institutionalized individuals before institutionalized individuals. Investigators and IRBs should consider the extent to which a proposed subject population is already burdened by poverty, illness, poor classification or chronic disabilities in deciding whether they are suitable subject populations.

With these caveats in mind, investigators and IRBs must be careful not to overprotect vulnerable populations so that they are excluded from research in which they wish to participate. Also, patients with serious or poorly understood disorders may want to participate in studies designed to provide a better understanding of their condition. Under-representation of special groups in study populations ensure that they will not benefit from research. The NIH requires that research grantees include minorities and women in study populations “so that the research funding can be of benefit to all persons at risk of the disease, disorder or condition under study.” Investigators must provide “a clear and compelling rationale for their exclusion or inadequate representation” in the grant application.

1.8. Payment to Research Subjects

It is not uncommon for persons to be paid for participating in clinical research. Although payments are usually monetary, both patients and healthy volunteers may be offered other rewards in lieu of or in addition to money. Financial incentives are often used when health benefits to subjects are remote or non-existent. Taking into consideration the subject's medical, employment and educational status, and their financial, emotional and community resources, the IRB and the investigator must be certain that the rewards offered for participating in research do not constitute undue inducement.

Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive.

The consent document must contain, and the IRB must carefully consider, a detailed account of the terms of payment, including a description of the condition under which a subject would receive partial or no payment (for example, what would happen if the subject withdraws part way through the research). The IRB must review both the amount of payment and the proposed method and timing of disbursement to assure that neither is coercive or presents undue influence.

Determining the appropriateness of the payment (or other incentive) can be difficult because there must always be a balance between fairness to the subject and the possibility of coerciveness. For research that requires subjects to undergo only minor inconvenience or discomfort, a modest payment will usually be adequate. Reimbursement for travel, babysitting, and so forth may also be provided. In more complex research studies, other considerations are important, e.g. the degree of risk, number of tissue or blood samples to be taken, the type and number of other procedures to be performed, admission to a research unit in a hospital, dietary restriction, etc. In these circumstances, the appropriateness of payment should be made on a case-by-case basis.

2. FEDERAL REGULATIONS

2.1 Differences Between FDA Regulations and the Common Rule

Clinical researchers and the IRB must deal with two sets of federal regulations. The DHHS regulations, 45 CFR 46, apply to research in human subjects conducted by DHHS or funded in whole or in part by the DHHS, ex. NIH. The Office for Human Research Protection (OHRP)*, a unit within DHHS and the Office with which our Federal Wide Assurance was negotiated, follows 45 CFR 46.

The Food and Drug Administration (FDA) regulations, 21 CFR, parts 50 & 56, apply to research involving products (drugs and devices) regulated by the FDA. Federal support is not necessary for the FDA regulations to apply. When research involving products regulated by the FDA is funded, supported or conducted by DHHS (ex. NIH), both DHHS and FDA regulations apply.

Similarities exist between the DHHS and FDA regulations. For example, 45 CFR 46.107 and 21 CFR 50.107 which describe IRB membership and 45 CFR 46.116 and 21 CFR 50.25, which list the basic and optional elements of informed consent, are virtually the same. However, significant differences in DHHS and FDA regulations do exist and are as follows:

Significant Differences Between Regulations

IRB Regulations:

56.102 (FDA) 46.102 (DHHS)	FDA definitions are included for terms specific to the type of research covered by FDA regulations (test article, applications for research or marketing permit, clinical investigations). FDA also adopted the Federal policy's wording for the definition of minimal risk. A definition for emergency use is provided in the regulations.
46.103 (DHHS)	DHHS requires that institutions provide an Assurance of Compliance which is negotiated with OHRP (OPRR). FDA does not require an Assurance of Compliance.
56.104 (FDA) 46.116 (DHHS)	Types of research covered by the Regulations are different and, therefore, research exempted by the Regulations VI is also different. For example, FDA exempts from prospective IRB review the "emergency use" of a test article in specific situations (50.23).
56.109 (FDA) 46.109 (DHHS) 46.117 (DHHS)	Unlike DHHS, FDA does not provide that an IRB may waive the requirement for signed consent when the principal risk is a breach of confidentiality because FDA does not regulate studies that would fall into that category of research. (Both regulations allow for IRB waiver of documentation of informed consent in instances of minimal risk).

56.115 (FDA) 46.115 (DHHS)	DHHS, not FDA, requires the IRB or institution to report changes in membership. FDA has neither an assurance mechanism nor files of IRB membership; there is, therefore, no reason for FDA to be informed about changes in membership.
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Informed Consent Regulations:

50.23 (FDA)	FDA, but not DHHS, provides explicit guidance for an exemption from the informed consent requirement in emergency situations. This may be used in investigations involving investigational drugs, device and other FDA regulated products. This is a single patient use situation and cannot be used for research.
50.24 (FDA)	FDA, but not DHHS, provides explicit guidance for the exemption from informed consent requirements for <u>emergency research</u> .
46.116(c) and (d) (DHHS)	DHHS provides for waiving or altering elements of informed consent under certain circumstances. FDA has no such provision because the type of studies that would qualify are not regulated by the FDA or are covered by emergency treatment provision of 50.23.
50.25(a)(5) (FDA) 46.116(a)(5) (DHHS)	FDA requires that subjects be informed that FDA may inspect records of the study. While DHHS has the right to inspect records, it does not require a statement in the informed consent.

2.2 45 CFR 46 (The Common Rule)

Code of Federal Regulations
TITLE 45 PUBLIC WELFARE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 46
PROTECTION OF HUMAN SUBJECTS

* * *

Revised June 23, 2005

Effective June 23, 2005

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Basic HHS Policy for Protection of
Human Research Subjects

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Authority: 5 U.S.C. 301; 42 U.S.C. 289(a).

Editorial Note: The Department of Health and Human Services issued a notice of waiver regarding the requirements set forth in part 46, relating to protection of human subjects, as they pertain to demonstration projects, approved under section 1115 of the Social Security Act, which test the use of cost-sharing, such as deductibles, copayment and coinsurance, in the Medicaid program. For further information see 47 FR 9208, Mar. 4, 1982.

Subpart A - Basic HHS Policy for Protection of Human Research Subjects

Authority: 5 U.S.C. 301; 42 U.S.C. 289(a); 42 U.S.C. 300v-1(b).

Source: 56 FR 28003, June 18, 1991; 70 FR 36325, June 23, 2005.

§46.101 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.

Sec.

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46.409 Wards.

- (1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in §46.102(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 §46.102(e) must be reviewed and approved, in compliance with §46.101, §46.102, and §46.107 through §46.117 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 or 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 Human Research Protections, Department of Health and Human

Services (HHS), or any successor office, and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in Department or Agency procedures.⁶

[56 FR 38012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991; 70 FR 36325, June 23, 2005]

§46.102 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

⁶ 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, subpart 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.

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.

§46.103 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 Human Research Protections, HHS, or any successor office, 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 Human Research Protections, HHS, or any successor office.
- (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 §46.101 (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 §46.103(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 Human Research Protections, HHS, or any successor office.
 - (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 §46.101 (b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §46.103 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 §46.103 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.

(Approved by the Office of Management and Budget under control number 0990-0260.)

[56 FR 38012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991; 70 FR 36325, June 23, 2005]

§§46.104--46.106 [Reserved]

§46.107 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

§46.108 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 §46.103(b)(4) and to the extent required by §46.103(b)(5).
- (b) Except when an expedited review procedure is used (see §46.110), 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

§46.109 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 §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, 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 §46.117.
- (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.

(Approved by the Office of Management and Budget under control number 0990-0260.)

§46.110 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 Human Research Protections, HHS, or any successor office.
- (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 §46.108(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.

§46.111 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 §46.116.
 - (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.
 - (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.

§46.112 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.

§46.113 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.

(Approved by the Office of Management and Budget under control number 0990-0260.)

§46.114 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.

§46.115 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 §46.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in §46.103(b)(4) and §46.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by §46.116(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.

(Approved by the Office of Management and Budget under control number 0990-0260.)

§46.116 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 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; 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.

(Approved by the Office of Management and Budget under control number 0990-0260.)

§46.117 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 §46.116. 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 §46.116 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.

(Approved by the Office of Management and Budget under control number 0990-0260.)

§46.118 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 §46.101 (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.

§46.119 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.

§46.120 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.

§46.121 [Reserved]

§46.122 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.

§46.123 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).

§46.124 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.

Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Source: 66 FR 56778, Nov. 13, 2001, unless otherwise noted.

§46.201 To what do these regulations apply?

- (a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services (DHHS). This includes all research conducted in DHHS facilities by any person and all research conducted in any facility by DHHS employees.
- (b) The exemptions at §46.101(b)(1) through (6) are applicable to this subpart.
- (c) The provisions of §46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in §46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.
- (d) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.202 Definitions.

The definitions in §46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

- (a) Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.
- (b) Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.
- (c) Fetus means the product of conception from implantation until delivery.
- (d) Neonate means a newborn.
- (e) Nonviable neonate means a neonate after delivery that, although living, is not viable.
- (f) Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.
- (g) 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.

- (h) Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat 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 neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

§46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.

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 and the other subparts of this part.

§46.204 Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

- (a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
- (b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
- (c) Any risk is the least possible for achieving the objectives of the research;
- (d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;
- (e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

- (f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
- (g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;
- (h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- (i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
- (j) Individuals engaged in the research will have no part in determining the viability of a neonate.

§46.205 Research involving neonates.

- (a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:
 - (1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
 - (2) Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
 - (3) Individuals engaged in the research will have no part in determining the viability of a neonate.
 - (4) The requirements of paragraph (b) or (c) of this section have been met as applicable.
- (b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:
 - (1) The IRB determines that:
 - (i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
 - (ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
 - (2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is

obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

- (1) Vital functions of the neonate will not be artificially maintained;
- (2) The research will not terminate the heartbeat or respiration of the neonate;
- (3) There will be no added risk to the neonate resulting from the research;
- (4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
- (5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

(d) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

§46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.

- (a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.
- (b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

§46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of §46.204 or §46.205 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 pregnant women, fetuses or neonates; and
- (b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:
 - (1) That the research in fact satisfies the conditions of §46.204, 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 pregnant women, fetuses or neonates;
 - (ii) The research will be conducted in accord with sound ethical principles; and
 - (iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Source: 43 FR 53655, Nov. 16, 1978, unless otherwise noted.

§46.301 Applicability.

- (a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.
- (b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.
- (c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.302 Purpose.

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§46.303 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) DHHS means the Department of Health and Human Services.
- (c) Prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.
- (d) Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

§46.304 Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

- (a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
- (b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

[43 FR 53655, Nov. 16, 1978, as amended at 46 FR 8366, Jan. 26, 1981]

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

- (a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:
 - (1) The research under review represents one of the categories of research permissible under §46.306(a)(2);
 - (2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
 - (3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;
 - (4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
 - (5) The information is presented in language which is understandable to the subject population;
 - (6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is

clearly informed in advance that participation in the research will have no effect on his or her parole; and

- (7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§46.306 Permitted research involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:

- (1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under §46.305 of this subpart; and

(2) In the judgment of the Secretary the proposed research involves solely the following:

- (i) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
- (ii) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
- (iii) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or
- (iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with

appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.

- (b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Subpart D - Additional Protections for Children Involved as Subjects in Research

Source: 48 FR 9818, March 8, 1983, unless otherwise noted.

§46.401 To what do these regulations apply?

- (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 (i) of §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 §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §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 §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.]

§46.402 Definitions.

The definitions in §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.

§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.

§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 §46.408.

§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 §46.408.

§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 §46.408.

§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 §46.404, §46.405, or §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 §46.404, §46.405, or §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 §46.408.

§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 §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 §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 §46.404 or §46.405. Where research is covered by §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 §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 §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.

§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 §46.406 or §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.

Code of Federal Regulations
TITLE 21—FOOD AND DRUGS
CHAPTER I—FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A—GENERAL

PART 50
PROTECTION OF HUMAN SUBJECTS

Subpart A—General Provisions

Sec. 50.1 Scope.

- (a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 403, 406, 409, 412, 413, 502, 503, 505, 510, 513-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.
- (b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 36390, May 30, 1980; 46 FR 8979, Jan. 27, 1981, as amended at 63 FR 26697, May 13, 1998; 64 FR 399, Jan. 5, 1999; 66 FR 20597, Apr. 24, 2001]

Sec. 50.3 Definitions.

As used in this part:

- (a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040et seq. as amended (21 U.S.C. 321-392)).
- (b) Application for research or marketing permit includes:
- (1) A color additive petition, described in part 71.
 - (2) A food additive petition, described in parts 171 and 571.
 - (3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in 170.30 and 570.30.
 - (4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in 180.1.

- (5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.
 - (6) An investigational new drug application, described in part 312 of this chapter.
 - (7) A new drug application, described in part 314.
 - (8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.
 - (9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.
 - (10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.
 - (11) [Reserved]
 - (12) An application for a biologics license, described in part 601 of this chapter.
 - (13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.
 - (14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809.
 - (15) An Application for an Investigational Device Exemption, described in part 812.
 - (16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.
 - (17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.
 - (18) An application for premarket approval of a medical device, described in section 515.
 - (19) A product development protocol for a medical device, described in section 515.
 - (20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.
 - (21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in 1010.4.
 - (22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in 1010.5.
 - (23) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.
 - (24) Data and information submitted in a petition for a nutrient content claim, described in 101.69 of this chapter, or for a health claim, described in 101.70 of this chapter.
 - (25) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in 190.6 of this chapter.
- (c) Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and

Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

- (d) Investigator means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.
- (e) Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.
- (f) Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.
- (g) Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.
- (h) Institution means any public or private entity or agency (including Federal, State, and other agencies). The word facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.
- (i) Institutional review board (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.
- (j) Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).
- (k) 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.
- (l) 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.
- (m) Family member means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.
- (n) Assent means a child's affirmative agreement to participate in a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as assent.

- (o)Children means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.
 - (p)Parent means a child's biological or adoptive parent.
 - (q)Ward means a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.
 - (r)Permission means the agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation. Permission must be obtained in compliance with subpart B of this part and must include the elements of informed consent described in 50.25.
 - (s)Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. For purposes of subpart D of this part, a guardian also means an individual who is authorized to consent on behalf of a child to participate in research.
- [45 FR 36390, May 30, 1980, as amended at 46 FR 8950, Jan. 27, 1981; 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 61 FR 51528, Oct. 2, 1996; 62 FR 39440, July 23, 1997; 64 FR 399, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 66 FR 20597, Apr. 24, 2001]

Subpart B—Informed Consent of Human Subjects

Sec. 50.20 General requirements for informed consent.

Except as provided in 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations 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. [46 FR 8951, Jan. 27, 1981, as amended at 64 FR 10942, Mar. 8, 1999]

Sec. 50.23 Exception from general requirements.

- (a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:
 - (1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.
 - (2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
 - (3) Time is not sufficient to obtain consent from the subject's legal representative.
 - (4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.
- (b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.
- (c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.
- (d)(1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements of section 505(i)(4) of

the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved the Secretary of Defense must first request such a determination from the President, and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met.

- (i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND.
- (ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness.
- (iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug.
- (iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission.
- (v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by 56.115(a)(2) of this chapter.
- (vi) DOD has explained:
 - (A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional;
 - (B) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and
 - (C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.
- (vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient.
- (viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.
- (ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section.

- (x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter.
 - (xi) DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.
 - (xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence.
 - (xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request.
 - (xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use.
 - (xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria.
 - (xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent.
 - (xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in the Federal Register describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.
 - (xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law.
- (2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain any necessary security clearances. This IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by 56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review.
- (3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve:
- (i) The required information sheet;
 - (ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written);
 - (iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and
 - (iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved.
- (4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

- (5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations.
- (e)(1) Obtaining informed consent for investigational in vitro diagnostic devices used to identify chemical, biological, radiological, or nuclear agents will be deemed feasible unless, before use of the test article, both the investigator (e.g., clinical laboratory director or other responsible individual) and a physician who is not otherwise participating in the clinical investigation make the determinations and later certify in writing all of the following:
 - (i) The human subject is confronted by a life-threatening situation necessitating the use of the investigational in vitro diagnostic device to identify a chemical, biological, radiological, or nuclear agent that would suggest a terrorism event or other public health emergency.
 - (ii) Informed consent cannot be obtained from the subject because:
 - (A) There was no reasonable way for the person directing that the specimen be collected to know, at the time the specimen was collected, that there would be a need to use the investigational in vitro diagnostic device on that subject's specimen; and
 - (B) Time is not sufficient to obtain consent from the subject without risking the life of the subject.
 - (iii) Time is not sufficient to obtain consent from the subject's legally authorized representative.
 - (iv) There is no cleared or approved available alternative method of diagnosis, to identify the chemical, biological, radiological, or nuclear agent that provides an equal or greater likelihood of saving the life of the subject.
- (2) If use of the investigational device is, in the opinion of the investigator (e.g., clinical laboratory director or other responsible person), required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (e)(1) of this section in advance of using the investigational device, the determinations of the investigator shall be made and, within 5 working days after the use of the device, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.
- (3) The investigator must submit the written certification of the determinations made by the investigator and an independent physician required in paragraph (e)(1) or (e)(2) of this section to the IRB and FDA within 5 working days after the use of the device.
- (4) An investigator must disclose the investigational status of the in vitro diagnostic device and what is known about the performance characteristics of the device in the report to the subject's health care provider and in any report to public health authorities. The investigator must provide the IRB with the information required in 50.25 (except for the information described in 50.25(a)(8)) and the procedures that will be used to provide this information to each subject or the subject's legally authorized representative at the time the test results are provided to the subject's health care provider and public health authorities.
- (5) The IRB is responsible for ensuring the adequacy of the information required in section 50.25 (except for the information described in 50.25(a)(8)) and for ensuring that procedures are in place to provide this information to each subject or the subject's legally authorized representative.
- (6) No State or political subdivision of a State may establish or continue in effect any law, rule, regulation or other requirement that informed consent be obtained before an investigational in vitro diagnostic device may be used to identify chemical, biological,

radiological, or nuclear agent in suspected terrorism events and other potential public health emergencies that is different from, or in addition to, the requirements of this regulation.

[46 FR 8951, Jan. 27, 1981, as amended at 55 FR 52817, Dec. 21, 1990; 64 FR 399, Jan. 5, 1999; 64 FR 54188, Oct. 5, 1999; 71 FR 32833, June 7, 2006; 76 FR 36993, June 24, 2011]

Sec. 50.24 Exception from informed consent requirements for emergency research.

- (a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:
- (1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
 - (2) Obtaining informed consent is not feasible because:
 - (i) The subjects will not be able to give their informed consent as a result of their medical condition;
 - (ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
 - (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
 - (3) Participation in the research holds out the prospect of direct benefit to the subjects because:
 - (i) Subjects are facing a life-threatening situation that necessitates intervention;
 - (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
 - (iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
 - (4) The clinical investigation could not practicably be carried out without the waiver.
 - (5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
 - (6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a

family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

- (7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:
- (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
 - (ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
 - (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
 - (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
 - (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.
- (b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.
- (c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.
- (d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already

exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.

- (e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

[61 FR 51528, Oct. 2, 1996]

Sec. 50.25 Elements of informed consent.

- (a) Basic elements of informed consent. 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 and that notes the possibility that the Food and Drug Administration may inspect the records.
 - (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.
 - (8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that 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.
 - (6) The approximate number of subjects involved in the study.
 - (c) When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: "A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."
 - (d) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.
 - (e) Nothing in these regulations 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.
- [46 FR 8951, Jan. 27, 1981, as amended at 76 FR 270, Jan. 4, 2011]

Sec. 50.27 Documentation of informed consent.

- (a) Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.
- (b) Except as provided in 56.109(c), the consent form may be either of the following:
 - (1) A written consent document that embodies the elements of informed consent required by 50.25. 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.
 - (2) A short form written consent document stating that the elements of informed consent required by 50.25 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 the 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.

[46 FR 8951, Jan. 27, 1981, as amended at 61 FR 57280, Nov. 5, 1996]

Subpart C [Reserved]

Subpart D--Additional Safeguards for Children in Clinical Investigations

Sec. 50.50 IRB duties.

In addition to other responsibilities assigned to IRBs under this part and part 56 of this chapter, each IRB must review clinical investigations involving children as subjects covered by this subpart D and approve only those clinical investigations that satisfy the criteria described in 50.51, 50.52, or 50.53 and the conditions of all other applicable sections of this subpart D.

Sec. 50.51 Clinical investigations not involving greater than minimal risk.

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in 50.55.

Sec. 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which 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, may involve children as subjects only if the IRB finds and documents 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 50.55.

Sec. 50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which 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 that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds and documents 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 that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- (d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

Sec. 50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If an IRB does not believe that a clinical investigation within the scope described in 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of 50.51, 50.52, or 50.53, the clinical investigation may proceed only if:

- (a) The IRB finds and documents that the clinical investigation 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 Commissioner of Food and Drugs, 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, determines either:
 - (1) That the clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or
 - (2) That the following conditions are met:
 - (i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
 - (ii) The clinical investigation will be conducted in accordance with sound ethical principles; and
 - (iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 50.55.

Sec. 50.55 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 D, the IRB must 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.
- (b) In determining whether children are capable of providing assent, the IRB must 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 clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.
- (c) The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines:
 - (1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or
 - (2) That the intervention or procedure involved in the clinical investigation 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 clinical investigation.
- (d) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:
 - (1) The clinical investigation involves no more than minimal risk to the subjects;
 - (2) The waiver will not adversely affect the rights and welfare of the subjects;
 - (3) The clinical investigation could not practicably be carried out without the waiver; and
 - (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

- (e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that the permission of each child's parents or guardian is granted.
 - (1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient, if consistent with State law, for clinical investigations to be conducted under 50.51 or 50.52.
 - (2) Where clinical investigations are covered by 50.53 or 50.54 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 if consistent with State law.
- (f) Permission by parents or guardians must be documented in accordance with and to the extent required by 50.27.
- (g) When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

Sec. 50.56 Wards.

- (a) Children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations approved under 50.53 or 50.54 only if such clinical investigations are:
 - (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 clinical investigation is approved under paragraph (a) of this section, the IRB must require appointment of an advocate for each child who is a ward.
 - (1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.
 - (2) One individual may serve as advocate for more than one child.
 - (3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.
 - (4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.

Authority: 21 U.S.C 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.

Source: 45 FR 36390, May 30, 1980, unless otherwise noted.

Code of Federal Regulations
TITLE 21—FOOD AND DRUGS
CHAPTER I—FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A—GENERAL

PART 56
INSTITUTIONAL REVIEW BOARDS

Subpart A--General Provisions

Sec. 56.101 Scope.

- (a) This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations.
- (b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[46 FR 8975, Jan. 27, 1981, as amended at 64 FR 399, Jan. 5, 1999; 66 FR 20599, Apr. 24, 2001]

Sec. 56.102 Definitions.

As used in this part:

- (a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040et seq., as amended (21 U.S.C. 321-392)).
- (b) Application for research or marketing permit includes:
 - (1) A color additive petition, described in part 71.
 - (2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in 170.35.
 - (3) A food additive petition, described in part 171.
 - (4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in 180.1.

- (5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.
- (6) An investigational new drug application, described in part 312 of this chapter.
- (7) A new drug application, described in part 314.
- (8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.
- (9) Data and information regarding an over-the-counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330.
- (10) An application for a biologics license, described in part 601 of this chapter.
- (11) Data and information regarding a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, as described in part 601 of this chapter.
- (12) An Application for an Investigational Device Exemption, described in part 812.
- (13) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in part 860.
- (14) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in part 861.
- (15) An application for premarket approval of a medical device for human use, described in section 515 of the act.
- (16) A product development protocol for a medical device for human use, described in section 515 of the act.
- (17) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act.
- (18) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in 1010.4.
- (19) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in 1010.5.
- (20) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of

compliance with a radiation safety performance standard, described in subpart D of part 1003.

(21) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(22) Data and information submitted in a petition for a nutrient content claim, described in 101.69 of this chapter, and for a health claim, described in 101.70 of this chapter.

(23) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in 190.6 of this chapter.

(c) Clinical investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.

(d) Emergency use means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

(e) Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

(f) Institution means any public or private entity or agency (including Federal, State, and other agencies). The term facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.

(g) Institutional Review Board (IRB) means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

(h) Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(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) Sponsor means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.
- (k) Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.
- (l) Test article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.
- (m) IRB approval means the determination of the IRB that the clinical investigation 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.

[46 FR 8975, Jan. 27, 1981, as amended at 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 64 FR 399, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 65 FR 52302, Aug. 29, 2000; 66 FR 20599, Apr. 24, 2001; 74 FR 2368, Jan. 15, 2009]

Sec. 56.103 Circumstances in which IRB review is required.

- (a) Except as provided in 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.
- (b) Except as provided in 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.
- (c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

[46 FR 8975, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981]

Sec. 56.104 Exemptions from IRB requirement.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

- (a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.
- (b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.
- (c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.
- (d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or 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.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]

Sec. 56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

Subpart B--Organization and Personnel

Sec. 56.106 Registration.

- (a) Who must register? Each IRB in the United States that reviews clinical investigations regulated by FDA under sections 505(i) or 520(g) of the act and each IRB in the United States that reviews clinical investigations that are intended to support applications for research or marketing permits for FDA-regulated products must register at a site maintained by the Department of Health and Human Services (HHS). (A research permit under section 505(i) of the act is usually known as an investigational new drug application (IND), while a research permit under section 520(g) of the act is usually known as an investigational device exemption (IDE).) An individual authorized to act on the IRB's behalf must submit the registration information. All other IRBs may register voluntarily.
- (b) What information must an IRB register? Each IRB must provide the following information:
- (1) The name, mailing address, and street address (if different from the mailing address) of the institution operating the IRB and the name, mailing address, phone number, facsimile number, and electronic mail address of the senior officer of that institution who is responsible for overseeing activities performed by the IRB;
 - (2) The IRB's name, mailing address, street address (if different from the mailing address), phone number, facsimile number, and electronic mail address; each IRB chairperson's name, phone number, and electronic mail address; and the name, mailing address, phone number, facsimile number, and electronic mail address of the contact person providing the registration information.
 - (3) The approximate number of active protocols involving FDA-regulated products reviewed. For purposes of this rule, an "active protocol" is any protocol for which an IRB conducted an initial review or a continuing review at a convened meeting or under an expedited review procedure during the preceding 12 months; and
 - (4) A description of the types of FDA-regulated products (such as biological products, color additives, food additives, human drugs, or medical devices) involved in the protocols that the IRB reviews.
- (c) When must an IRB register? Each IRB must submit an initial registration. The initial registration must occur before the IRB begins to review a clinical investigation described in paragraph (a) of this section. Each IRB must renew its registration every 3 years. IRB registration becomes effective after review and acceptance by HHS.
- (d) Where can an IRB register? Each IRB may register electronically through <http://ohrp.cit.nih.gov/efile>. If an IRB lacks the ability to register electronically, it must send its registration information, in writing, to the Good Clinical Practice Program (HF-34), Office of Science and Health Coordination, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.
- (e) How does an IRB revise its registration information? If an IRB's contact or chair person information changes, the IRB must revise its registration information by submitting any

changes in that information within 90 days of the change. An IRB's decision to review new types of FDA-regulated products (such as a decision to review studies pertaining to food additives whereas the IRB previously reviewed studies pertaining to drug products), or to discontinue reviewing clinical investigations regulated by FDA is a change that must be reported within 30 days of the change. An IRB's decision to disband is a change that must be reported within 30 days of permanent cessation of the IRB's review of research. All other information changes may be reported when the IRB renews its registration. The revised information must be sent to FDA either electronically or in writing in accordance with paragraph (d) of this section.

[74 FR 2368, Jan. 15, 2009]

Sec. 56.107 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, 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 the 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 or 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 those 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 the scientific area 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 complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

[46 FR 8975, Jan 27, 1981, as amended at 56 FR 28028, June 18, 1991; 56 FR 29756, June 28, 1991]

Subpart C--IRB Functions and Operations

Sec. 56.108 IRB functions and operations.

In order to fulfill the requirements of these regulations, each IRB shall:

- (a) Follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that 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 where necessary to eliminate apparent immediate hazards to the human subjects.
- (b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.
- (c) Except when an expedited review procedure is used (see 56.110), 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.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991; 67 FR 9585, Mar. 4, 2002]

Sec. 56.109 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 these regulations.
- (b) An IRB shall require that information given to subjects as part of informed consent is in accordance with 50.25. The IRB may require that information, in addition to that specifically mentioned in 50.25, 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 in accordance with 50.27 of this chapter, except as follows:
 - (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds 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 the research context; or

- (2) The IRB may, for some or all subjects, find that the requirements in 50.24 of this chapter for an exception from informed consent for emergency research are met.
- (d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.
- (e) 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. For investigations involving an exception to informed consent under 50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under 50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.
- (f) An IRB shall conduct continuing review of research covered by these regulations 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.
- (g) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under 50.24 of this chapter a copy of information that has been publicly disclosed under 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter. The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.
- (h) When some or all of the subjects in a study are children, an IRB must determine that the research study is in compliance with part 50, subpart D of this chapter, at the time of its initial review of the research. When some or all of the subjects in a study that is ongoing on April 30, 2001 are children, an IRB must conduct a review of the research to determine compliance with part 50, subpart D of this chapter, either at the time of continuing review or, at the discretion of the IRB, at an earlier date.

[46 FR 8975, Jan. 27, 1981, as amended at 61 FR 51529, Oct. 2, 1996; 66 FR 20599, Apr. 24, 2001]

Sec. 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

- (a) The Food and Drug Administration has established, and published 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, through periodic republication in the Federal Register.
- (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 1 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 IRB chairperson from among the 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 nonexpedited review procedure set forth in 56.108(c).

- (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 Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

Sec. 56.111 Criteria for IRB approval of research.

- (a) In order to approve research covered by these regulations 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 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 that 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, handicapped, or 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 part 50.
 - (5) Informed consent will be appropriately documented, in accordance with and to the extent required by 50.27.
 - (6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

- (7) Where 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, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.
- (c) In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with part 50, subpart D of this chapter.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991; 66 FR 20599, Apr. 24, 2001]

Sec. 56.112 Review by institution.

Research covered by these regulations 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. 56.113 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 Food and Drug Administration.

Sec. 56.114 Cooperative research.

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

Subpart D--Records and Reports

Sec. 56.115 IRB records.

- (a) An institution, or where 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 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, a member of governing panel or board, stockholder, paid or unpaid consultant.
 - (6) Written procedures for the IRB as required by 56.108 (a) and (b).
 - (7) Statements of significant new findings provided to subjects, as required by 50.25.
- (b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.
- (c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991; 67 FR 9585, Mar. 4, 2002]

Subpart E--Administrative Actions for Noncompliance

Sec. 56.120 Lesser administrative actions.

- (a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.
- (b) On the basis of the IRB's or the institution's response, FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the agency may:
 - (1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;
 - (2) Direct that no new subjects be added to ongoing studies subject to this part;
 - (3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or
 - (4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.
- (c) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

Sec. 56.121 Disqualification of an IRB or an institution.

- (a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under 56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in part 16.
- (b) The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:
 - (1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and

- (2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.
- (c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in the Federal Register.
- (d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in 56.123.

Sec. 56.122 Public disclosure of information regarding revocation.

A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under part 20.

Sec. 56.123 Reinstatement of an IRB or an institution.

An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under 56.121(c).

Sec. 56.124 Actions alternative or additional to disqualification.

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.

Authority: 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.

Source: 46 FR 8975, Jan. 27, 1981, unless otherwise noted.

3. POLICIES AND PROCEDURES

3.1 Organization and Conduct of Meetings and Review of Protocols

1. Organization and Conduct of Meetings

- 1.01. Requirements for Holding the Meeting. No meeting may begin without a quorum of members present. A quorum is defined as the presence of a majority of the voting members listed on the OHRP-approved roster for the IRB, which majority must include a non-scientific member. If the quorum is not present or is lost during the meeting as members leave, the meeting must be adjourned. These situations must be reported in the minutes of the meeting.
- 1.02. Absence of the Chairman. In the absence of the Chairman, the Vice Chairman, or another member of the IRB designated by the Chairman, may chair the meeting.
- 1.03. Generation of Board Minutes. The Coordinator of the IRB or his or her designee collates all of the information from new full reviews obtained from the IRB members into a letter (or e-mail) to the Principal Investigator. The letter informs the Principal Investigator of the decision of the IRB and of the changes required to get the study approved, if it was approved with requested changes. Working from the agenda for the meeting, these changes and decisions are incorporated to generate the minutes of the meeting in accordance with Section 3 below.
- 1.04. Approval and Circulation of the Minutes. Minutes are circulated to the IRB members, the administrative staff, and to anyone requesting a copy. Minutes are voted upon for approval or modification by the full IRB at the next or earliest subsequent meeting.

2. Review of the Protocol

- 2.01. A new full protocol is sent to each IRB member for review one week in advance of the meeting. Each IRB member receives the entire protocol, the informed consent form, the Wills Internal Forms, and the Investigators Brochure, if available.
- 2.02. For each new full protocol to be considered at a meeting, the Principal Investigator or an experienced, knowledgeable Investigator designated by the Principal Investigator presents the protocol to the IRB members and responds to questions, unless the presentation is waived. Then, after the presenter leaves the meeting, the IRB members present their reviews and comments in depth and deliberate. Special attention is paid to the design of the study, the comprehensibility of the consent to the lay reader, the need for an IND or IDE number, the degree of risk involved, and any benefits to the subjects.

3. Recording of the Actions on the Protocols

During the Board meeting, deliberations concerning each protocol (initial and continuing reviews) will be recorded in sufficient detail by the IRB Coordinator or his or her

designee to show the vote on each protocol, which will include the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving a protocol; a written summary of the discussion of controversial issues and their resolution; and the final action taken by the IRB.

4. Voting on New Protocols

- 4.01. Upon review of a protocol, there are five (5) possible outcomes to be determined: (1) approval; (2) approval subject to the making of required changes; (3) deferral; (4) disapproval; (5) suspend or terminate, in the case of an active protocol. A simple majority vote of the voting members of the IRB is required to effect the final outcome. The number of members voting for or against the motion or abstaining is recorded. An IRB member having an interest in any protocol before the IRB must remove him/herself from the meeting during the vote. This fact is recorded in the minutes of the meeting.
- 4.02. Subsequent to the voting on one of the five (5) possible decisions listed above, the IRB Coordinator or his or her designee who records the comments of the IRB members collates all of the comments and sends them to the Principal Investigator with the IRB's decision. If the decision is to approve, a formal approval letter and a consent form are issued. If a study is disapproved, a letter of notification is sent to the Principal Investigator. A disapproval indicates considerable issues with the design of the study and/or with the construction of the consent form which prevent the study from being approved. The Principal Investigator may resubmit the study to the IRB as a new full submission after addressing the concerns of the IRB.
- 4.03. Only when the convened IRB stipulates specific revisions requiring simple concurrence by the Principal Investigator may the IRB approve the protocol subject to the making of the required changes. The required changes are sent to the Principal Investigator and the study file is placed in the "waiting-for-change" file where it remains until the Principal Investigator provides the IRB administrative staff with the requisite changes. The study is held in the "waiting-for-change" file for thirty (30) days after which it may be administratively terminated. If the Principal Investigator has made the required changes, as confirmed by the Chairman or another IRB member designated by the Chairman, a formal approval letter and consent form are issued.

5. Final Approval of a Protocol

- 5.01. Upon completion of all of the IRB requirements, the Principal Investigator receives a formal approval letter that indicates the type of review and the length of time for which the study is approved by a listing of the initiation and expiration dates of the approval. The Principal Investigator also receives a copy of the IRB-approved informed consent document with a version number in the footer. Each subsequent informed consent document issued due to modifications, whether major or minor, will get a new version number. It is the Principal Investigator's

responsibility to ensure that Continuing Review is obtained in a timely manner to avoid a lapse in the approval period.

- 5.02. Approval letters for Amendments and Continuing Reviews are processed in a similar manner.

6. Signage of Approval Letters

Approval letters may be signed by the Vice Chairman or the Chairman, or in their absence, another member designated by the Chairman.

7. Continuing Reviews

The IRB shall conduct continuing reviews of research protocols approved by the IRB at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or to have a third party observe the consent process and the research. All protocols undergoing continuing review will be individually presented and discussed at the convened meeting by the IRB.

8. Expedited Review

- 8.01. New Full Protocols or Continuing Reviews previously approved by the IRB that present no more than minimal risk and that qualify under 45 CFR § 46.110 and 21 CFR §56.110 are reviewed and approved by the Chairman or the Chairman's designee. Their comments and/or decisions are communicated to the full IRB at the next regular meeting and Principal Investigator and entered into the minutes.
- 8.02. Expedited review does not imply that the requirements for informed consent are unnecessary. Supporting documentation must be submitted to the IRB for review. Each IRB member reserves the right to have any new protocol submitted for expedited review be given a full review. For further guidance as to whether any given procedure is entitled to expedited review, contact one of the IRB staff.
- 8.03. Expedited review cannot be used if a protocol is to be disapproved.

3.2 Informed Consent: Form of Consent and Documentation

Policy

No investigator may involve a human being as a subject in research covered by this policy unless the Principal Investigator or his or her designee has obtained a legally effective informed consent of the subject or the subject's legally authorized representative. The exceptions to this requirement are limited and must be approved by the IRB before the commencement of the study. 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. According to federal regulations (45 CFR §46.109(e)), the IRB has authority to observe or have a third party observe the consent process.

Procedure

The most common reason for delay of IRB approval of a protocol is a poorly written consent form. Therefore, it is important for all investigators to read this section carefully and become familiar with both the elements of informed consent required by federal regulation and the particular requirements of Wills Eye Hospital's IRB. Attached and made part of this Policy and Procedure Regarding Informed Consent is a checklist to be used by the investigators to assure that the required basic and additive elements of informed consent are properly addressed. Consent forms which do not conform to these guidelines will be returned for revisions and may cause unnecessary delays in the review process.

Who May Obtain Informed Consent?

In order for the consent obtained to be truly informed, the person obtaining consent should have sufficient background, education, experience, and knowledge of the study to answer the questions of potential subjects. The Principal Investigator may designate consent procedures to be performed by qualified and experienced members of the study team at his or her discretion. The Informed Consent Form template assumes that a Principal or Co-Investigator will conduct the consent interviews. When the duty of conducting the consent interview is given to another member of the study team who is not an Investigator, this fact should be noted on the signature lines of the final page of the consent form.

Basic Elements of Informed Consent

1. Project Identification & Approval. The name of the institution(s) and the Principal Investigator's name(s) and telephone number(s) must be included. The title of the project should be on the face page, and in the header of every subsequent page. In addition, a lay title should be included that is written in plain English.
2. Introduction and Purpose. The research project title and a short, non-technical title, in easy to understand words. An explanation of the purpose of the research and the expected duration of the subject's participation should be included here. Be certain to include a statement that this is a "research" study.

3. Procedures/Treatment. A description of the procedures to be followed, as well as identification of any procedures which are experimental. This is not to be a repetition of technical details. It is in lay language and should address the following points:
- a. Number of patients at Wills Eye Hospital
 - b. Is it a multi-center trial? If so, how many centers and how many patients will be involved? Children, mentally disabled individuals, prisoners, and pregnant women require special attention.
 - c. How will patients be selected?
 - d. Intervention
 - 1) What will be done: random assignment will be explained in lay terms, e.g., “You will be assigned by chance, like the flip of a coin.”
 - 2) When it will be done.
 - 3) Has the intervention been used before in man or animals?
 - 4) How many subjects have had the intervention before?
 - 5) How long will the study involve patient participation?
 - 6) If “washout” is used, will the risks to the patient be changed?
 - e. Measurements
 - 1) What will be measured?
 - 2) How it will be measured (lab tests [if blood, discuss the amount in lay terms, e.g., teaspoonful], interviews, questionnaires). If radiation is used, how much? If the amount of radiation exceeds the amount that would have been received in the process of customary, i.e., non-research, treatment, it must be evaluated by the Radiation Committee and stated in the informed consent form using lay terms.
 - 3) When will it be measured?
4. Pregnancy Statement. Include the following statement, if applicable:
- “Exposure to investigational drugs may be hazardous to a fetus carried by a mother who is receiving an investigational drug or agent. Therefore, adequate birth control measures must be taken by all participants, and their sexual partners, while participating in this study. If you are a woman of childbearing potential, you will have a pregnancy test before being allowed to participate in this study. This requires that blood be drawn from a vein in your arm (i.e., ____ tsp.) one or two days prior to the start of the treatment program. The results of the pregnancy test must be made available to you prior to the start of the treatment program. Presently, you are not pregnant and should not plan to become pregnant while participating in this study. You have been advised to routinely practice a medically-accepted method of birth control. Such methods will be discussed with

you by your physician. Should you become pregnant during the course of this study, you should notify your study doctor immediately.”

Describe any reproductive effects that the investigational drug may have on male sperm production.

5. Risks/Discomforts. A description of any reasonably foreseeable risk or discomfort to the subject, including risk of being taken off therapy (placebo or wash-out periods) and risks of any procedures related to the research. Whenever possible, describe potential risks in terms of probability (e.g., 1%, 5%, etc.). Include a patient/subject denominator, if relevant data are available.
6. Alternative Treatment. Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
 - a. In therapeutic studies, what choices does the subject have other than study interventions? If alternative treatment is not applicable (e.g., studies of “normal” volunteers) state that the alternative is not to participate.
7. Confidentiality. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration (FDA), National Institutes of Health (NIH), Wills Eye Hospital internal audit, Wills Eye Hospital Institutional Review Board, or another sponsor may inspect the records.
8. Right of Refusal, Compensation, and Reimbursement. An explanation as to whether compensation (for injury) and/or medical treatments are available and where further information may be obtained. Also, this section must include a statement that refusal of the patient to participate in the research will not affect his or her medical care.

At Wills Eye Hospital, the “standard” phrases and definitions used in the following paragraphs have been approved by the IRB. The language used is determined in part by whether the research is sponsored by an outside proprietary agency. The issue is compensation or payment for injury, loss of work, or pain. Routinely, the IRB policy has been that, in cases in which research is sponsored by for-profit organizations, such sponsors should provide for medical care, including hospitalization, at no cost to the patient, in the event of adverse effects. The term “compensation” is used in the consent form to refer to payment for injury, and does not refer to any payments to patients for travel or inconvenience associated with participation in a study. The following samples illustrate the form this statement should take:

- a. To be used when financial support for a project is provided by any “not for profit” agency, i.e., Department research funds, NIH, a Foundation, or other government funds:

“You may refuse to participate in this investigation or withdraw your consent and discontinue participation in this investigation without penalty

and without affecting your future care or ability to receive alternative medical treatment at Wills Eye Hospital. In the event of physical injury or illness resulting to you (or your child) as a direct result of the experiments, treatment(s), and/or procedure(s) used in this investigation, comprehensive medical and/or surgical care (including hospitalization) is available and will be provided. However, Wills Eye Hospital cannot assure that this comprehensive medical and/or surgical care will be provided to the extent needed without charge, and the costs incurred for this care may ultimately be your responsibility. There is no compensation or payment for loss of work or pain.”

- b. To be used when financial support is provided by a for-profit organization:

“You may refuse to participate in this investigation or withdraw your consent and discontinue participation in this investigation without penalty and without affecting your future care or ability to receive alternative medical treatment at Wills Eye Hospital. In the event of physical injury resulting to you as a direct result of the experiments, treatment(s), and/or procedure(s) used in this investigation, medical care (including hospitalization) is available, and any costs beyond that provided by your health insurance carrier will be covered by (INSERT NAME OF CORPORATE SPONSOR). No other financial compensation is available.” **[NOTE: Failure of a sponsoring company to provide such coverage may have an impact on the wording of this indemnification as well as the risks section of the consent form, and will therefore require additional administrative review.]**

9. Benefits to Subject. An explanation of what individuals can expect to gain by directly participating in the planned research, and/or what benefit will accrue to society. Please do not include any financial or monetary compensation language under this heading. Doing so could potentially cause the institution to appear coercive, or unduly persuasive, in its recruitment process.
10. Additional Information. An explanation of whom to contact for answers to pertinent questions about the research, for answers about research subjects’ rights, and in the event of a research-related injury to the subject. Include telephone numbers. The IRB does provide a phone number for patients who wish information about the IRB (215-440-3145). The consent form should also indicate whether the patient is participating in another research study. A suggested format is as follows:

Check one:

- () I am not currently involved in any other study.
- () I am presently enrolled in another study but after discussion with my physician and the investigator, I consent to participate in this study also.

11. Voluntary Consent. A statement that participation is voluntary, and that the refusal to participate, or subsequent withdrawal, will involve no penalty or loss of benefits to which the subject is otherwise entitled (usually included with Section 7).
12. Final Statement. "I have read and understand I will receive a signed copy of this (*fill in #*)-page informed consent form."
13. Signatures. Subject's name, signature, and date; signatures of the investigator and a witness. Signature cannot be on a page by itself. However, it may be on the reverse side of a page. Subject will receive a signed copy of the consent form.

Additional Elements of Informed Consent, as appropriate

14. Additional Risks. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant), which are currently unforeseeable.
15. Termination of Participation. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
16. Additional Costs. Any additional costs to the subject that may result from participation in the research.
17. Consequences of Withdrawal. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
18. Significant new Findings. 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.
19. Number of subjects. The approximate number of subjects involved in the study.

The checklist at the end of Form-5 Informed Consent Template should be used by investigators to ensure that the required elements of informed consents have been properly addressed.

Informed Consent and FDA Registry

Effective March 2012, FDA requires that the Responsible Party for applicable clinical trials must register on ClinicalTrials.gov and submit results. Additionally, the following statement must appear in the Informed Consent Form:

"A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at anytime."

3.3 Risk/Benefit Analysis

Policy

One of the major responsibilities of the IRB in reviewing a research protocol involving human subjects, and one of the major ethical judgments that the IRB must make, is to assess the risks and benefits of the proposed research. Risks to human subjects posed by participation in clinical research should be justified by the anticipated benefits to the subjects or society. This requirement is central to both research ethics and federal regulations.

When reviewing a research protocol involving human subjects, the IRB must assess the risks and benefits of the proposed research as tested against the following information.

Definitions

- **Benefit**: a valued or desired outcome; an advantage.
- **Minimal Risk**: a risk is minimal if the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than that encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- **Risk**: the probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in a research study. “Risk” is a word expressing probabilities. “Benefits” is a word expressing a fact or state of affairs. In a clinical research study, it is more accurate to speak as if both were in the realm of probability, i.e., risks and expected or anticipated benefits. An IRB is responsible for evaluating risk in the context of conditions that make a situation dangerous per se. A judgment must then be made as to whether the anticipated benefit, either of new knowledge or of improved health for the research subjects, justifies inviting any person to undertake the risks.

Assessment of Risk

The assessment of risks and anticipated benefits by an IRB involves a series of steps. The IRB must: (1) identify the risks associated with the research per se as distinguished from the risks of any treatment the subject would be given if not participating in the research (i.e., standard of care); (2) determine that the risks will be minimized to the extent possible; (3) identify the probable benefits to be derived from participation; (4) determine that the risks are reasonable in relation to the benefits to the subject, if any, and the importance of the knowledge to be gained; (5) assure that potential subjects will be provided with an accurate and fair description of the risks and discomforts and the anticipated benefits; and (6) determine the intervals of periodic review based on the risks and, where appropriate, determine that adequate provisions are in place for monitoring the data collected.

In reviewing a research protocol involving human subjects, the IRB should consider the following points:

- Are both risks and anticipated benefits accurately identified, evaluated, and described?
- Are the risks greater than minimal risk? Are there any special vulnerabilities among the study subjects that are relevant to evaluating risk of participation?
- If the research involves a therapeutic procedure, have the risks and benefits of the research intervention(s) been evaluated separately from the therapeutic interventions?
- Has due care been taken to minimize the risks and maximize the benefits?
- Are there adequate provisions for the interim analysis of data, if necessary, to provide a continuing reassessment of the risk/benefit ratio?

It is important to recognize that the potential risks faced by research subjects may be posed by design features employed to assure valid results, as well as by a particular intervention or maneuver that may be performed in the course of the research.

The IRB should disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

Minimal Risk vs. Greater Than Minimal Risk

Once the risks have been identified, the IRB must assess whether the research presents greater than minimal risk. In research presenting more than minimal risk, potential subjects must be informed of the availability of medical treatment and compensation in the case of a research-related injury, including who will pay for the treatment and the availability of other financial compensation.

Determination that Risks are Minimized

The IRB is responsible for assuring that the risks are minimized to the extent possible. Even when unavoidable, risks can be reduced or managed. Precautions, safeguards, and alternatives can be incorporated into the research to reduce the probability of harm or limit its severity or duration.

In reviewing a protocol, the IRB should obtain complete information regarding the:

- Experimental design and scientific rationale
- Statistical basis for the structure of the research
- Beneficial and harmful effect anticipated
- Effects of any treatment administered in ordinary practice and those associated with no treatment at all
- Research design and the yield of useful data

Assessment of Anticipated Benefits

The benefits of human subjects research fall into two categories: Benefits to Subjects and Benefits to Society. Research subjects often undergo treatment, diagnosis, or examination for an illness or abnormal condition that involves evaluation of a procedure that may benefit the subject by ameliorating that condition or providing a better understanding of the disorder. Subjects may also agree to participate in research that is either not related to any illnesses they might have or

that is related to their conditions but not designed to provide any diagnostic or therapeutic benefit. Such research is designed principally to increase our understanding and knowledge about human physiology and behavior that may benefit society as a whole in the form of increased knowledge, improved safety, technological advances, and better health.

Direct payment or other remuneration offered to potential subjects as an incentive or reward for participation may not be considered a “benefit” to be gained from the research.

Determination that Risks are Reasonable in Relation to Anticipated Benefits

Determining whether the risks are reasonable in relation to the benefits to be derived depends on a number of factors, and each case must be reviewed individually. The risk/benefit assessment is not a technical one valid under all circumstances; rather it is a judgment that often depends on community standards and subjective determinations of risk and benefit. An IRB decision depends not only on currently available information about the risks and benefits of the interventions involved in the research, but also on the degree of confidence about this knowledge. An IRB’s assessment of risks and benefits must take into account the proposed subjects of the research (e.g., children, pregnant women, terminally ill, etc.) IRBs should also be sensitive to the fact that individuals may have different feelings about risks and benefits. IRB members should also remember that their appraisal of risks and benefits are subjective.

In research involving an intervention expected to provide direct benefit to the subject, a certain amount of risk is justifiable. In a study designed to evaluate a therapy for a life-threatening illness, the risk of serious adverse events may be acceptable. However, in a trial of a new or not-yet-validated treatment the ratio of benefits to risks should be similar to those presented by any alternative treatment.

In research where no direct benefit to the subjects is anticipated, the IRB must evaluate whether the risks presented by procedures performed solely to gain generalizable knowledge are ethically acceptable. There should be a limit to the risks society (through the government and research institutions) asks individuals to accept for the benefit of others.

Source Document: OHRP- “Protecting Human Research Subjects: Institutional Review Board Guidebook”, 1993, NIH, Chapter 3.

3.4 Expedited Review of Protocols

Research activities involving no more than minimal risk and in which the only involvement of human subjects falls into one of the categories listed below would qualify for expedited review. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

The expedited review procedure **may not be used** where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

For further guidance as to whether any given procedure is entitled to expedited review, contact one of the IRB staff.

Expedited review does not imply that the requirements for informed consent are unnecessary. Supporting documentation must be submitted to the IRB for review. Every member of the IRB reserves the right to have any new proposal that has already been submitted for expedited review also given a full review.

Research that may be entitled to expedited review:

1. Clinical studies of drugs and medical devices where condition (a) or (b) is met.
 - a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - b. Research on medical devices for which (i) an investigation device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - a. From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or
 - b. From other children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed

the lesser of 50 ml or 3ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- or subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected, solely for non-research purposes (such as medical treatment or diagnosis). (NOTES: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication,

cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

8. Continuing review of research previously approved by the convened IRB as follows:
 - a. Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
 - b. Where no subjects have been enrolled and no additional risks have been identified; or
 - c. Where the remaining research activities are limited to data analysis.
9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Source: 63 FR 60364-60367. November 9, 1998

3.5 Children as Participants in Research

The ethical mandate of the IRB is to protect the rights and welfare of human research subjects. The IRB is obligated to ensure that research studies do not endanger the safety or well-being of human subjects or undermine public confidence in the conduct of research. The special vulnerability of children makes consideration of involving them as research subjects particularly important. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations are in place for reviewing research involving children. Title 45 C.F.R. Part 46 Subpart D provides for “Additional Protections for Children Involved as Subjects of Research.” Research that is contrary to the rights and welfare of the child-subject is prohibited.

With regards to research involving children subjects, federal regulations require the researcher obtain the permission of the parent(s) or guardian(s) and the assent of the child prior to medical research regardless of the level of risk involved. The IRB is responsible for establishing adequate provisions for soliciting the assent of child subjects, when the children are capable of providing that assent. In determining whether children involved in a research protocol are capable of providing assent, the IRB shall take into account age, maturity, and psychological state. While there is no specific age where assent is required under Pennsylvania law, based on the practice of other institutions, the IRB requires that children age 7 to 17 indicate their assent on the consent form. In addition to the child’s assent, one or more parent must consent to the child’s participation on the study depending on the risk involved and whether a benefit is expected. To the extent parental consent is required, the IRB is responsible for making sure adequate provisions are made for soliciting the permission of **each** child’s parent or guardian.

General provisions for parental consent are as follows:

- Parental permission by one parent is sufficient for research involving no greater than minimal risk to children (45 C.F.R § 46.404) or posing greater than minimal risks, but holding out prospects of direct benefit to the patient (45 C.F.R. § 46.405);
- Permission must be obtained by both parents for research involving greater than minimal risk with no anticipated direct benefit to the patients but likely to yield generalizable knowledge about the subject’s disease or condition (45 C.F.R § 46.406), or for research not otherwise approvable under §§ 46.404, 46.405, and 46.406; ***Permission from two parents is required unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parents has legal responsibility for the care and custody of the child.***
- Parental consent must be documented according to the general procedures for informed consent contained in “Policies and Procedures Regarding Informed Consent.”

National Institutes of Health (NIH) Policy on Children

The NIH has promulgated the “NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.” This policy guidance applies to all initial (Type 1) applications/proposals submitted to NIH after October 1, 1998.

This policy applies ONLY to human subject research supported or conducted by the NIH that is funded under a Type 1 Investigator-initiated grant.

The NIH policy guidance was developed because medical treatments applied to children are often based upon testing of drugs/devices only in adults and scientifically evaluated treatments are often less available to children due to barriers in their inclusion in research studies. The American Academy of Pediatrics has reported that only a small fraction of all drug and biological products marketed in the U.S. have had clinical trials performed in pediatric patients and a majority of marketed drugs are not labeled for use in pediatric patients. Consequently, the goal is to increase participation of children in clinical research protocols so adequate data will be obtained to support treatment for disorders and conditions affecting them

Under the policy, children, who are defined as individuals under the age of 21 years, must be included in all clinical trial protocols unless there are scientific or ethical reasons to exclude them. If children are not excluded, proposals must have a section entitled “Participation of Children” that must 1) describe plans for inclusion of children; 2) justify the age range used; 3) indicate the expertise of the research team with regard to children; 4) describe the facilities for the children; 5) and indicate the number of children to be included in order to have sufficient power for meaningful analysis. Effective immediately, it is expected that children will be included in NIH Type 1 research involving human subjects unless one or more of the following permissible exclusionary circumstances can be fully justified:

- The research topic is irrelevant for children
- Children are barred from participation by law because of the risk
- Study is redundant; the knowledge is being obtained in another study or is already available;
- Separate age-specific children study is preferable
- Rarity of the disorder makes inclusion of children extremely difficult
- The limited number of available children are already enrolled in a nation-wide pediatric disease network;
- Study design precludes direct applicability to children
- Insufficient adult data to judge potential risk for children
- Study design is a follow-up of an adult study

An important part of this policy is the provision for obtaining and documenting assent. A child’s assent in a clinical trial protocol implies that he/she has agreed to participate after being fully informed in lay language geared to the level of the child’s comprehension of the procedures involved and the attendant risks and benefits. Mere failure to object should not be construed as assent. How the assent process will be carried out must be clearly stated in the protocol. It is the presumption in Pennsylvania that an individual 18 years of age is emancipated and can sign for him/herself.

See Form-5 (Informed Consent) for a sample child’s assent form

3.6 Adverse Reaction Report Submission and Review

Both the Department of Health and Human Services (DHHS) 45 C.F.R. § 46 and the Federal Drug Administration (FDA) 21 C.F.R. § 56 regulations for the protection of human subjects require that the process of continuing review ensures that the risk-benefit relationship of the research remains acceptable and that the consent form contains all of the pertinent information necessary for valid informed consent. IRB ongoing review of adverse reactions is a necessary part of continuing review. Unanticipated adverse reactions may alter the risk-benefit relationship substantially and may precipitate disclosure requirements where current and even previously enrolled subjects must be re-consented.

Definition of a Serious Adverse Drug Reaction

A serious adverse drug reaction is any reaction that results in any of the following outcomes:

1. Death;
2. A life-threatening adverse drug experience;
3. Inpatient hospitalization or prolongation of existing hospitalization;
4. A persistent or significant disability or incapacity;
5. A congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Definition of Unexpected Adverse Drug Reaction

1. Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or
2. If an investigator brochure is not required or available the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

“Unexpected” refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Definition of Unanticipated Adverse Device Effect

An unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The IRB is required to establish a procedure for the prompt reporting by a Principal Investigator of any unanticipated adverse reaction involving risk. In consideration of these criteria, any adverse reaction not previously reported or noted in the investigator brochure or in the consent document must be reported to the IRB according to the following procedure.

Procedure

Off-Site Adverse Reactions – Serious and/or unanticipated adverse reactions occurring in studies conducted off-site are subject to review by the investigator, the sponsor, and the FDA, if applicable. Any serious and unexpected sponsor-generated adverse reaction that is probably or definitely related to the research and necessitates a change to the protocol and/or consent form must be reported to the IRB by the Principal Investigator (PI) within five (5) days of receipt of the adverse reaction report. The adverse reaction is to be reported using **Form-3A** – Adverse Reaction Report (Off-Site) and **Form-6** – Amendment to Research Protocol, if applicable.

On-Site Adverse Reactions – Any serious and/or unanticipated adverse reaction occurring at Wills Eye Hospital must be reported to the IRB within forty-eight (48) hours. Fatal reactions which are unanticipated must be reported within twenty-four (24) hours. Fatalities not related to the research must be reported within five (5) days. The original copy of **Form-3B** – Adverse Reaction Report (On-Site) must be submitted to the IRB and **Form-6** – Amendment to Research Protocol, if applicable.

IRB Review of an Adverse Reaction Report – Once the IRB receives an ARR, the IRB incurs an obligation to review the report. The type of IRB review, i.e. full board or expedited, will be dictated by the nature of the adverse reaction. Federal regulations do not dictate the type of review required for adverse reactions. Regulations 45 C.F.R. § 46.110(b) and 21 C.F.R. § 56.110(b) permit the IRB to use an expedited review procedure in performing continuing review of minimal risk research and minor administrative changes. If the adverse reaction is minor in terms of clinical significance, it would be appropriate to use expedited review. The full IRB must review any reaction that is serious and/or unexpected and related or probably related to the research, as well as any reaction the investigator has determined warrants a change to the protocol and/or the informed consent form.

The IRB relies heavily on the responsibility, expertise, and decision of the Principal Investigator, who is required to analyze the adverse reaction in terms of its relationship to the research and to address the minimization of risks and the adequacy of the consent form in reflecting those risks. It is the Principal Investigator who bears the ultimate responsibility for protecting his/her patients enrolled in clinical trials and for appropriate conduct of the study. Consequently, the investigator bears the burden of the review of the adverse reaction and is required to justify why changes are not necessary on the basis of the type and severity of the reaction.

The IRB will acknowledge, in writing, the receipt of only those ARRs that require an amendment to the protocol and/or changes to the consent form. **Reminder:** It is federally mandated that all serious, unexpected adverse reactions be reported by the Principal Investigator to both the sponsor and the FDA, if applicable, with the additional requirement that written notification be made to the IRB.

Attachments:

Form 3A (Adverse Reaction Report – Off-Site)

Form 3B (Adverse Reaction Report – On-Site)

3.7 Continuing Review of Protocols

Policy

The IRB shall conduct continuing reviews of each research protocol approved by the IRB at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or to have a third party observe the consent process and the research.

Procedure

The Department of Health and Human Services Regulation, Title 45 Code of Federal Regulations, Part 46 (45 C.F.R. § 46) at Section 46.109(e) as well as Food and Drug Administration Regulations (21 C.F.R. § 56.108(a)(1)) require that an IRB conduct continuing review of human subjects protocols at intervals appropriate to the degree of risk, but not less than once per year. Each protocol undergoing continuing review will be individually presented, discussed, and voted upon by the convened IRB, which proceedings shall be recorded in accordance with 45 C.F.R § 46.115(a)(2) and with Section 3 of the IRB's Policy and Procedures on the Organization and Conduct of Meetings and Review of Protocols. The purpose of continuing review is to review the entire study, not just changes in it, and consequently the review must be substantive and meaningful.

In conducting continuing review, the IRB shall review, at a minimum,

A status report on the progress of the research that is to include:

1. Number of subjects accrued.
2. Completed demographic profile.
3. Description of any adverse events or unanticipated problems involving risks to subjects.
4. Any change in the risk vs. benefit ratio of each study.
5. Withdrawal of subjects from the research.
6. Attrition (e.g. moved, didn't keep appointments, etc.)
7. Any amendment to the protocol.
8. Any serious adverse drug event or any unanticipated adverse drug or device events.
9. Complaints from participants about the research.
10. Summary of new information or unanticipated risks discovered during research.
11. A copy of any publications.
12. A copy of the latest approved consent form or a revised consent form showing tracked changes, and documentation that all subjects have received a copy of their **signed consent form** as presented.
13. Final Reports.

Both OHRP and FDA regulations view the continuation of research after expiration of IRB approval as a violation of the regulations (45 C.F.R 46.109(e); 21 C.F.R §56.103(a)).

IRB approval is given for a period of time based on the determination of risk, but never more than a one-year period from the date of review. Therefore, any project which is not determined to be exempt from annual review must be submitted sufficiently in advance of the expiration date to allow the protocol to be reviewed at a regularly scheduled IRB meeting.

Continuing Review for studies classified as having greater than moderate risk will generally be approved for a specified cohort of subjects and/or a fixed period less than the potential one-year. In the case of such a high-risk study, the review will place increased attention on adverse events, the interim analysis of the data, and any increase in the risk as the study progressed.

The following forms must be submitted for a continuing review (i.e., applies to all annual or interim reviews)

Continuing Review: Please submit an original progress report as described in the Form-4 Instructions.

1. Form-4 (Continuing Annual Reviews) – This form must be filled out completely, and signed by the Principal Investigator. If no patients have been enrolled into the protocol since the previous IRB review, “0” shall be entered into the appropriate spaces. If any adverse reactions or unanticipated problems were experienced, documentation of the events, their outcome, and their relation to the study drug and procedures should accompany the report if they have not been previously reported.

It is recommended by the IRB office that you begin planning for your submission for continuing review early on into your project. This holds true for each year that the project is actively renewed, and is suggested in order to allow you ample time to formally explain any modifications in protocol, study design or patient consent prior to submission of your documents yearly. Please keep in mind that the IRB must be notified of any and all modifications to the project (regardless of how minor) since the last review. **Please remember that the Principal Investigator completing Form-4 must affix his/her personal signature ensuring compliance with Wills Eye Hospital and Federal guidelines governing the continuing review process.**

2. Copy of the currently approved consent form(s), or
3. Copy of the consent form showing tracked changes, if any revisions are proposed.

Federal Regulations require that if the IRB has not reviewed and approved a study by the study's current expiration dated, ***research activities must stop, unless it is determined to be in the best interests of already enrolled subjects to continue participating in the research.*** Continuing participation of already enrolled subjects may be appropriate, for example, when interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects. Enrollment of new subjects cannot occur after the expiration of IRB approval.

The determination regarding whether it is in the best interests of already enrolled subjects to continue to participate in the research after IRB approval has expired may be made *initially* by the investigator, possibly in consultation with the subject's treating physician, but the

investigator as soon as possible should submit a request for confirmation that the IRB agrees with this determination. The determination by the IRB may be made by the IRB Chairperson, by another IRB member or group of IRB members designated by the IRB Chairperson, or at a convened meeting of the IRB. If the IRB determines that it is not in the best interest of already enrolled subjects to continue to participate, investigators must stop all human subjects research activities, including intervening or interacting with subjects and obtaining or analyzing identifiable private information about human subjects. The continuation of research after IRB determination that it is not in the best interest of already enrolled subjects will constitute non-compliance with the requirements for continuing review. Such non-compliance, especially if serious and ongoing, may be reported to appropriate institutional officials, the HHS agency that supported the research, and OHRP.

Although a courtesy reminder may be sent out by the IRB in advance of the expiration date, **it is the responsibility of the investigator to know the expiration date of the study.**

The IRB meets on the 3rd Tuesday of each Month. Although this schedule results in an actual meeting date spanning the 15th to the 21st in any given month, this interval is considered to be immaterial to the IRB, and a study renewed during the anniversary month will be deemed timely regardless of any such interval. For example, a study initially approved in May of one year must be reapproved by May of the following year in order to ensure timely continuing review.

Anniversary Dates of Approval

At the time of initial approval, the IRB will specify the duration of the approval period and the interval by which continuing review must occur (e.g. 1 year) in order for research to continue. The effective date of this approval will be the date of the convened meeting, regardless of whether the research was approved with or without conditions.

The IRB recognizes the logistical advantages of keeping the expiration date of the IRB approval period constant from year to year throughout the life of a research project. Therefore, when the IRB conducts its continuing review and re-approves the research within 30 days *before* the IRB approval period expires, the IRB may retain the anniversary of the expiration date of the initial IRB approval as the expiration date of each subsequent one-year approval period.

Additionally, when the IRB conducts its continuing review and re-approves the research within 30 days *after* the IRB approval period expires, the IRB may grant approval for less than one full year in order to retain the anniversary date of the expiration of the initial IRB approval.

When the IRB performs the continuing review and re-approves the research more than 30 days *after* the IRB approval period expires, a new anniversary date will be established.

Lapse in IRB Approval

When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. Such expirations do not constitute suspensions or terminations of research and do not need to be reported to the OHRP.

When IRB approval lapses, and the study has not yet been administratively closed, and the investigator wishes to continue the project, research activities may resume once continuing review and approval by the IRB has occurred.

When a protocol is expired for a prolonged time and no continuing review has been submitted, the IRB may administratively close the protocol. If the investigator wishes to continue the project, the proposed research must be resubmitted in its entirety as a New Study.

Attachments:

Form 4 (Continuing/Final Review of Research)

3.8 Regulations Governing Emergent Use of a Drug or Biological

There has been considerable confusion as to “compassionate use” versus “emergency use” and how to proceed when such situations are encountered. The term “compassionate use” has been used in the past to refer to the provision of investigational drugs outside of an ongoing clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term “compassionate use” does not appear in FDA or DHHS regulations pertaining to drugs or biologics. Refer to the IRB Policy on Expanded Access for “compassionate use” to investigational articles in non-emergent situations.

FDA human subjects regulations allow for a test article to be used in emergency situations without prior IRB approval provided there is no sufficient time to call a meeting of the IRB [Title 21 CFR 56.102(d)], and that the emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article must have prior review by the full IRB (21 CFR 56.104).

DHHS regulations require that research involving human subjects receive full IRB review. Physicians do, however, retain the authority to provide emergency medical care to their patients [45 CFR 46.116(f)]. OHRP regulations stipulate that, “Whenever emergent care is initiated without prior IRB review and approval, the patient may not be considered to be a research subject. The emergency care may not be considered research, nor may the outcome of such care be included in any report of a research activity.” In summary, DHHS regulations do not permit research activities to be started even in an emergency without prior full IRB approval.

Procedure for Notifying the IRB of an Emergent Use Procedure

1. The investigator/physician seeking to administer a drug in an emergent use capacity must determine whether the proposed use meets the following definition from the FDA regulations:
 - a. The patient is in a life-threatening situation;
 - b. There is no standard acceptable treatment available; and
 - c. There is not sufficient time to convene a meeting of the full IRB.
2. If the proposed use meets this definition, the investigator/physician may proceed with the emergency use but should – prior to that use if possible – immediately notify the IRB. This notification should not be construed as IRB approval.
3. The investigator/physician must file a written report with the IRB within 5 days of the emergency use. This report shall include the following:
 - a. Response to the above items in #1;
 - b. Basic clinical information about the proposed use;
 - c. Information regarding the status of the IND that covers this use; and
 - d. A copy of the signed consent form. If obtaining informed consent from the subject or the subject’s legally authorized representative (or surrogate) is not possible, the

investigator/physician must certify that conditions for an exception to the informed consent requirements are met. [See 21 CFR 23 (a).]

4. If a manufacturer requires an “IRB approval letter” before releasing the test article for an emergency use, the IRB may – upon request from the investigator/physician – provide the sponsor with a written statement that the IRB is aware of the proposed use and considers the use to meet the FDA’s definition for “emergency use.”
5. The IRB will subsequently respond to the investigator/physician acknowledging the emergent use procedure.

Subsequent Emergent Use of Additional Doses of a Drug or Biologic

After an initial emergent use, FDA regulations require that any subsequent use of the test article must be subject to prospective IRB review. However, the FDA has also acknowledged in supplemental materials that the emergency use exception to IRB approval should not be so narrowly construed as to deny emergency treatment to patients, and that it would be inappropriate to deny such treatment to patients if the only obstacle is that the IRB has not had sufficient time to convene and review the issue.

The following policies are consistent with these goals:

1. Additional Doses. The term “use” should be interpreted as “course of treatment” rather than “a single dose” of a drug.

This interpretation provides for those instances where more than one dose of a drug is required (i.e., daily or twice daily doses) before the IRB can be convened and is consistent with the spirit of the “emergent use” doctrine. Accordingly, additional doses of a test article may be given to a patient only until the IRB is able to convene, provided that the above-stated procedures are followed and all of the conditions for emergency use continue to be met.

2. Emergency Treatment of a Second Patient. Should a situation arise which would require the emergency use of the same test article for a second patient, either by the same or a second physician, subsequent use should not be withheld for the purpose of obtaining IRB approval provided all of the above-stated procedures are followed and conditions for emergency use are met.
3. Recurrent Use of a Test Article under Emergent Conditions. Under FDA regulations in an emergent use, it is not permissible to administer the test drug repeatedly as an “emergency use” and thereby avoid prospective IRB review. Therefore, if a drug is administered a second time under the above-outlined “Emergent Use” policy, a physician/investigator MUST contact the Chairman of the IRB if he/she anticipates future uses under emergent conditions.

In the event the Chairman requires the development and/or amending of a protocol, the physician/investigator will be required to take the following action before any additional uses of the drug will be permitted:

- a. When there is an existing protocol covering the intended use of the drug:
 - i. Amend the protocol to include a “rescue arm.” The “rescue arm” should list all possible providers who will likely administer the drug as co-investigators.
 - ii. Amend the existing consent form to include details of the “rescue protocol.”
- b. When there is no existing protocol covering the intended use of the drug:
 - i. Submit a protocol to the IRB covering the intended use.
 - ii. Develop a consent form for that protocol for approval by the IRB.

Under both situations above, the drug in question cannot be used again until approval from the IRB is obtained.

3.9 Emergency Use of a Device

Policy

An unapproved medical device is defined as a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §360(3)). An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved application for an Investigational Device Exemption (“IDE”) under section 510(g) of the Act (21 U.S.C. §360(i)(g) and 21 CFR part 812). Medical devices that have not received marketing clearance under section 510(k) of the FD&C Act are also considered unapproved devices which require an IDE.

The Food and Drug Administration (“FDA”) recognizes that emergencies arise where (i) an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or (ii) the proposed use is not approved under an existing IDE, or (iii) the physician or institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to FDA that an emergency actually existed.

Each of the following conditions must exist to justify emergency use of an unapproved medical device:

1. The patient is in a life-threatening condition that needs immediate treatment;
2. No generally acceptable alternative for treating the patient is available; and
3. Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

It is the responsibility of the physician to determine (i) whether these criteria have been met, (ii) to assess the potential for benefits from the unapproved use of the device, and (iii) to have substantial reason to believe that benefits will exist. The physician may not conclude that an “emergency” exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physicians should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

Procedure

In the event that a device is to be used in circumstances meeting the criteria listed above, the device developer should notify the FDA Center for Devices and Radiological Health (CDRH) Program Operation Staff by telephone at (301) 594-1190 immediately after shipment is made. (Note: An unapproved device may not be shipped in anticipation of an emergency.) Nights and weekends, contact the FDA Office of Emergency Operations at (301) 443-1240. The FDA expects physician to follow as many subject protection procedures as possible. These include:

1. Obtaining an independent assessment by an uninvolved physician;
2. Obtaining informed consent from the patient or a legal representative;
3. Notifying institutional officials as specified by institutional policies;

4. Notifying the Institutional Review Board; and
5. Obtaining authorization from the IDE holder if an approved IDE for the device exists.

Within five (5) working days following the emergency use of a device, the physician must notify the IRB in writing of the emergency use. This report should include an explanation of the use, how and when the use took place, and justification based on FDA criteria for “emergency use” including (i) why prospective IRB review was not possible, (ii) the informed consent process, and, (iii) if applicable, how IDE requirements were met. This report should include a copy of the properly executed (signed) informed consent document or a statement that an informed consent document could not be obtained because of difficult in communication with the patient and/or insufficient time to contact the patient’s legal representative. The report should also include follow-up information on the condition of the patient in the days after the device has been administered.

If further use of a device is anticipated, a study application must be submitted for review and approval by the convened IRB in addition to the submission of the 5-day report. Subsequent use of the device is contingent upon this IRB approval and an FDA-approved IDE.

3.10 Expanded Access – Individual Patients or Small Groups

Expanded access, sometimes called "compassionate use," is the use of an investigational drug or device outside of a clinical trial to treat a patient with a serious or immediately life-threatening disease or condition who has no comparable or satisfactory alternative treatment options. FDA regulations allow access to investigational drugs and devices for treatment purposes on a case-by-case basis for an individual patient, or for intermediate-size groups of patients with similar treatment needs who otherwise do not qualify to participate in a clinical trial. They also permit expanded access for large groups of patients who do not have other treatment options available, once more is known about the safety and potential effectiveness of a drug from ongoing or completed clinical trials.

Just as in clinical trials, these investigational drugs and devices have not yet been approved by the FDA as safe and effective. They may be effective in the treatment of a condition, or they may not. They also may have unexpected serious side effects.

This policy is intended to delineate the steps required for permitting expanded access to an investigational drug or device for an individual patient or small group.

Policy

The treatment use of an investigational drug or device (i.e., a drug with an IND or a device with an IDE) on an individual patient or small group of patients is permitted, provided that such patient has or patients have a serious condition in which no standard acceptable alternative treatment is available and provided that the procedures of this Policy are followed. These procedures apply to expanded use or compassionate use, but do not apply to the emergency use of an investigational drug or device.

Procedure

A. Requesting Approval.

1. All questions for possible expanded access should be forwarded to the IRB Coordinator.
2. The attending physician requesting expanded access must submit a letter to the IRB detailing (a) information about the drug or device, (b) reference to the appropriate FDA submissions, such as an IND number, an IDE number for a significant risk IDE, or documentation for a non-significant risk (NSR) device, (c) the requested treatment use, (d) the name of the IND or IDE sponsor and contact information, (e) a letter from an uninvolved physician concurring with the recommended expanded access for the patient(s), and (f) a letter from the sponsor approving the expanded access and agreeing to make the drug or device available.
3. The request letter will be reviewed by the IRB Chairperson and submitted to the IRB for full IRB review.

4. If the expanded access treatment use is approved by the IRB, a notification letter will be sent to the requesting physician by the IRB Chairperson.
5. The sponsor should recognize the treatment use as a protocol deviation and make any reports of such deviation that might be required.
6. In the event that Wills Eye Hospital is the sponsor, the Department of Research will make any necessary filings and/reports for pre-approval or notification that are required by law or regulation. For an investigational drug or a significant risk investigational device, a supplemental application to FDA will be submitted and approved as required. If applicable law provides that a treatment use is solely under the supervision of the IRB without pre-approval of, or notification to a regulatory body (such as a non-significant risk investigational device), then all aspects of the treatment use shall be solely monitored by Wills Eye Hospital and the Wills Eye Hospital IRB.
7. As a sponsor, Wills Eye Hospital is committed to providing reasonable assistance so that seriously ill patients who have exhausted other appropriate treatment options may, under appropriate conditions, and in accordance with applicable law, have appropriate access to investigational drugs and devices before they are commercially available. When considering a treatment use of a drug or device when Wills Eye Hospital is the sponsor, the following requirements shall apply:
 - (a) The investigational drug or device is being studied under an appropriate regulatory authorization or all investigational studies of the product have been completed.
 - (b) The patient(s) for whom a treatment use is sought: (i) is suffering from a serious disease or condition; (ii) has undergone appropriate standard treatments without success, or no comparable or satisfactory alternative treatment is available, or no standard treatment exists for the disease or condition; (iii) is ineligible for participation in any ongoing clinical study of the investigational product, including lack of access due to geographic limitations; and (iv) meets any other relevant medical criteria for expanded access as established by Wills Eye Hospital.
 - (c) There are meaningful human clinical data to support an assessment that the potential benefits to the patient outweigh the risks to the patient.
 - (d) Providing the investigational drug or device for expanded access will not interfere with development of the product.

B. Safety Monitoring

1. The attending physician should devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the drug or device and the specific needs of the patient.

2. Following the treatment use of the drug or device, a follow-up report in which summary information regarding patient outcome is presented should be submitted to the IRB. If any problems occurred as a result of device use, these should be reported to the IRB within five (5) working days of the event or knowledge of the event.

3.11 Use of Humanitarian Use Device

The provisions of the FDA Safe Medical Devices Act of 1990 regarding humanitarian use devices (HUDs) became effective on October 26, 1996. An HUD is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4000 individuals in the United States per year. The manufacturer's research and development costs for bringing such a device to market could exceed its market returns for diseases or conditions affecting small populations. The FDA developed and published this regulation to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

To be considered for HUD status, the sponsor must complete an (HDE) for a humanitarian device exemption. Because of the impractical cost of conducting large-scale clinical trials for devices designed for potentially small user populations, the HDE application is not required to present the results of scientifically valid clinical investigations that demonstrate the device is effective for its intended purpose. The application must, however, contain sufficient information for the FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of illness or injury from its use. Additionally, the applicant must demonstrate that no comparable devices are available for that purpose and that they could not otherwise bring the device to market without receiving HUD status.

An approved HDE authorizes marketing of the HUD. An HUD may only be used after IRB approval and supervision of the clinical testing of the device. The labeling for the HUD must state that the device is a humanitarian use device and that, although federal law authorizes the device, the effectiveness of the device for the specific indication has not been demonstrated. HDE applications do not have to be renewed and are valid as long as the device continues to meet the conditions of the HDE application.

The IRB has a unique role in the humanitarian use device setting. This is the only situation where federal regulations require the IRB to approve and monitor an activity that is clearly not research. An approved HDE application authorizes the applicant to market the device and the local physicians to use the device to treat or diagnose a medical condition. All IRB regulations and guidance documents are written from the point of regulation of human subjects research. In approving an HDE application, the IRB is put in a position where it must operate without guidance from a federal IRB system designed to regulate research.

Consequently, when evaluating a request to use an HUD for medical treatment or diagnosis, each IRB is left to its own discretion to establish its own criteria for IRB approval.

In evaluating a request to use a HUD, the IRB will consider the following that are generally included in the HDE application:

- The generic and trade name of the device
- The FDA HDE number (6 digits)
- The date of the HUD designation
- Indications for the use of the device

- Description of the device
- Any contraindications, warnings, and precautions for the use of the device
- Adverse effects of the device on health
- Alternative practices and procedures
- Marketing history
- Summary of studies using the device

There is no time limit on the FDA approval of an HDE. The IRB must conduct both initial and continuing review of the HUD. Approval may be granted for a maximum of one year or less depending on the perceived risk.

While the regulations do not require a consent form as the device will be used outside a research setting, the IRB will make a determination as to whether it would be prudent to require a consent form, particularly to indicate the unproven status of the device.

The IRB has discretion to determine the conditions of HUD use, and may limit the use of the HUD based on any criteria it deems appropriate.

The IRB shall require a statement from the investigator that the HUD is not being used as part of a research project or clinical investigation designed to collect data to support an FDA pre-market approval application.

3.12 Determining Whether a Device Study Involves a Significant Risk (SR) or Non-Significant Risk (NSR) Device

The Investigational Device Exemption (IDE) regulations (21 CFR part 812) describe two types of device studies, SR and NSR.

A SR device study is identified (21 CFR 812.3) as the study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents a potential for serious risk to the health, safety or welfare of the subject.

A NSR device investigation is one that does not meet the definition for a significant risk study.

For both SR and NSR devices, IRB approval is required prior to conducting the study, and continuing review is required to continue the study for another year. A consent form is required for both types of device studies.

Distinguishing between SR and NSR Device Studies

SR device studies are governed by IDE regulations as stated above. NSR device studies are governed by the abbreviated requirements of 21 CFR 812.2(b). The major differences are in the approval process and in the record keeping and reporting requirements.

The SR/NSR decision is important to the FDA, because the IRB serves as the FDA surrogate with respect to the review and approval of NSR device studies. In addition, sponsors and IRBs are not required to report NSR device study approvals to the FDA; consequently, the FDA is not generally apprised of such studies.

The IRB Decision Process

Non-Significant Risk Device

If an investigator or sponsor proposes a device study to the IRB that is claimed to use a NSR device, the IRB must review the device according to FDA policy for devices. The sponsor provides the IRB with an explanation of its determination of the device as NSR, and the rationale used in making its determination [21 CFR 812.150(b)(10)]. The sponsor also must provide the IRB with a description of the device, reports of prior investigations with the device, whether other IRBs have reviewed the study and their determinations, and all other information that the IRB would need to review and approve the study. The risk determination should be based on the *proposed use of the device* in the specific investigation and not on the device alone.

The IRB must consider the potential harm that may result from the use of the device. The IRB may consult with the FDA for its opinion.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor that the study involves a NSR device and the IRB approves the study, the study may begin when the investigator receives the approval letter from the IRB. Submission of an IDE application to the FDA is not required. If the IRB disagrees, the sponsor must notify the FDA that a SR determination has been made. In this case the study can be conducted as a SR study following FDA approval of an IDE.

Once the NSR/SR decision has been made by the IRB, the IRB should determine whether the study should be approved or not. The criteria for approval are the same as those for any other FDA regulated study (21 CFR 56.111).

Generally, NSR studies require IRB review at a convened meeting of the IRB. In some cases, a NSR study may qualify as minimal risk, in which case the IRB may review that study under its expedited review procedures.

Significant Risk Device

In deciding if a device to be employed in a study poses a significant risk, the IRB must consider the nature of the harm that may result from the use of the device. Studies where the potential harm to subjects could be life threatening, could result in permanent impairment of a body function or permanent damage to a body structure, or could necessitate medical or surgical intervention to preclude permanent damage to body structure should be considered a SR device. If the subject must undergo a procedure as part of the investigational study, e.g., surgery, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

The FDA considers studies of SR devices to present more than minimal risk thus requiring full IRB review at a convened meeting.

FDA has the ultimate decision in determining if a device is SR or NSR. If the agency does not agree with the IRB's decision that a device study presents a NSR, an IDE application must be submitted to the FDA. If a sponsor files an IDE with the FDA because it believes the device to be a SR, but the FDA classifies the device as NSR, the FDA will return the IDE application to the sponsor and the IRB will be responsible for determining whether it represents a NSR device.

IRB Responsibilities following SR/NSR Determination

If the IRB determines that the study is significant risk then the responsibilities of the IRB are to:

- Notify the sponsor and investigator of the SR decision
- Review the study according to the requisite criteria (21 CFR 56.111) after the sponsor obtains the IDE.

3.13 Conflict Of Interest Disclosure

Policy

The Principal Investigator, the Co-Investigators, and designated key personnel (collectively, “Covered Persons”) conducting research within Wills Eye Hospital must disclose conflicts of interest in the appropriate section of Form-1. For research initially submitted using Form-1A where a conflict exists, or if a conflict arises during the course of the clinical trial, you must submit a separate Form-7 Conflicts of Interest Form.

Procedure

For clinical trials, a conflict of interest exists when a Covered Person, any of the Covered Person’s immediate family members of Wills Eye have a 5% equity ownership interest or greater than \$5,000 investment interest in any entity supporting the clinical trial. In addition, a conflict of interest exists when the Covered Person or any immediate family member accepts any compensation, gifts, gratuities, or entertainment from a sponsor of the Covered Person’s clinical trial. Lastly, a Covered Person or any immediate family member’s involvement whether paid or unpaid, as a manager, scientific advisor, or board member of the Covered Person’s clinical trial sponsor will be considered a conflict of interest.

In addition to disclosure to the IRB, this conflict of interest must be defined in the appropriate section in all consent forms used by the Covered Person and given to human subjects while conducting the clinical trial. See the sample form in “Policy and Procedures Regarding Informed Consent” for appropriate language or contact the IRB for assistance in drafting this section. If a conflict of interest arises or a current conflict of interest changes significantly during the course of the clinical trial, this conflict must be disclosed immediately to the IRB. At that time, all current informed consent forms must be amended to reflect the existence of the changed circumstances of the conflict of interest.

See: Form-7 (Conflict of Interest Disclosure)

3.14 Substituted Consent

Policy

Federal regulations require that the researcher obtain the legally effective informed consent of the subject or the subject's legally authorized representative prior to medical research. Federal law defers to state law to determine what surrogate is legally authorized to substitute consent. Pennsylvania law requires the informed consent of the patient or the patients' authorized representative before the administration of an experimental medication, the use of an experimental device, or the use of an unapproved medication or device in an experimental manner. By statute, Pennsylvania authorizes substitute consent to the performance of experimental biomedical or behavioral medical procedure or participation in any biomedical or behavioral experiment by the subject's court-appointed guardian pursuant to a court order issued after act finding. Pennsylvania statutory law further authorizes a person named in the patient's power of attorney to consent to medical, therapeutic, and surgical procedures.

While Pennsylvania statutory law does not explicitly authorize substitute consent in the absence of a power of attorney or court-appointed guardian, case law strongly supports substituted consent by close family members when patients lack capacity to make medical decisions. See In re Fiori, 673 A.2d 905, 543 Pa. 592 (1996). When the patient is unable to give informed consent, the patient's close family member is in the best position to determine the wishes of the patient regarding participation in therapeutic research.

It is the policy of Wills Eye Hospital that its Institutional Review Board protect the research subject's right to autonomy. It is also Wills Eye Hospital's policy to protect those with diminished autonomy. Wills Eye recognizes, however, that in order to offer patients incapable of making autonomous choices experimental treatments where the potential direct benefit exceeds the risk of harm, substituted consent is necessary. Accordingly, the following procedure will be followed when the researcher determines that a patient is unable to give informed consent for participation in research.

Procedure

Once the research investigator determines that the prospective subject is unable to provide informed consent, the investigator will determine whether the risk of harm posed by the research is reasonable in relation to the potential or direct benefit of the research to the subject. If the risk of harm is considered reasonable in relation to the potential direct benefit to the research subject, the investigator may obtain substitute consent.

When obtaining substitute consent, the investigator should complete **Form-8** (Substituted Consent for a Research Protocol), documenting as thoroughly as possible the reason for the subject's inability to provide informed consent. The investigator should also have the patient's legal representative read and sign **Form-5** (Informed Consent). Their substitute consent should be documented according to the general procedures for informed consent listed under "Policy and Procedures Regarding Informed Consent."

The investigator may obtain the informed consent of a court-appointed guardian authorized to consent to the subject's participation in the protocol in a current court order issued within the subject's jurisdiction. In the alternative, the investigator may obtain the substituted consent of a health care proxy appointed by the subject in a power of attorney. In the absence of a court order or a duly appointed health care proxy, the investigator may obtain the informed consent of the following next of kin, in the order listed:

- Spouse;
- Natural or adoptive parent;
- Adult child;
- Adult brother or sister;
- Any other available adult relative related through blood or marriage.

The consent process will comply with the policies and procedures set forth by the IRB and by state and federal law. The surrogate should base his or her decision on the subject's expressed wishes or, if unknown, what the subjects would have desired in light of his or her prognosis, values, and beliefs. When a surrogate provides consent, it is preferable for that surrogate to remain the responsible party for all research decisions.

In the event of a disagreement among potential patient surrogates, an attempt to reach consensus shall be made. If consensus is not possible, a court appointed guardian should be obtained before the subject is enrolled in the study. Once a surrogate has provided consent, the investigator may obtain the assent of the subject if it is determined that the subject is alert, communicable, and capable of understanding that permission for his inclusion in a research study has been granted.

If at some time after the subject is enrolled in the study via the consent of a substitute, the subject's condition improves and he or she regains the capacity to provide informed consent, the investigator shall obtain the legally effective informed consent of the subject for continued participation in the research.

See also: **Form-5 (Informed Consent)**
 Form-8 (Substitute Consent for Research Protocol)

3.15 Protection of Patient Health Information in Research

In the course of conducting research, it is necessary for Wills Eye Hospital (“Wills”) to obtain and maintain protected health information. Protected health information includes, but is not limited to, name, address, social security number, and other personally identifiable information as well as diagnosis, treatment, and other documentation. Patients expect, and Wills demands, that all protected health information be held in confidence and be protected from unauthorized use and disclosure, whether intended or unintended. In addition, the Health Insurance Portability and Accessibility Act of 1996 (“HIPAA”) imposes specific legal duties on Wills and grants specific rights to patients concerning protected health information.

Wills Eye Hospital and its medical staff may use or disclose protected health information for research, regardless of the source of funding of the research, only if:

1. The research obtains written authorization from the research subject pursuant to the policies and procedures of the Wills Eye Hospital and the IRB; or
2. The IRB approves a waiver of written authorization pursuant to this policy.

Waivers of Written Authorization

1. As a general matter, research subjects should provide a written authorization in order for their protected health information to be used or disclosed in research activities. However, the written authorization may be waived or altered, in whole or in part, by the IRB if the following criteria are satisfied:
 - The use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals, based on, at least, the presence of the following elements: (i) an adequate plan to protect the identifiers from improper use and disclosure; (ii) an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and (iii) adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research activity, or for the research for which the use or disclosure of protected health information would be permitted by this policy of HIPAA;
 - The research could not practicably be conducted without the waiver or alteration; and
 - The research could not practicably be conducted without access to and use of the protected health information.

Waivers of written authorizations in retrospective chart reviews should be requested using **Form-1A**.

2. In the event of a waiver or alteration of written authorization, the IRB must document all of the following:
 - A statement identifying the IRB and the date on which the alteration or waiver of authorization was approved;

- A statement in the minutes of the IRB that the IRB has determined that the waiver or alteration satisfies the criteria for waiver/alteration set forth in this policy;
- A brief description of the protected health information to be used and disclosed;
- A statement that the waiver or alteration of authorization has been reviewed and approved under either normal or expedited review procedures.

The documentation of the alteration or waiver of authorization must be signed by the chair of the IRB or other member, as designated by the chair.

Reviews Preparatory to Research

Researchers or potential researchers at Wills may access protected health information in preparation for research or potential research only if the IRB obtains from such researchers or potential researchers the following representations, in writing:

- The use or disclosure is sought solely to review protected health information as necessary to prepare a research protocol or for similar purposes preparatory to research;
- No protected health information is to be removed from Wills by the researcher in the course of the review; and
- The protected health information for which use or access is sought is necessary for the research purposes.

Research of Decedents' Information

Researchers at Wills may access decedents' protected health information only if the IRB obtains from such researchers the following representation, in writing:

- The use or disclosure sought is solely for research on the protected health information of decedents;
- The protected health information for which use or disclosure is sought is necessary for the research purposes;
- A brief description of the protected health information to be used or disclosed.

The IRB may request that such researchers produce documentation of the death of individuals whose protected health information will be used or disclosed.

Introduction to HIPAA and Research

What is HIPAA?

The Health Insurance Portability and Accountability Act of 1996 ("HIPAA") is intended to improve the efficiency and effectiveness of the health care system.

HIPAA directly regulates three types of "covered entities":

- Healthcare providers (including organizations and individuals);
- Health plans (insurers and payors); and
- Healthcare clearinghouses (billing services).

Wills Eye Hospital is considered a health care provider.

HIPAA has three main parts. The first, the “Administrative Simplification” provisions, include national standards for transactions of electronic patient health, administrative and financial data between health care providers and health plans. The second and third parts concern security and privacy, and protect the confidentiality and integrity of health information. This Guide focuses on the Privacy Rule, which has special regulations affecting clinical research particularly.

What is the Privacy Rule?

The Privacy Rule includes standards to:

- Limit the use and disclosure of health information
- Restrict most use and disclosure of health information to the minimum necessary to carry out the intended purpose
- Give patients the right to:
 - Receive a Notice of Privacy Practices describing how Wills Eye Hospital uses and discloses their health information; each patient must receive this document at least one time
 - Receive a listing of certain releases by Wills Eye Hospital of their health information
 - Inspect, copy, and request amendments to their medical records
 - Request restrictions on uses and disclosures of their health information
 - Request alternate forms of communication (e.g., use work address instead of home; no postcards, etc.)
 - File a formal complaint about violations of privacy protections with Wills Eye Hospital, or with the Department of Health and Human Services
 - Revoke and authorization for use/disclosure of identifiable health information to extent the researchers have not already “relied on it”

The Privacy Rule also:

- Establishes criminal and civil penalties for improper use of disclosure (\$25,000 for multiple violations in the same year, \$250,000 and/or up to 10 years imprisonment for knowingly misusing a person’s protected health information)
- Establishes new requirements for access to health-related records by researchers and their use and further disclosure information

What does the Privacy Rule protect?

The Rule protects information acquired by Wills Eye Hospital, including demographic information, that could reasonably identify an individual and:

- Relates to the past, present, or future physical or mental health, condition or treatment of an individual; OR
- Describes the past, present, or future payment for the provision of healthcare to an individual

Why are researchers covered?

Researchers who provide health care to individuals (i.e., in a clinical trial) are directly covered as health care providers. Researchers who access existing protected health information (i.e., medical record, computer databases) must comply with the HIPAA Privacy Rule because the Wills Eye Hospital, as a “covered entity,” must protect the privacy of individually identified health information used or released for research.

When do I need to be in compliance?

The compliance date for the Privacy Rule is April 14, 2003.

What are the major implications for researchers?

The Privacy Rule is extremely complex and requires that Wills Eye Hospital put into place new policies and procedures. Clinical research is one area that is uniquely impacted by the regulations.

From a clinical investigator perspective, the new regulations will affect how you access existing health information (medical/database record reviews) and how you handle identifiable information created as part of clinical research.

In practical terms, the major changes are as follows:

- In addition to informed consent requirements, investigators will need to obtain an authorization with more detailed information, in order to use and release identified protected health information for research.
- The criteria that the IRB will use to waive the authorization and informed consent for medical record/database review have become much more stringent. You will be asked to provide more detailed information on your protocol applications and medical records/database request.
- The institute, and investigators, will need to track individually identified information that is released for research when waivers of authorization are granted. The purpose of this tracking is to provide patients, upon their request, with a list of how information about them was released for research and other non-treatment purposes without their knowledge.
- In some cases, before arrangements are made with other provider organizations and individual consultants to either use protected information or to generate, analyze, or process such information on behalf of Wills Eye Hospital or its researchers, a “business associate” agreement will need to be established. The business associate agreement is a form mandated by HHS, in which the other organization or consultant satisfactorily assures you and Wills Eye Hospital that they will protect the information. Before data is released, there will need to be some specific assurances of the methods the recipient will use to assure the privacy of the information is protected. This will be documented in a data use agreement or business associate agreement, depending on the situation.

There are many other changes that will be part of Wills Eye Hospital HIPAA compliance effort. This summary is intended to provide a synopsis of the major changes investigators and the IRB will need to implement.

What is protected health information (PHI)?

Protected health information (PHI) is identifiable health information that Wills Eye Hospital has acquired in the course of serving patients. Data elements that make health information identifiable include: name, address, employer, relatives' names, date of birth, date of death, date of service(s), telephone and fax numbers, email addresses, social security number, member or account numbers, certificate or license numbers, voice recordings, fingerprints, photographs, or any other linked number, code or characteristic.

4. FORM INSTRUCTIONS

INSTRUCTIONS for Completion Of
Wills Eye Hospital IRB Form-1
“RESEARCH STUDY PROPOSAL”

A. Complete the fill-in items on the Research Study Proposal Form-1 as directed by the following instructions:

NOTE: THIS FORM IS NOT TO BE USED FOR RESEARCH INVOLVING ONLY EXISTING PATIENT RECORDS AND/OR SPECIMENS. FOR THIS TYPE OF RESEARCH, USE FORM-1A.

1. Research Study Identifying Information:

Fill in the blanks on the form for the Study Title, the name of the Principal Investigator (Residents/Fellows conducting a study must have an Attending Physician act as Principal Investigator), the name(s) of the Co-Investigator(s), and the name of the principal Service/Department.

Industry sponsored studies will be invoiced for a one-time review fee.

NOTE: If you wish to add additional Co-Investigators after your Research Study Proposal has been approved by the IRB, you must submit a Form-6 Addendum certifying that the person has met the requirements for Co-Investigator status, is sufficiently qualified to be added to your study as a clinical investigator, and has completed the mandated training program. Each new Investigator must sign and submit a Co-Investigator Statement.

2. What type of IRB review are you requesting for this Research Study Proposal?

Check either **Standard Review** or **Expedited Review**. Expedited Review is applicable only to Research Studies that pose Minimal Risk and fall into specific enumerated categories. Please review the IRB’s Policy Regarding Expedited Review for these categories. If you request Expedited Review, you will need to compose a separate letter to the IRB Chairman to indicate why the Research Study Proposal qualifies for expedited review.

3. Was this Research Study Proposal ever reviewed previously by the Wills Eye Hospital IRB?

Check either **YES** or **NO**. If your answer is **YES**, provide the IRB # of the original Research Study Proposal.

4. Does the study involve research activities (including enrollment, consent, and study treatment) to be conducted at the Wills Eye Emergency Room?

Note that the Wills Eye Emergency Room is located in the Jefferson Hospital for Neuroscience building and is a part of Jefferson Hospital. Therefore, any research

activities conducted at Jefferson (including but not limited to access of Jefferson EMR, subject enrollment, consent interviews, and study related treatment) requires joint approval of both IRBs. Contact the Wills IRB Office immediately for additional guidance.

5. Are you requesting a waiver or alteration of the Written Informed Consent Form or Process?

Check either **YES** or **NO**. If your answer is **YES**, you will need to compose a separate letter to the IRB Chairman outlining the reasons for the alteration or waiver of the Informed Consent Form and submit this letter to the IRB when you submit the completed Research Study Proposal.

Studies Regulated by the FDA. The IRB may waive, on a case-by-case basis, the requirement that the Research Investigator document consent by means of a signed consent form for some or all subjects if the IRB determines that: (1) the only record linking the subject and the research would be the consent document and the principal risk would be the potential harm resulting from a breach of confidentiality and each subject will be asked whether the subject wants documentation linking the subject with the research and the subject's wishes will govern; (2) 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; (3) 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. The written statement must be approved by the IRB.

Studies Not Regulated by the FDA. The IRB may approve a consent procedure which does not include, or which alters some or all of the elements of informed consent or waive the requirement to obtain informed consent if it 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. Programs under the Social Security Act, or other public benefit or service program;
 - ii. Procedures for obtaining benefits or services under these programs;
 - iii. Possible changes in or alternatives to those programs or procedures;
 - iv. Possible changes in methods or levels of payment for benefits of services under those programs; or

2. The 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 requirement to obtain informed consent provided that the IRB finds and documents that:

- i. The research involves no more than minimal risk to the subjects;

- ii. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- iii. The research could not practicably be carried out without the waiver or alteration; and
- iv. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

6(a). Does this Research Study Proposal involve the use of drugs/biologics/vaccines in humans?

Check either **YES** or **NO**. If your answer is **YES**, list the drugs/biologics/vaccines to be used in the study.

6(b). Are these drugs/biologics/vaccines (i) approved by the FDA, (ii) for the use indicated, and (iii) the dose indicated?

Check either **YES**, **NO**, or **N/A**. If your answer is **NO** for any of the above, you must submit a Form-1 IND.

6(c). Are the drugs/biologics/vaccines listed in the Wills Eye Hospital Formulary?

Check either **YES**, **NO**, or **N/A**.

6(d). If the drugs/biologics/vaccines are not listed in the WEH Formulary, will the drugs/biologics/vaccines be dispense on the 7th Floor of Wills?

Check either **YES**, **NO**, or **N/A**. If your answer is **YES**, complete a Form-2 Drug Statement.

6(e). If the drugs/biologics/vaccines are not listed in the WEH Formulary, will the Sponsor provide the drugs/biologics/vaccines to be dispensed by the Investigator?

Check either **YES**, **NO**, or **N/A**. If your answer is **YES**, complete a Form-2 Drug Statement.

7(a). Does this Research Study Proposal involve the use of medical devices?

Check either **YES** or **NO**. If your answer is **YES**, list the devices to be used in the study.

7(b). Has the device been approved by the FDA for the use indicated?

Check either **YES**, **NO**, or **N/A**. If your answer is **NO**, provide the Investigational Device Exemption (“IDE”) Number and, if applicable, Sponsor for each device. Or, you must provide a letter from the Sponsor or evidence from the scientific literature justifying why an IDE is not needed, and provide a description of that justification in the space provided.

7(c). Is this a Non-Significant Risk (NSR) or Significant Risk (SR) Device?

Check either **NSR** or **SR**. This determination is initially made by the Sponsor and/or Principal Investigator. The IRB may agree or disagree with the Sponsor's initial assessment and may consult FDA for its opinion. If a device is deemed SR, the Sponsor must submit an IDE (Investigational Device Exemption) application to FDA.

A Significant Risk device is a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents a potential for serious risk to the health, safety or welfare of the subject.

A Non-Significant Risk device is one that does not meet the definition for a Significant Risk device.

8. Does this Proposed Research Study involve an investigational procedure?

Check either **YES** or **NO**. If your answer is **YES**, provide a description of the procedure in the space provided.

9. Does this Proposed Research Study involve radiation exposure(s); or the use of any radioactive substance(s) other than standard radiography, radionuclide scanning or radiation therapy; or require additional radiation exposure(s) from any of the foregoing solely as a result of participation in the Study?

Check either **YES** or **NO**. If your answer is **YES**, you must obtain approval for the proposed radiation exposure(s) and/or use of the radioactive substance(s) from the appropriate Radiation Safety Committee prior to your submission of your Research Study Proposal to the IRB and you must submit a copy of your approval letter from that committee to the IRB when you submit the completed Research Study.

10. Does this Proposed Research Study involve use of rDNA, synthetic nucleic acid, nanotechnology, stem cells, infectious agents (pathogens), or biological toxins?

Check either **YES** or **NO**. If your answer is **YES**, you must obtain approval for the exposure(s) and/or use of the substance(s) from the appropriate Institutional Biosafety Committee prior to your submission of your Research Study Proposal to the IRB and you must submit a copy of your approval letter from that committee to the IRB when you submit the completed Research Study Proposal. It may be possible to have these reviews occur simultaneously. Contact the IRB Office for additional guidance.

11. Does this Research Study Proposal involve research to be performed at/in/with another institution?

Check either **YES** or **NO**. If your answer is **YES**, list the other institutions in the space provided. Note that Wills Eye Hospital IRB only reviews research activities that takes place at Wills. Outside institutions often have separate IRBs, and review by the local IRB may be required. If any research activity will involve Jefferson (its personnel, patients, data, specimens, etc.), check YES and provide an explanation in the Protocol of which activities will take place at Wills. Note that joint approval of both IRBs will be required. Contact the IRB Office for additional guidance.

12. Does this Research Study Proposal involve research involving any of the following special subject populations?

Check all categories that apply. If your answer is **YES**, describe the additional risks or discomforts you anticipate for the proposed population. Note that research regulations require additional protections for Children, Prisoners, and Pregnant Women/ Fetuses/ Neonates. Other subject populations may require additional protection, including but not limited to: economically or educationally disadvantaged individuals, cognitively impaired individuals, the very sick, comatose, or traumatized individuals. Be sure to address the subject populations in your Protocol and describe any additional safeguards to be followed.

13. What is the level of risk for participants in the study?

Check either **Minimal Risk** or **Greater Than Minimal Risk**. A risk is minimal if the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than that encountered in daily life or during the performance of routine physician or psychological examinations or tests.

14. Will notices or advertisements be employed to recruit participants into this Study?

Check either **YES** or **NO**. If your answer is **YES**, the IRB must review and approve the recruitment materials prior to implementation. Recruitment materials include but are not limited to: newspaper, radio, television, internet, bulletin boards, posters, and flyers that are intended to be seen by prospective subjects. Attach a copy of the notice or advertisement when submitting this Form-1.

15(a). Are you, or any co-investigator, receiving any compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of this study or in the form of compensation tied to sales of the product, such as a royalty interest?

Check either **YES** or **NO**. If your answer is **YES**, provide an explanation.

15(b). Are you, or any co-investigator, when aggregated with a spouse and any dependent children, have any ownership interest (including stock and stock options) or other financial interest in the sponsor of this study whose value cannot be readily

determined through reference to public prices (generally, interests in a non-publicly traded corporation), or any equity interest in the sponsor of this study which is publicly traded that exceeds \$5,000 determined through reference to public prices or other reasonable measure of fair market value (and does not represent more than a five percent ownership interest in any single entity) during the time of the study and for one (1) year following completion of the study?

Check either YES or NO. If your answer is YES, provide an explanation.

15(c). Do you have any property or other financial interest in the product, including, but not limited to, a patent, trademark, copyright, royalties, or licensing agreement?

Check either YES or NO. If your answer is YES, provide an explanation.

15(d). Have any payments or contributions been made, directly or indirectly, by the sponsor of this study to you or to any co-investigator (when aggregated with a spouse and any dependent children), or to the institution, of \$5,000 or more to support activities, exclusive of the cost of conducting the clinical study or other clinical studies (e.g., a salary, royalty, grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria, or other payments) during the time of the study and for one (1) year following the ?

Check either YES or NO. If your answer is YES, provide an explanation.

B. Research Study Protocol

Describe your Proposed Research Study according to the following format. Be as concise as possible without omitting necessary information.

1. Specific Aims

Describe the purpose(s) of your Proposed Research Study and the hypothesis to be tested.

2. Background

Describe prior studies and observations pertaining to your Proposed Research Study and cite pertinent references. If a drug/biologic/vaccine or a medical device is to be used, indicate its current FDA status.

3. Materials and Methods

Describe the materials and methods of your Proposed Research Study, including at least, the following:

- a) Physical requirements of the subjects;
- b) Anticipated duration of the study;
- c) Likely effects, potential benefits, and risks of the research on the subjects;

- d) What are the alternatives to the proposed research subjects;
- e) Follow-up requirements of the subjects;
- f) Requirements of confinement of the subjects during the study;
- g) Precautions to be observed by the subject before, during, and following the study;
- h) Methods of data analysis;
- i) Projected number of subjects that will be figured for the study; and
- j) Methods of assignment of subjects to different options in the study.

4. Human Subjects

If the subjects of your Proposed Research Study are humans, describe the following:

- a) The source of potential subjects, derived materials, or data;
- b) The characteristics of the subject population(s), including expected age range, sex distribution, ethnic background, race, state of health, and any other pertinent factors;
- c) The criteria for inclusion and exclusion of potential subjects;
- d) The rationale for the use of special classes of subjects, such as fetuses, pregnant women, children, or other distinct groups;
- e) The recruitment and consent procedures to be followed, including the circumstances under which consent will be solicited and obtained, who will seek it, the nature of information to be provided to prospective subjects, and the method of documenting consent;
- f) Real or potential physical, psychological, social, legal, or unspecified risks to the subjects as a result of their participation in the study and comment on the likelihood and seriousness of these risks;
- g) Standard options to the proposed research and the reasons why you believe them to be unsatisfactory;
- h) The procedures for protecting against or minimizing any potential risks and comment on their probable effectiveness;
- i) Confidentiality safeguards that will be taken;
- j) Arrangements for providing medical treatment of subjects for problems arising out of their participation in the study;
- k) The potential benefits of your proposed research to the subjects or to society in general;
- l) The risks in relation to the anticipated benefits of your research to the subjects and society;
- m) The cost may not be covered by insurance companies because of the research status; and
- n) Advertisements for recruitment must be submitted and reviewed by the IRB Committee.

5. Will this Research Study involve payment(s) to participants or involve material inducements for participation in the Study?

If your answer is **YES**, please describe the amount of payment and partial payment, in the event the study is not completed, and include any material inducements and the terms under which they are offered to participants.

6. Conflicts of Interest

Potential conflicts of interest and conflicts of interest must be disclosed by the Principal Investigators, Co-Investigators, and other key personnel with respect to all research studies. Please review the IRB's Policy Regarding Conflict of Interest Disclosure. Conflicts of interest can exist when the Principal Investigator, Co-Investigator, or key personnel has an ownership or investment interest in the entities supporting the clinical trial, when any of them accept compensation, gifts, gratuities from that sponsor and if the immediate family member of any of these personnel acts as a paid or unpaid manager, scientific advisor, or board member of that sponsor. These are very serious matters and should be given adequate and thoughtful consideration and disclosure must be made in all instances. By executing this Research Study Proposal, the Principal Investigator is certifying that this research project has been evaluated under the IRB's Policy on Disclosure of Conflicts of Interest and that no conflicts exist.

C. Written Informed Consent

Compose a Written Informed Consent Form for your study according to the IRB's Policy and Procedure regarding Informed Consent and Form of Informed Consent, or attach a letter requesting an Alteration or Waiver of the informed consent requirement.

D. Principal and Co-Investigator Investigators' Statements

You and every Co-Investigator must read the appropriate Investigator's Statement and sign your name legibly on the appropriate line of the form and date the form before submitting the completed Research Study Proposal to the IRB.

INSTRUCTIONS for Completion Of

Wills Eye Hospital IRB Form-1A “Research Study Proposal”

A. Complete the fill-in items on the Research Study Proposal Form-1A as directed by the following instructions:

NOTE: THIS FORM IS FOR RESEARCH INVOLVING EXISTING PATIENT RECORDS AND/OR SPECIMENS ONLY. FOR ALL OTHER TYPES OF RESEARCH, USE FORM-1.

1. Research Study Identifying Information:

Fill in the blanks on the form for the Study Title, the name of the Principal Investigator (Residents/Fellows conducting a study must have an Attending Physician act as Principal Investigator), the name(s) of the Co-Investigator(s), and the name of the principal Service/Department.

Industry sponsored studies will be invoiced for a one-time review fee.

NOTE: If you wish to add additional Co-Investigators after your Research Study Proposal has been approved by the IRB, you must submit Form-6 Addendum certifying that the person has met the requirements for Co-Investigator status, is sufficiently qualified to be added to your study as a clinical investigator, and has completed the mandated training program. Each new Investigator must sign and submit a Co-Investigator statement.

2. Proposal for research involving:

Check the applicable box(es).

3. Where are the data/specimens located now?

Provide the physical location of all data/specimens, before any research activity is undertaken.

Please note that Wills Eye Hospital Institutional Review Board review is limited to research conducted at Wills Eye Hospital. If your study requires use of data/specimens that are physically located outside of Wills Eye Hospital, separate review by the local IRB of each involved entity may be required.

3(a). Do you require access to Jefferson EMR (EPIC) for this study?

Check YES, NO or N/A.

Note that the Wills Eye Emergency Room is located in the Jefferson Hospital for Neuroscience building and is a part of Jefferson Hospital. Therefore, any research of the

Wills Eye ER records requires access to Jefferson's EMR and requires joint approval of both institutions. Contact the IRB Office immediately for additional guidance.

4. The data/specimens were originally gathered for:

Check **Clinical Use, Research Use**, or **N/A**.

Please Note: If data/specimens were originally gathered for research use, that original research must be IRB approved, and the purpose (whether clinical or research) for which the specimens were originally gathered must be met, as certified by the pathologist in charge or the clinical laboratory director.

5. Will any of the following identifiers be recorded from the medical record and/or used to label specimens?

Check either **YES** or **NO**. If your answer is **YES**, specify which identifiers will be recorded from the medical record or used to label specimens, and then specify what additional patient data will be recorded. Additionally, you must describe how privacy and confidentiality will be protected.

6. Do you plan, as part of this research, any intervention or interaction (e.g. questionnaire, interview) with the persons whose data and/or specimens will be used in this research?

Check either **YES** or **NO**. If your answer is **YES**, STOP HERE. A full research application may be required. Contact the IRB Office for additional guidance.

7. Do you request a waiver of the requirement to seek the informed consent (including HIPAA written authorization to use and disclose protected health information) of subjects?

Check either **YES** or **NO**. If an alteration is requested, you must specify in your Protocol which element(s) of informed consent is being altered, and you must fully describe the methods used to obtain and document consent.

If you are seeking a waiver or alteration, complete sections (a) through (d). If you are not seeking a waiver or alteration, go on to Question #8.

7(a). Will the research involve more than minimal risk to the health of subjects?

Check either **YES** or **NO**. If your answer is **YES**, your study does not qualify and your request will be denied.

7(b). Will the research involve more than minimal risk to the privacy of subjects' protected health information?

Check either **YES** or **NO**. If your answer is **YES**, your study does not qualify and your request will be denied.

7(c). If you had to obtain written informed consent and HIPAA authorization from each subject, would it still be feasible to conduct the study?

Check either **YES** or **NO**. If your answer is **YES**, your study does not qualify and your request will be denied. If your answer is **NO**, you must provide justification for why such a requirement would make the research impracticable. Please Note: impracticability is not to be understood as merely *difficult* or *inconvenient*.

7(d). Will the research yield information of direct clinical relevance for the subjects whose data is to be used in this study?

Check either **YES** or **NO**. If your answer is **YES**, and you wish to conduct the study without first obtaining the informed consent of the patients whose records/specimens you wish to use, please describe the manner in which the information of direct clinical relevance will be disclosed to the subjects whose data was used in the study. Specify what information you anticipate will be relevant to the subject, who will disclose that information, and when.

8. If the answer to Question #7 is “no,” will informed consent be Written or Oral?

Check either **Written** or **Oral**. If your answer is **Written**, you must provide a copy of the informed consent form proposed for use in this study. If your answer is **Oral**, you must provide a copy of the consent script proposed for use in this study, with a detailed description of how oral consent to participate in a research study will be documented. Please Note: oral informed consent is not sufficient for patient privacy (for use and disclosure of protected health information) purposes. Use the standard Wills Eye Hospital written authorization form for use and disclosure of protected health information or seek a separate waiver of HIPAA written authorization if you wish to use oral informed consent.

B. Research Study Protocol. Describe your Proposed Research Study according to the following format. Be as concise as possible without omitting necessary information.

1. Specific Aims

Describe the purpose(s) of your Proposed Research Study and the hypothesis to be tested.

2. Background

Describe prior studies and observations pertaining to your Proposed Research Study and cite pertinent references. If any of the data/specimens were originally collected for research use, provide the name of the IRB that reviewed and approved the original data/specimen collection, and the IRB Control # if applicable. If your study involves

specimens, the original purpose (whether clinical or research) for which the specimens were collected must be met prior to the removal of any excess, as certified by the pathologist/laboratory director in charge of those specimens.

3. Materials and Methods

Describe the materials and methods of your Proposed Research Study, including at least, the following:

- a) Physical location of the data/specimens prior to initiation of research;
- b) Physical location where research activities will take place, including data collection and analysis;
- c) Anticipated duration of study;
- d) Number of records/specimens to be reviewed;
- e) Range of dates of records/specimens to be reviewed; and
- f) Methods of data analysis.

4. Human Subjects

If your study requires the use of data/specimens of living individuals, describe the following:

- a) The characteristics of the subject population(s) under investigation, including expected age range, sex distribution, ethnic background, race, state of health, and any other pertinent factors;
- b) Inclusion and exclusion criteria for determining which data/specimens will be used;
- c) A list of the data that will be recorded from the medical record/specimen;
- d) The consent procedures to be followed, including the circumstances under which consent will be solicited and obtained, who will seek it, the nature of information to be provided to prospective subjects, and the method of documenting consent; or a statement that a waiver/alteration of the requirement to obtain and/or document consent is also being sought;
- e) Real or potential physical, psychological, social, legal, or unspecified risks to the subjects as a result of their participation in the study and comment on the likelihood and seriousness of these risks;
- f) The procedures for protecting against or minimizing any potential risks and comment on their probable effectiveness;
- g) Confidentiality safeguards that will be taken;
- h) The potential benefits of your proposed research to the subjects or to society in general;

5. Conflicts of Interest

Potential conflicts of interest and conflicts of interest must be disclosed by the Principal Investigators, Co-Investigators, and other key personnel with respect to all research studies. Please review the IRB's Policy Regarding Conflict of Interest Disclosure.

Conflicts of interest can exist when the Principal Investigator, Co-Investigator, or key personnel has an ownership or investment interest in the entities supporting the clinical

trial, when any of them accept compensation, gifts, gratuities from that sponsor and if the immediate family member of any of these personnel acts as a paid or unpaid manager, scientific advisor, or board member of that sponsor. These are very serious matters and should be given adequate and thoughtful consideration and disclosure must be made in all instances. By executing this Research Study Proposal, the Principal Investigator is certifying that this research project has been evaluated under the IRB's Policy on Disclosure of Conflicts of Interest and that no conflicts exist.

C. Research Study Informed Consent

Compose an Informed Consent Form or Informed Consent Script for your study according to the IRB's Policy and Procedure regarding Informed Consent. If Oral Consent will be used, you must describe the process for documenting consent, AND you must use the standard Wills Eye Hospital written HIPAA authorization for use and disclosure of personal health information or else seek a separate waiver of the requirement.

D. Principal and Co-Investigator Investigators' Statements

You and every Co-Investigator must read the appropriate Investigator's Statement and sign your name legibly on the appropriate line of the form and date the form before submitting the completed Research Study Proposal to the IRB.

INSTRUCTIONS for Completion Of

Wills Eye Hospital IRB Form-2 “Non-Formulary Drug Statement”

This form is to be completed and submitted to the IRB along with WEH IRB Form-1 if you have answered YES to Questions on Form-1 indicating that this form is required:

Complete the following fill-in items on Wills Eye Hospital IRB Form-2 as direction by the following instructions:

1. Name(s) and/or code number of drug: Obtain the name and/or code number of the drug from the manufacturer and enter this information on the lines provided.

2. Form(s) and strength(s) of drug: Obtain this information from the manufacturer and enter this information on the lines provided.

3. Drug(s) supplied by whom? Enter the name and location from which drug(s) will be obtained.

4. Mixing, reconstitution and/or dilution of drug(s): If any mixing, reconstitution and/or dilution of drug is necessary, attach a form stating the size/strength of the original drug and size/strength of drug to be dispensed. All calculations for dilutions, mixing, and/or reconstitution must be approved by the Directors of Research and Pharmacy. Attach a copy of approval letter(s).

5. Therapeutic Application: Obtain this information from the manufacturer and enter this information on the lines provided.

6. Dose(s) of drug -- Include normal dose per protocol and any variation from that dosage: Obtain this information from the manufacturer and from previous experimental studies and enter this information on the lines provided.

7. Special storage requirements for drug: Obtain this information from the manufacturer and from previous experimental studies regarding special storage requirements (include the need for refrigeration, humidity control, avoidance of light exposure, etc.) and enter this information on the lines provided.

8. Basic pharmacologic category of drug, chemical formula, generic name, and pharmacologic activity: Obtain this information from the manufacturer and from previous experimental studies and enter this information on the lines provided.

9. Medication to be used by whom? Check one of the three categories in the appropriate space.

10. Medication stored by whom? Check one of the three categories in the appropriate space. If you check “Other,” specify the name and location where medication will be stored on the line provided to this right of this option.

11. Medication dispensed by whom? Check one of the three categories in the appropriate space. If you check “Other,” specify the name and location where medication will be dispensed on the line provided to the right of this option.

12. In case of emergency, name of area and individual (other than pharmacy) where medication records are available (drug code, patient/drug records, etc.): Enter this information on the lines provided.

13. Name(s) of investigator(s) authorized to order medication: Indicate the name(s) of the investigator(s) who may order the drug(s) to be used in this study on the lines provided. If other than the Principal Investigator, these names should be listed on WEH IRB Form-1, Page 1, “Co-Investigator(s).”

14. What type of study is this? Indicate the type of study being conducted (e.g. single blind, double blind, randomized, sham-controlled, etc.) on the lines provided.

15(a) What are the recognized, reported, or possible ophthalmic/topical side or toxic effects of medication? Attach reports and/or bibliography. Obtain this information from the manufacturer and from previous experimental studies. Enter this information on the lines provided and attach materials as indicated.

15(b) What measures are to be taken if these effects are manifested? Obtain this information from the manufacturer and from previous experimental studies regarding what to do in the case of ophthalmic/topical side or toxic effects of the drug(s), and enter this information on the lines provided.

16(a) What are the recognized, reported, or possible systemic side or toxic effects of the medication? Attach reports and/or bibliography. Obtain this information from the manufacturer and from previous experimental studies. Enter this information on the lines provided and attach materials as indicated.

16(b) What measures are to be taken if these effects are manifested? Obtain this information from the manufacturer and from previous experimental studies regarding what to do in the case of systemic side or toxic effects of the drug(s) and enter this information on the lines provided.

17. What classes or specific medications are contraindicated during the course of this study? Obtain this information from the manufacturer and from previous experimental studies regarding those drug classes or particular drugs which would be rendered improper or undesirable during the course of this study, and enter this information on the lines provided.

18. What preexisting conditions or medication will exclude the patient from this study? Obtain this information from the manufacturer and from previous experimental studies regarding those pre-existing conditions and/or medications which would render a subject ineligible for the study, and enter this information on the lines provided.

19. Approval signature: Have the Principal Investigator sign and submit with Form-1 Research Study Proposal.

**INFORMED CONSENT CHECKLIST
WILLS EYE HOSPITAL IRB**

<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Description of requirement</u>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The name of the institution(s)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Principal investigator's name(s) and telephone number(s).
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The title of the project should be on the face page, and in the header of every subsequent page.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Project title and a short, non-technical title, in easy to understand words.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	An explanation of the purpose of the research.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The expected duration of the subject's participation.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	A statement that this is a "research" study.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Description of the procedures to be followed as well as identification of any procedures which are experimental, in lay language.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Number of patients at Wills Eye Hospital.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Is it a multi-center trial? If so, how many centers and how many patients will be involved?
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	How will patients be selected?
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	What intervention will be done.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Random assignment will be explained in lay terms, e.g. "You will be assigned by chance, like the flip of a coin."
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	When will intervention be done.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Has the intervention been used before in man or animals?
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	How many subjects have had the intervention before?
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	How long will the study involve patient participation?
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	What will be measured.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	How it will be measured (lab tests [if blood, discuss the amount in lay terms, e.g. teaspoonful], interviews, questionnaires).
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	When it will be measured.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Description of discomforts to be expected by the subject.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Pregnancy Statement.

- | | | | |
|--------------------------|--------------------------|--------------------------|---|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Description of any reasonably foreseeable risk or to the subject, including risk of being taken off therapy (placebo or wash-out periods) and risks of any procedures related to the research. |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Disclosure of appropriate alternative procedures or courses of treatment, if any. If alternative treatment is not applicable, state that the alternative is not to participate. |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Describe the extent, if any, to which confidentiality of records identifying the subject will be maintained. [Note the possibility that the Food and Drug Administration, National Institutes of health (NIH), Wills Eye Hospital internal audit, Wills Eye Hospital Institutional Review Board, or another sponsor may inspect the records]. |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Whether compensation (for injury) and/or medical treatments are available and where further information may be obtained. |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | A statement that refusal of the patient to participate in the research will not affect his or her medical care. |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Whether there is compensation or payment for injury, loss of work, or pain. |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Explanation of what individuals can expect to gain by directly participating in the planned research, and/or what benefits will accrue to society. [Do not include any financial or monetary compensation language.] |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 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. |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Statement that participation is voluntary, and that the refusal to participate, or subsequent withdrawal, will involve no penalty or loss of benefits to which the subject is otherwise entitled. |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | "I have read and understand I will receive a signed copy of this ___-paged informed consent form." |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Subject's name, signature, and date; signatures of the investigator and a witness. Signature cannot be on a page by itself. Subject will receive a signed copy of the form. |

5. REFERENCES

5.1 GLOSSARY OF TERMS

[From OHRP Website]

ABUSE-LIABLE. Pharmacological substances that have the potential for creating abusive dependency. Abuse-labile substances can include both illicit drugs (e.g. heroine) and licit drugs (e.g. methamphetamines).

ADAMHA. Alcohol, Drug Abuse, and Mental Health Administration; reorganized in October 1992 as the Substance Abuse and Mental Health Service Administration (SAMHSA). ADAMHA included the National Institute of Mental Health (NIMH), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), the Office for Substance Abuse Prevention (OSAP), and the Office for Treatment Intervention (OTI). NIMH, NIAAA, and NIDA are now part of the National Institutes of Health (NIH). (See also: SAMHSA).

ADJUVANT THERAPY. Therapy provided to enhance the effect of a primary therapy; auxiliary therapy.

ADVERSE EFFECT. An undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention (e.g., headache following spinal tap or intestinal bleeding associated with aspirin therapy).

ASSENT. Agreement by an individual not competent to give legally valid informed consent (e.g., a child or cognitively impaired person) to participate in research.

ASSURANCE. A formal written, binding commitment that is submitted to a federal agency in which an institution promises to comply with applicable regulations governing research with human subjects and stipulates the procedures through which compliance will be achieved.

AUTHORIZED INSTITUTIONAL OFFICIAL. An officer of an institution with the authority to speak for an legally commit the institution to adherence to the requirements of the federal regulations regarding the involvement of human subjects in biomedical and behavioral research.

AUTONOMY. Personal capacity to consider alternatives, make choices, and act without undue influence or interference of others.

BELMONT REPORT. A statement of basic ethical principles governing research involving human subjects issued by the National Commission for the Protection of Human Subjects in 1978.

BENIFICENCE. An ethical principle discussed in the Belmont Report that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: (1) do no harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm.

BENEFIT. A valued or desired outcome; an advantage.

BIOLOGIC. Any therapeutic serum, toxin, anti-toxin, or analogous microbial product applicable to the prevention, treatment, or cure of diseases or injuries.

BLIND STUDY DESIGNS. See: Masked Study Designs; Double-Masked Design; and Single-Masked Design.

CADAVER. The body of a deceased person.

CASE-CONTROL STUDY. A study comparing persons with a given condition or disease (the cases) and persons without the condition or disease (the controls) with respect to antecedent factors. (See also: Retrospective Studies.)

CAT SCAN. Abbreviation for Computerized Axial Tomography, an X-ray technique for producing images of internal bodily structures through the assistance of a computer.

CHIDLREN. Persons who have not attained the legal age for consent or treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted.

CDC. Centers for Disease Control and Prevention; an agency within the Public Health Service, Department of Health and Human Services.

CLASS I, II, III DEVICES. Classification by the Food and Drug Administration of medical devices according to potential risks or hazards.

CLINICAL TRIAL. A controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or devices or of behavioral interventions.

COGNITIVELY IMPAIRED. Having either a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders, or dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional function to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interest.

COHORT. A group of subjects initially identified as having one or more characteristics in common who are followed over time. In social science research, this term may refer to any group

of persons who are born at about the same time and share common historical or cultural experiences.

COMPENSATION. Payment or medical care provided to subjects injured in research; does not refer to payment (remuneration) for participation in research. (Compare: Remuneration.)

COMPETENCE. Technically, a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. (See also: Incompetence, Incapacity.)

CONFIDENTIALITY. Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure.

CONSENT. See: Informed Consent.

CONTRACT. An agreement; as used here, an agreement that a specific research activity will be performed at the request, and under the direction, of the agency providing the funds. Research performed under contract is more closely controlled by the agency than research performed under a grant. (Compare: Grant.)

CONTROL (SUBJECTS) or CONTROLS. Subject(s) used for comparison who are not given a treatment under study or who do not have a given condition, background, or risk factor that is the object of the study. Control conditions may be concurrent (occurring more or less simultaneously with the condition under study) or historical (preceding the condition under study). When the present condition of subjects is compared with their own condition on a prior regimen or treatment, the study is considered historically controlled.

CONTRAINDICATED. Disadvantageous, perhaps dangerous; a treatment that should not be used in certain individuals or conditions due to risks (e.g., a drug may be contraindicated for pregnant women or persons with high blood pressure).

CORRELATION COEFFICIENT. A statistical index of the degree of relationship between two variables. Values of correlation coefficients range from -1.00 through zero to +1.00. A correlation coefficient of 0.00 indicates no relationship between the variables. Correlations approaching -1.00 or +1.00 indicate strong relationships between the variables. However, casual inferences about the relationship between two variables can never be made on the basis of correlation coefficients, no matter how strong a relationship is indicated.

CROSS-OVER DESIGN. A type of clinical trial in which each subject experiences, at different times, both the experimental and control therapy. For example, half of the subjects might be randomly assigned first to the control group and then to the experimental intervention, while the other half would have the sequence reversed.

DATA AND SAFETY MONITORING BOARD. A committee of scientists, physicians, statisticians, and others that collects and analyzes data during the course of a clinical trial to monitor for adverse effects and other trends (such as an indication that one treatment is significantly better than another, particularly when one arm of the trial involves a placebo control) that would warrant modification or termination of the trial or notification of subjects about new information that might affect their willingness to continue in the trial.

DEAD FETUS. An expelled or delivered fetus that exhibits no heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord (if still attached). Generally, some organs, tissues, and cells (referred to collectively as fetal tissue) remain alive for varying periods of time after the total organism is dead.

DEBRIEFING. Giving subjects previously undisclosed information about the research project following completion of their participation in research. (Note that this usage, which occurs within the behavioral sciences, departs from standard English, in which debriefing is obtaining rather than imparting information.)

DECLARATION OF HELSINKI. A code of ethics for clinical research approved by the World Medical Association in 1964 and widely adopted by medical associations in various countries. It was revised in 1975 and 1989.

DEPENDENT VARIABLES. The outcomes that are measured in an experiment. Dependent variables are expected to change as a result of an experimental manipulation of the independent variable(s).

DESCRIPTIVE STUDY. Any study that is not truly experimental (e.g., quasi-experimental studies, correlational studies, record reviews, case histories, and observational studies).

DEVICE (MEDICAL). See: Medical Device.

DHEW. A federal agency: U.S. Department of Health, Education and Welfare; reorganized in 1980 as the Department of Health and Human Services (DHHS) and the Department of Education.

DHHS. A federal agency: U.S. Department of Health and Human Services; formerly the Department of Health, Education and Welfare (DHEW).

DIAGNOSTIC (PROCEDURES). Tests used to identify a disorder or disease in a living person.

DOUBLE-MASKED DESIGN. A study in which neither the investigators nor the subjects know the treatment group assignments of individual subjects. Sometimes referred to as “double-blind.”

DRUG. Any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation, or prevention of disease or other abnormal conditions.

EMANCIPATED MINOR. A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law (for such purposes as consenting to medical care), but who are entitled to treatment as if they had by virtue of assuming adult responsibilities such as being self-supporting and not living at home, marriage, or procreation. (See also: Mature Minor).

EMBRYO. Early stages of a developing organism, broadly used to refer to stages immediately following fertilization of an egg through implantation and very early pregnancy (i.e., from conception to the eighth week of pregnancy). (See also: Fetus.)

EPIDEMIOLOGY. A scientific discipline that studies the factors determining the causes, frequency, and distribution of diseases in a community or given population.

EQUITABLE. Fair or just; used in the context of selection of subjects to indicate that the benefits and burdens of research are fairly distributed.

ETHICS ADVISORY BOARD. An interdisciplinary group that advises the Secretary of DHHS on general policy matters and on research proposals (or classes of proposals) that pose ethical problems.

ETHNOGRAPHIC RESEARCH. Ethnography is the study of people and their culture. Ethnographic research, also called fieldwork, involves observation of and interaction with the persons or group being studied in the group's own environment, often for long periods of time. (See also: Fieldwork.)

EXPANDED AVAILABILITY. Policy and procedure that permits individuals who have serious or life-threatening diseases for which there are no alternative therapies to have access to investigational drugs and devices that may be beneficial to them. Examples of expanded availability mechanisms include Treatment INDs, Parallel Track, and open study protocols.

EXPEDITED REVIEW. Review of proposed research by the IRB chair or a designated voting member or group of voting members rather than by the entire IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research.

EXPERIMENTAL. Term often used to denote a therapy (drug, device, procedure) that is unproven or not yet scientifically validated with respect to safety and efficacy. A procedure may be considered "experimental" without necessarily being part of a formal study (research) to evaluate its usefulness. (See also: Research.)

EXPERIMENTAL STUDY. A true experimental study is one in which subjects are randomly assigned to groups that experience carefully controlled interventions manipulated by the experimenter according to a strict logic allowing casual inference about the effects of the interventions under investigation. (See also: Quasi-Experimental Study).

FALSE NEGATIVE. When a test wrongly shows an effect or condition to be absent (e.g., that a woman is not pregnant when, in fact, she is).

FALSE POSITIVE. When a test wrongly shows an effect or condition to be present (e.g., that a woman is pregnant when, in fact, she is not).

FDA. Food and Drug Administration; an agency of the federal government established by Congress in 1912 and presently part of the Department of Health and Human Services.

FEDEARL POLICY (THE). The federal policy that provides regulations for the involvement of human subjects in research. The Policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency that takes appropriate administrative action to make the Policy applicable to such research. Currently, sixteen federal agencies have adopted the Federal Policy. (Also known as “Common Rule.”)

FETAL MATERIAL. The placenta, amniotic fluid, fetal membranes, and umbilical cord.

FETUS. The product of conception from the time of implantation until delivery. If the delivered or expelled fetus is viable, it is designated an infant. The term “fetus” generally refers to later phases of development; the term “embryo” is usually used for earlier phases of development. (See also: Embryo.)

FIELDWORK. Behavioral, social, or anthropological research involving the study of persons or groups in their own environment and without manipulation for research purposes (distinguished from laboratory or controlled settings). (See also: Ethnographic Research.)

510(K) DEVICE. A medical device that is considered substantially equivalent to a device that was or is being legally marketed. A sponsor planning to market such a device must submit notification to the FDA 90 days in advance of placing the device on the market. If the FA concurs with the sponsor, the device may then be marketed. 510(k) is the section of the Food, Drug and Cosmetic Act that describes premarket notification; hence the designation “510(k) device.”

FULL BOARD REVIEW. Review of proposed research at a convened meeting at which a majority of the membership of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those members present at the meeting.

GENE THERAPY. The treatment of genetic disease accomplished by altering the genetic structure of either somatic (nonreproductive) or germline (reproductive) cells.

GENERAL ASSURANCE. Obsolete term, previously used to denote an institutional assurance covering multiple research projects. (See also: Assurance.)

GENERAL CONTROLS. Certain FDA statutory provisions designed to control the safety of marketed drugs and devices. The general controls include provisions on adulteration, misbranding, banned devices, good manufacturing practices, notification and record keeping, and other sections of the Medical Device Amendments to the Food, Drug and Cosmetic Act.

GENETIC SCREENING. Tests to identify persons who have an inherited predisposition to a certain phenotype or who are at risk of producing offspring with inherited diseases or disorders.

GENOTYPE. The genetic constitution of an individual.

GRANT. Financial support provided for research study designed and proposed by the principal investigator(s). The granting agency exercises no direct control over the conduct of approved research supported by a grant. (Compare: Contract.)

GUARDIAN. An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care.

HELSINKI DECLARATION. See: Declaration of Helsinki.

HISTORICAL CONTROLS. Control subjects (followed at some time in the past or for whom data are available through records) who are used for comparison with subjects being treated concurrently. The study is considered historically controlled when the present condition of subjects is compared with their own condition on a prior regimen or treatment.

HUMAN IN VITRO FERTILIZATION. Any fertilization involving human sperm and ova that occurs outside the human body.

HUMAN SUBJECTS. Individuals whose physiologic or behavioral characteristics and response are the object of study in a research project. Under the federal regulations, human subjects are defined as: living individual(s) about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information.

IDE. See: Investigational Device Exemptions.

INCAPACITY. Refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence. (See also: Incompetence.)

INCOMPETENCE. Technically, a legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity. (See also: Incapacity.)

IND. See: Investigational New Drug.

INDEPENDENT VARIABLES. The conditions of an experiment that are systematically manipulated by the investigator.

INFORMED CONSENT. A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventative procedure. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the institution or agents thereof from liability for negligence.

INSTITUTION (1). Any public or private entity (including federal, state, and local agencies).

INSTITUTION (2). A residential facility that provides food, shelter, and professional services (including treatment, skilled nursing, intermediate or long-term care, and custodial or residential care). Examples include general, mental, or chronic disease hospitals; inpatient community mental health centers; halfway houses and nursing homes; alcohol and drug addiction treatment centers; homes for the aged or dependent, residential schools for the mentally or physically handicapped; and homes for dependent and neglected children.

INSTITUTIONAL REVIEW BOARD. A specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral research.

INSTITUTIONALIZED. Confined, either voluntarily or involuntarily (e.g., a hospital, prison, or nursing home).

INSTITUTIONALIZED COGNITIVELY IMPAIRED. Persons who are confined, either voluntarily or involuntarily, in facilities for care of the mentally or otherwise disabled (e.g., a psychiatric hospital, home, or school for the retarded).

INVESTIGATIONAL DEVICE EXEMPTIONS (IDE). Exemptions from certain regulations found in the Medical Device Amendments that allow shipment of unapproved devices for use in clinical investigations.

INVESTIGATIONAL NEW DRUG OR DEVICE. A drug or device permitted by FDA to be tested in humans but not yet determined to be safe and effective for a particular use in the general population and not yet licensed for marketing.

INVESTIGATOR. In clinical trials, an individual who actually conducts an investigation. Any interventions (e.g., drugs) involved in the study are administered to subjects under the immediate direction of the investigator. (See also: Principal Investigator.)

IN VITRO. Literally, “in glass” or “test tube;” used to refer to processes that are carried out outside the living body, usually in the laboratory, as distinguished from in vivo.

IN VIVO. Literally, “in the living body;” processes, such as the absorption of a drug by the human body, carried out in the living body rather than in a laboratory (in vitro).

IRB. See: Institutional Review Board.

JUSTICE. An ethical principle discussed in the Belmont Report requiring fairness in distribution of burdens and benefits; often expressed in terms of treating persons of similar circumstances or characteristics similarly.

LACTATION. The period of time during which a woman is providing her breast milk to an infant or child.

LEGALLY AUTHORIZED REPRESENTATIVE. A person authorized either by statute or by court appointment to make decisions on behalf of another person. In human subjects research, 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.

LOD SCORE. An expression of the probability that a gene and a marker are lined.

LONGITUDINAL STUDY. A study designed to follow subjects forward through time.

MASKED STUDY DESIGNS. Study designed comparing two or more interventions in which either the investigators, the subjects, or some combination thereof do not know the treatment group assignments of individual subjects. Sometimes called “blind” study designs. (See also: Double-Masked Design; Single-Masked Design.)

MATURE MINOR. Someone who has not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (e.g., consenting to medical care). Note that a mature minor is not necessarily an emancipated minor. (See also: Emancipated Minor.)

MEDICAL DEVICE. A diagnostic or therapeutic article that does not achieve any of its principal intended purposes through chemical action within or on the body. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intraocular lenses, and orthopedic pins or other orthopedic equipment.

MEDICAL DEVICE AMENDMENTS (MDA). Amendments to the Federal Food, Drug and Cosmetic Act passed in 1979 to regulate the distribution of medical devices and diagnostic products.

MENTALLY DISABLED. See: Cognitively Impaired.

METABOLISM (OF A DRUG). The manner in which a drug is acted upon (or taken up, converted to other substances, or excreted) by various organs in the body.

MINIMAL RISK. A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed 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. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

The definition of minimal risk for research involving prisoners differs somewhat from that given for noninstitutionalized adults.

MONITORING. The collection and analysis of data as the project progresses to assure the appropriateness of the research, its design and subject protections.

NATIONAL COMMISSION. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. An interdisciplinary advisory body, established by Congressional legislation in 1974, which was in existence until 1978, and which issued a series of reports and recommendations on ethical issues in research and medicine, many of which are now embodied in federal regulations.

NDA. See: New Drug Application.

NEW DRUG APPLICATION. Request for FDA approval to market a new drug.

NIAAA. National Institute on Alcohol Abuse and Alcoholism; an institute in NIH.

NIDA. National Institute on Drug Abuse; an institute in NIH.

NIH. National Institutes of Health; a federal agency within the Public Health Service, DHHS, comprising 21 institutes and centers. It is responsible for carrying out and supporting biomedical and behavioral research.

NIMH. National Institute of Mental Health; an institute in NIH.

NONAFFILIATED MEMBER. Member of an Institutional Review Board who has no ties to the parent institution, its staff, or faculty. This individual is usually from the local community (e.g., minister, business person, attorney, teacher, homemaker).

NONSIGNIFICANT RISK DEVICE. An investigational medical device that does not present significant risk to the patient. (See also: Significant Risk Device.)

NONTHERAPEUTIC RESEARCH. Research that has no likelihood or intent of producing a diagnostic, preventive, or therapeutic benefit to the current subjects, although it may benefit subjects with a similar condition in the future.

NONVIABLE FETUS. An expelled or delivered fetus which, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy. Although it may be presumed that an expelled or delivered fetus is nonviable at a gestational age less than 20 weeks and weight less than 500 grams, a specific determination as to viability must be made by a physician in each instance. (See also: Viable Infant.)

NORMAL VOLUNTEERS. Volunteer subjects used to study a normal physiology and behavior or who do not have the condition under study in a particular protocol, used as comparisons with subjects who do have the condition. “Normal” may not mean normal in all respects. For example, patients with broken legs (if not on medication that will affect the results) may serve as normal volunteers in studies on metabolism, cognitive development, and the like. Similarly, patients with heart disease but without diabetes may be the “normals” in a study of diabetes complicated by heart disease.

NULL HYPOTHESIS. The proposition, to be tested statistically, that the experimental intervention has “no effect,” meaning that the treatment and control groups will not differ as a result of the intervention. Investigators usually hope that the data will demonstrate some effect from the intervention, thereby allowing the investigator to reject the null hypothesis.

NUREMBERG CODE. A code of research ethics developed during the trials of Nazi war criminals following World War II and widely adopted as a standard during the 1950s and 1960s for protecting human subjects.

OPEN DESIGN. An experimental design in which both the investigator(s) and the subjects know the treatment group(s) to which the subjects are assigned.

PATERNALISM. Making decisions for others against or apart from their wishes with the intent of doing them good.

PERMISSION. The agreement of parent(s) or guardian to the participation of their child or ward in research.

PHARMACOLOGY. The scientific discipline that studies the action of drugs on living systems (animals or human beings).

PHASE 1, 2, 3, 4 DRUG TRIALS. Different stages of testing drugs in humans, from first application in humans (Phase 1) through limited and broad clinical tests (Phase 3), to postmarketing studies (Phase 4).

PHASE 1 DRUG TRIAL. Phase 1 trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses

(to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of action in biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.

PHASE 2 DRUG TRIAL. Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects.

PHASE 3 DRUG TRIAL. Phase 3 trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, efficacy, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient-subjects.

PHASE 4 DRUG TRIAL. Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

PHENOTYPE. The physical manifestations of a gene function.

PHS. Public Health Service. Part of the U.S. Department of Health and Human Services, it includes FDA, NIH, CDC, SAMHSA, and HRSA.

PLACEBO. A chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side effects may reflect imagination or anticipation rather than actual power of a drug.

POSTAMENDMENTS DEVICES. Medical devices marketed after enactment of the 1976 Medical Devices Amendments.

PREAMENDMENTS DEVICES. Medical devices marketed before enactment of the 1976 Medical Devices Amendments.

PRECLINICAL INVESTIGATIONS. Laboratory and animal studies designed to test the mechanisms, safety, and efficacy of an intervention prior to its applications to humans.

PREDICATE DEVICES. Currently legally marketed devices to which new devices may be found substantially equivalent under the 510(k) process.

PREGNANCY. The period of time from confirmation of implantation of a fertilized egg within the uterus until the fetus has entirely left the uterus (i.e., has been delivered). Implantation is confirmed through a presumptive sign of pregnancy such as missed menses or a positive pregnancy test. This “confirmation” may be in error, but, for research purposes, investigators would presume that a living fetus was present until evidence to the contrary was clear. Although fertilization occurs a week or more beyond implantation, the current inability to detect the fertilization event or the presence of a newly fertilized egg makes a definition of pregnancy based on implantation necessary.

PREMARKET APPROVAL. Process of scientific and regulatory review by the FDA to ensure the safety and effectiveness of Class III devices.

PRESIDENT’S COMMISSION. President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. An interdisciplinary advisory group, established by congressional legislation in 1978, which was in existence until 1983, and which issued reports on ethical problems in health care and in research involving human subjects.

PRINCIPAL INVESTIGATOR. The scientist or scholar with primary responsibility for the design and conduct of a research project. (See also: Investigator.)

PRISONER. An individual involuntarily confined in a penal institution, including persons: (1) sentenced under a criminal or civil statute; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (e.g., for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution.

PRIVACY. Control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally or intellectually) with others.

PROBAND. The person whose case serves as the stimulus for the study of other members of the family to identify the possible genetic factors involved in a given disease, condition, or characteristic.

PROPHYLACTIC. Preventative or protective; a drug, vaccine, regimen, or device designed to prevent, or provide protection against, a given disease or disorder.

PROSPECTIVE STUDIES. Studies designed to observe outcomes or events that occur subsequent to the identification of the group of subjects to be studied. Prospective studies need not involve manipulation or intervention but may be purely observational or involve only the collection of data.

PROTOCOL. The formal design or plan of an experiment or research activity; specifically, the plan submitted to an IRB for review and to an agency for research support. The protocol includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen(s), and the proposed methods of analysis that will be performed on the collected data.

PURITY. The relative absence of extraneous matter in a drug or vaccine that may or may not be harmful to the recipient or deleterious to the product.

QUASI-EXPERIMENTAL STUDY. A study that is similar to a true experimental study except that it lacks random assignments of subjects to treatment groups. (See also: Experimental Study.)

RADIOACTIVE DRUG. Any substance defined as a drug in §§201(b)(1) of the Federal Food, Drug and Cosmetic Act that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons. Included are any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of a radioactive drug and “radioactive biological products,” as defined in 21 CFR 600.3(ee). Drugs such as carbon-containing compounds or potassium-containing salts containing trace quantities of naturally occurring radionuclides are not considered radioactive drugs.

RADIOACTIVE DRUG RESEARCH COMMITTEE (RDRC). An institutional committee responsible for the use of radioactive drugs in human subjects for research purposes. Research involving human subjects that proposes to use radioactive drugs must meet various FDA requirements, including limitations on the pharmacological dose and the radiation dose. Furthermore, the exposure to radiation must be justified by the quality of the study and the importance of the information it seeks to obtain. The committee is also responsible for continuing review of the drug to ensure that the research continues to comply with FDA requirements, including reporting obligations. The committee must include experts in nuclear medicine and the use of radioactive drugs, as well as other medical and scientific members.

RADIOPAQUE CONTRAST AGENTS. Materials that stop or attenuate radiation that is passed through the body, creating an outline or film of the organ(s) being examined. Contrast agents, sometimes called “dyes,” do not contain radioisotopes. When such agents are used, exposure to radiation results only from the X-ray equipment used in the examination. The chemical structure of radiopaque contrast agents can produce a variety of adverse reactions, some of which may be severe and possible life-threatening in certain individuals.

RADIOPHARMACEUTICALS. Drugs (compounds or materials) that may be labeled or tagged with a radioisotope. These materials are largely physiological or subpharmacological in action, and, in many cases, function much like materials found in the body. The principal risk associated with these materials is the consequent radiation exposure to the body or to specific organ systems with they are injected into the body.

RANDOM, RANDOM ASSIGNMENT, RANDOMIZATION, RANDOMIZED. Assignment of subjects to different treatments, interventions, or conditions according to chance rather than systematically (e.g., as dictated by the standard or usual response to their condition, history, or prognosis, or according to demographic characteristics). Random assignment of subjects to conditions is an essential element of experimental research because it makes more likely the probability that differences observed between subject groups are the result of the experimental intervention.

RECOMBINANT DNA TECHNOLOGY. “The ability to chop up DNA, the stuff of which genes are made, and move the pieces, which permits the direct examination of the human genome,” and the identification of the genetic components of a wide variety of disorders. Recombinant DNA technology is also used to develop diagnostic screens and tests, as well as drugs and biologics for treating diseases with genetic components.

REM. Acronym for Roentgen Equivalent in Man; the unit of measurement for a dose of an ionizing radiation that produces the same biological effect as a unit of absorbed dose (1 rad) of ordinary X-rays. One millirem is equal to 1/1000 of a rem.

REMISSION. A period in which the signs and symptoms of a disease are diminished or in abeyance. The term “remission” is used when one cannot say with confidence that the disease has been cured.

REMUNERATION. Payment for participation in research. (NOTE: It is wise to confine use of the term “compensation” to payment or provision or care for research-related injuries.) (Compare: Compensation.)

RESEARCH. A systematic investigation (i.e., the gathering and analysis of information) designed to develop or contribute to generalizable knowledge.

RESPECT FOR PERSONS. An ethical principle discussed in the Belmont Report requiring that individual autonomy be respected and that persons with diminished autonomy be protected.

RETROSPECTIVE STUDIES. Research conducted by reviewing records from the past (e.g., birth and death certificates, medical records, school records, or employment records) or by obtaining information about past events elicited through interviews or surveys. Case control studies are an example of this type of research.

REVIEW (OF RESEARCH). The concurrent oversight of research on a periodic basis by an IRB. In addition to the at least annual reviews mandated by the federal regulations, reviews may, if deemed appropriate, also be conducted on a continuing or periodic basis.

RISK. The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only “minimal risk.” (See also: Minimal Risk.)

SAMHSA. Substance Abuse and Mental Health Services Administration; includes the Center for Substance Abuse Prevention, the Center for Substance Abuse Treatment and the Center on Mental Health Services. Previously the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). (See also: ADAMHA.)

SCIENTIFIC REVIEW GROUP. A group of highly regarded experts in a given field, convened by NIH to advise NIH on the scientific merit of applications for research grants and contracts. Scientific review groups are also required to review the ethical aspects of proposed involvement of human subjects. Various kinds of scientific review groups exist, and are known by different names in different institutes of the NIH (e.g., Study Selections, Initial Review Groups, Contract Review Committees, or Technical Evaluation Committees).

SECRETARY. A U.S. Cabinet Officer. In the context of DHHS-conducted or –supported research, usually refers to the Secretary of Health and Human Services.

SIGNIFICANT RISK DEVICE. An investigational medical device that presents a potential for serious risk to the health, safety, or welfare of the subject.

SINGLE-MASKED DESIGN. Typically, a study design in which the investigator, but not the subject, knows the identity of the treatment assignment. Occasionally the subject, but not the investigator, knows the assignment. Sometimes called “single-blind design.”

SITE VISIT. A visit by agency officials, representatives, or consultants to the location of research activity to assess the adequacy of IRB protection of human subjects or the capability of personnel to conduct the research.

SOCIAL EXPERIMENTATION. Systematic manipulation or, or experimentation in, social or economic systems; used in planning public policy.

SPONSOR (OF A DRUG TRIAL). A person or entity that initiates a clinical investigation of a drug usually the drug manufacturer or research institution that developed the drug. The sponsor does not actually conduct the investigation, but rather distributes the new drug to investigators and physicians for clinical trials. The drug is administered to subjects under the immediate direction of an investigator who is not also a sponsor. A clinical investigator may, however, serve as a sponsor-investigator. The sponsor assumes responsibility for investigation the new

drug, including responsibility for compliance with applicable laws and regulations. The sponsor, for example, is responsible for obtaining FDA approval to conduct a trial and for reporting the results of the trial to the FDA.

SPONSOR-INVESTIGATOR. An individual who both initiate and actually conducts, alone or with others, a clinical investigation. Corporations, agencies, or other institutions do not qualify as sponsor-investigators.

STATISTICAL SIGNIFICANCE. A determination of the probability of obtaining the particular distribution of the data on the assumption that the null hypothesis is true. Or, more simply put, the probability of coming to a false positive conclusion. If the probability is less than or equal to a predetermined value (e.g., 0.05 or 0.01), then the null hypothesis is rejected at that significance level (0.05 or 0.01).

STERILITY (1). The absence of viable contaminating microorganisms; aseptic state.

STERILITY (2). The inability to procreate; the inability to conceive or induce conception.

STUDY SECTION. See: Scientific Review Group.

SUBJECTS (HUMANS). See: Human Subjects.

SURVEYS. Studies designed to obtain information from a large number of respondents through written questionnaires, telephone interviews, door-to-door canvassing, or similar procedures.

THERAPEUTIC INTENT. The research physician's intent to provide some benefit to improving a subject's condition (e.g., prolongation of life, shrinkage of tumor, or improved quality of life, even though cure or dramatic improvement cannot necessarily be effected.) This term is sometimes associated with Phase 1 drug studies in which potentially toxic drugs are given to an individual with the hope of inducing some improvement in the patient's condition as well as assessing the safety and pharmacology of a drug.

THERAPY. Treatment intended and expected to alleviate a disease or disorder.

UNIFORM ANATOMICAL GIFT ACT. Legislation adopted by all 50 States and the District of Columbia that indicates procedures for donation or all or part of a decedent's body for such activities as medical education, scientific research, and organ transplantation.

VACCINE. A biological product generally made from an infectious agent or its components a virus, bacterium, or other microorganism that is killed (inactive) or live-attenuated (active, although weakened). Vaccines may also be biochemically synthesized or made through recombinant DNA techniques.

VARIABLE (NOUN). An element or factor that the research is designed to study, either as an experimental intervention or a possible outcome (or factor affecting the outcome) of that intervention.

VIABLE INFANT. When referring to a delivered or expelled fetus, the term “viable infant” means likely to survive to the point of sustaining life independently, given the benefits of available medical therapy. This judgment is made by a physician. In accordance with DHHS regulations, the Secretary, HHS, may publish guidelines to assist in the determination of viability. Such guidelines were published in 1975, and specify an estimated gestational age of 20 weeks or more and a body weight of 500 grams or more as indices of fetal viability. These indices depend on the state of present technology and may be revised periodically. (See also: Nonviable Fetus.)

VOLUNTARY. Free of coercion, duress, or undue inducement. Used in the research context to refer to a subject’s decision to participate (or to continue to participate) in a research activity.

5.2. Mandatory Training for Investigators

Human Subjects Protection education & HIPAA education are required of all key personnel involved in research with human subjects. To fulfill this requirement, Wills Eye Hospital and its partner Thomas Jefferson University now use the CITI Program, which is supported by the University of Miami.

- All new users are required to complete two courses: Biomedical Research Certification Basic Course and the accompanying Good Clinical Practice Basic Course.
- Biomedical Research Certification *will require* a Refresher Course every two years; Good Clinical Practice *will require* a Refresher Course every three years.

The CITI Program can be found at: <https://www.citiprogram.org>. Contact the IRB Office if you need instructions for completion.