Institutional Review Board (IRB) Resource Guide

The IRB Resource Guide was compiled by Ada Sue Selwitz and Jennifer Harris, University of Kentucky
Updated August 2014

Copyright 2014 by Public Responsibility in Medicine and Research (PRIM&R), Inc. All rights reserved. This book or parts thereof may not be used or reproduced in any manner without written permission.
### 2014 IRB Resource Guide: Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethics of Human Subjects Research</strong></td>
<td>1-24</td>
</tr>
<tr>
<td>Nuremberg Code</td>
<td>1</td>
</tr>
<tr>
<td>Declaration of Helsinki</td>
<td>2</td>
</tr>
<tr>
<td>Belmont Report</td>
<td>10</td>
</tr>
<tr>
<td>Council for International Organizations of Medical Sciences</td>
<td>22</td>
</tr>
<tr>
<td><strong>Basic IRB Regulations</strong></td>
<td>25-80</td>
</tr>
<tr>
<td>FDA 21 CFR 50</td>
<td>25</td>
</tr>
<tr>
<td>FDA 21 CFR 56</td>
<td>40</td>
</tr>
<tr>
<td>DHHS 45 CFR 46</td>
<td>53</td>
</tr>
<tr>
<td><strong>Selected Auxiliary Regulations/Policy</strong></td>
<td>81-298</td>
</tr>
<tr>
<td>Department of Health and Human Services (DHHS)</td>
<td>81-166</td>
</tr>
<tr>
<td>OHRP Human Research FAQs</td>
<td>81</td>
</tr>
<tr>
<td>OHRP Compliance Activities – Common Findings &amp; Guidance</td>
<td>149</td>
</tr>
<tr>
<td><strong>Food and Drug Administration (FDA)</strong></td>
<td>167-270</td>
</tr>
<tr>
<td>21 CFR 312 Investigational New Drug Application</td>
<td>167</td>
</tr>
<tr>
<td>21 CFR 812 Investigational Device Exemptions</td>
<td>221</td>
</tr>
<tr>
<td>Acute Care Waiver of Informed Consent Reference</td>
<td>246</td>
</tr>
<tr>
<td>Summary of FDA Regulations on Exemption from IND Requirements</td>
<td>251</td>
</tr>
<tr>
<td>Summary of FDA Regulations on Investigational Device Exemption and Exemption from IDE Requirements</td>
<td>261</td>
</tr>
<tr>
<td>Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Devices</td>
<td>265</td>
</tr>
<tr>
<td>Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Drugs</td>
<td>268</td>
</tr>
<tr>
<td>FDA Bioresearch Monitoring Program</td>
<td>270</td>
</tr>
<tr>
<td><strong>Other Selected Agency Information</strong></td>
<td>271-298</td>
</tr>
<tr>
<td>Summary of Requirements for Department of Defense Supported Human Research</td>
<td>271</td>
</tr>
<tr>
<td>U.S. Dept. of Education/Protection of Pupil Rights Amendment (PPRA)</td>
<td>277</td>
</tr>
<tr>
<td>Summary of Department of Education (DoED) Requirements</td>
<td>280</td>
</tr>
<tr>
<td>Summary of Department of Energy (DoE) Requirements</td>
<td>282</td>
</tr>
<tr>
<td>Summary of Department of Justice (DoJ), National Institute of Justice (NIJ), and Bureau of Prisons (BoP) Requirements</td>
<td>284</td>
</tr>
<tr>
<td>U.S. Department of Veteran Affairs</td>
<td>289</td>
</tr>
<tr>
<td>Summary of Environmental Protection Agency (EPA) Requirements</td>
<td>290</td>
</tr>
<tr>
<td>University of Kentucky (UK) Family Educational Rights and Privacy Act (FERPA) Guidance</td>
<td>294</td>
</tr>
</tbody>
</table>
# Table of Contents (Continued)

**IRB Expedited and Exemption Review Mechanisms** ............................... 299-312

- Issues to be Addressed When Conducting Exempt Review .................. 299
- Issues to be Addressed When Conducting Expedited Review ................. 309

**Educational Materials and Useful References** ................................. 313-335

- Educational Materials ................................................................. 313
- OHRP LISTSERV ................................................................. 320
- Electronic/Web Sites ............................................................... 321
- OHRP Contacts ................................................................. 326
- FDA Contacts ................................................................. 329
- U.S. Department of Veterans Affairs Contacts ............................... 333
Ethics of Human Subject Research

Nuremberg Code

Declaration of Helsinki

Belmont Report

Council for International Organizations of Medical Sciences
The Nuremberg Code

1. The voluntary consent of the human subject is absolutely essential.

   This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably 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 seemed 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 judgement required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA 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 in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by
individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

   Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

   Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

   When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**
19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

   All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21. 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 adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

   The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

   In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and
standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study’s findings and conclusions.

**Privacy and Confidentiality**

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

**Informed Consent**

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, 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, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject’s dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain
for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

   Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

   Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

   and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

   Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest
publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

© World Medical Association, Inc. - All Rights reserved.
© Asociación médica mundial - Todos los derechos reservados.
© L'Association Médicale Mondiale - Tous droits réservés.
THE BELMONT REPORT
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, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: (i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research and (iv) the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 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
Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.
Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.
Robert E. Cooke, M.D., President, Medical College of Pennsylvania.
Dorothy I. Height, President, National Council of Negro Women, Inc.
Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.
Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.
Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.
*** David W. Louisell, J.D., Professor of Law, University of California at Berkeley.
Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.
Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.

*** Deceased.

TABLE OF CONTENTS

Ethical Principles and Guidelines for Research Involving Human Subjects

A. Boundaries Between Practice and Research

B. Basic Ethical Principles
   1. Respect for Persons
   2. Beneficence
   3. Justice
C. Applications
   1. Informed Consent
   2. Assessment of Risk and Benefits
   3. Selection of Subjects

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 codes\textsuperscript{(1)} intended to assure that research involving human subjects would be carried out in an ethical manner.

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

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

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

\textbf{PART A: BOUNDARIES BETWEEN PRACTICE & RESEARCH}

\textbf{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.\textsuperscript{(2)} By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the
innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project. (3)

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 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 provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally 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 entitle.

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

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible 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) 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.

(2) 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.

(3) 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.
International Ethical Guidelines for Biomedical Research Involving Human Subjects

Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)

CIOMS
Geneva
2002

CONTENTS

ACKNOWLEDGEMENTS

BACKGROUND
INTRODUCTION
INTERNATIONAL INSTRUMENTS AND GUIDELINES
GENERAL ETHICAL PRINCIPLES
PREAMBLE
THE GUIDELINES

Ethical justification and scientific validity of biomedical research involving human subjects

Ethical review

Ethical review committees
Ethical review of externally sponsored research

Informed consent

Individual informed consent
Obtaining informed consent: Essential information for prospective research subjects
Obtaining informed consent: Obligations of sponsors and investigators
Inducement to participate
Benefits and risks of study participation
Special limitations on risk when research involves individuals who are not capable of giving informed consent

* * * * *
Research in populations and communities with limited resources

Choice of control in clinical trials

Vulnerable groups

Equitable distribution of burdens and benefits in the selection of groups of subjects in research
Research involving vulnerable persons
Research involving children
Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent

Women as research participants

Women as research participants
Pregnant women as research participants

Safeguarding confidentiality
Right of injured subjects to treatment and compensation
Strengthening capacity for ethical and scientific review and biomedical research
Ethical obligation of external sponsors to provide health-care services

Appendix 1: Items to be included in a protocol (or associated documents) for biomedical research involving human subjects.
Appendix 2: The Declaration of Helsinki
Appendix 3: The phases of clinical trials of vaccines and drugs

Basic IRB Regulations

FDA 21 CFR 50

FDA 21 CFR 56

DHHS 45 CFR 46
Title 21--Food and Drugs

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 50--PROTECTION OF HUMAN SUBJECTS

<table>
<thead>
<tr>
<th>Subpart A_General Provisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.1  Scope.</td>
</tr>
<tr>
<td>50.3  Definitions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subpart B_Informed Consent of Human Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.20 General requirements for informed consent.</td>
</tr>
<tr>
<td>50.23 Exception from general requirements.</td>
</tr>
<tr>
<td>50.24 Exception from informed consent requirements for emergency research.</td>
</tr>
<tr>
<td>50.25 Elements of informed consent.</td>
</tr>
<tr>
<td>50.27 Documentation of informed consent.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subpart C [Reserved]</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Subpart D_Additional Safeguards for Children in Clinical Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.50 IRB duties.</td>
</tr>
<tr>
<td>50.51 Clinical investigations not involving greater than minimal risk.</td>
</tr>
<tr>
<td>50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>50.55 Requirements for permission by parents or guardians and for assent by children.</td>
</tr>
<tr>
<td>50.56 Wards.</td>
</tr>
</tbody>
</table>
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.


Sec. 50.3 Definitions.

As used in this part:


(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 should 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.

(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.

### 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 follow-up 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.
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.

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.

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.

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.

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.

Use of the investigational drug without informed consent otherwise conforms with applicable law.

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.

The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve:

- The required information sheet;
- 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);
- 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
- 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.

DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

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.

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:

- 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.
- 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.

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.

(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.


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 that:

(a) No greater than minimal risk to children is presented; and
(b) 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.

[78 FR 12951, Feb. 26, 2013]

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 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 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 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, in accordance with and to the extent that consent is required under part 50, 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 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.

(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.

Link to an amendment published at 78 FR 12951, Feb. 26, 2013.

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.

Source: 45 FR 36390, May 30, 1980, unless otherwise noted.
CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 56--INSTITUTIONAL REVIEW BOARDS

Subpart A_General Provisions
56.101 Scope.
56.102 Definitions.
56.103 Circumstances in which IRB review is required.
56.104 Exemptions from IRB requirement.
56.105 Waiver of IRB requirement.

Subpart B_Organization and Personnel
56.106 Registration.
56.107 IRB membership.

Subpart C_IRB Functions and Operations
56.108 IRB functions and operations.
56.109 IRB review of research.
56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
56.111 Criteria for IRB approval of research.
56.112 Review by institution.
56.113 Suspension or termination of IRB approval of research.
56.114 Cooperative research.

Subpart D_Records and Reports
56.115 IRB records.

Subpart E_Administrative Actions for Noncompliance
56.120 Lesser administrative actions.
56.121 Disqualification of an IRB or an institution.
56.122 Public disclosure of information regarding revocation.
56.123 Reinstatement of an IRB or an institution.
56.124 Actions alternative or additional to disqualification.
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.


Sec. 56.102 Definitions.

As used in this part:


(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 biologies 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.
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.

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.

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.

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.

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.

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.

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.


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.


**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](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 Office of Good Clinical Practice, Office of Special Medical Programs, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, Rm. 5129, Silver Spring, MD 20993.

(e) **How does an IRB revise its registration information?** If an IRB's contact or chairperson 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, as amended at 78 FR 16401, Mar. 15, 2013]

---

**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 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 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.


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.


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 was 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.


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 non-expedited 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.


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.


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.


Source: 46 FR 8975, Jan. 27, 1981, unless otherwise noted.
Title 45--Public Welfare

**SUBTITLE A--DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**PART 46--PROTECTION OF HUMAN SUBJECTS**

<table>
<thead>
<tr>
<th>Subpart A_Basic HHS Policy for Protection of Human Research Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>46.101</td>
</tr>
<tr>
<td>46.102</td>
</tr>
<tr>
<td>46.103</td>
</tr>
<tr>
<td>46.104-46.106</td>
</tr>
<tr>
<td>46.107</td>
</tr>
<tr>
<td>46.108</td>
</tr>
<tr>
<td>46.109</td>
</tr>
<tr>
<td>46.110</td>
</tr>
<tr>
<td>46.111</td>
</tr>
<tr>
<td>46.112</td>
</tr>
<tr>
<td>46.113</td>
</tr>
<tr>
<td>46.114</td>
</tr>
<tr>
<td>46.115</td>
</tr>
<tr>
<td>46.116</td>
</tr>
<tr>
<td>46.117</td>
</tr>
<tr>
<td>46.118</td>
</tr>
<tr>
<td>46.119</td>
</tr>
<tr>
<td>46.120</td>
</tr>
<tr>
<td>46.121</td>
</tr>
<tr>
<td>46.122</td>
</tr>
<tr>
<td>46.123</td>
</tr>
<tr>
<td>46.124</td>
</tr>
</tbody>
</table>
Subpart B Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

46.201 To what do these regulations apply?
46.202 Definitions.
46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.
46.204 Research involving pregnant women or fetuses.
46.205 Research involving neonates.
46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.
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.

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

46.301 Applicability.
46.302 Purpose.
46.303 Definitions.
46.304 Composition of Institutional Review Boards where prisoners are involved.
46.305 Additional duties of the Institutional Review Boards where prisoners are involved.
46.306 Permitted research involving prisoners.

Subpart D Additional Protections for Children Involved as Subjects in Research

46.401 To what do these regulations apply?
46.402 Definitions.
46.403 IRB duties.
46.404 Research not involving greater than minimal risk.
46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
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.
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.
46.408 Requirements for permission by parents or guardians and for assent by children.
46.409 Wards.
Subpart E_ Registration of Institutional Review Boards

46.501 What IRBs must be registered?
46.502 What information must be provided when registering an IRB?
46.503 When must an IRB be registered?
46.504 How must an IRB be registered?
46.505 When must IRB registration information be renewed or updated?

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 28012, 28022, June 18, 1991, unless otherwise noted. |

§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.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in §46.102, 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
deptartment 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.¹

¹ 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.

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991, as amended at70 FR 36328,
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 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.)


§§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.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§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.

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§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.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§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.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§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.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§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.


§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 (e) 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.


§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.

Subpart E Registration of Institutional Review Boards

§46.501 What IRBs must be registered?

Each IRB that is designated by an institution under an assurance of compliance approved for
federalwide use by the Office for Human Research Protections (OHRP) under §46.103(a) and
that reviews research involving human subjects conducted or supported by the Department of
Health and Human Services (HHS) must be registered with HHS. An individual authorized to act
on behalf of the institution or organization operating the IRB must submit the registration
information.

§46.502 What information must be provided when registering an IRB?

The following information must be provided to HHS when registering an IRB:

(a) The name, mailing address, and street address (if different from the mailing address) of the
    institution or organization operating the IRB(s); and the name, mailing address, phone
    number, facsimile number, and electronic mail address of the senior officer or head official
    of that institution or organization who is responsible for overseeing activities performed by
    the IRB.

(b) The name, mailing address, phone number, facsimile number, and electronic mail address of
    the contact person providing the registration information.

(c) The name, if any, assigned to the IRB by the institution or organization, and the IRB's
    mailing address, street address (if different from the mailing address), phone number,
    facsimile number, and electronic mail address.

(d) The name, phone number, and electronic mail address of the IRB chairperson.

(e) (1) The approximate numbers of:

    (i) All active protocols; and

    (ii) Active protocols conducted or supported by HHS.

    (2) For purpose of this regulation, an "active protocol" is any protocol for which the IRB
        conducted an initial review or a continuing review at a convened meeting or under an
        expedited review procedure during the preceding twelve months.

(f) The approximate number of full-time equivalent positions devoted to the IRB's
    administrative activities.

§46.503 When must an IRB be registered?

An IRB must be registered before it can be designated under an assurance approved for
federalwide use by OHRP under §46.103(a).

IRB registration becomes effective when reviewed and accepted by OHRP.
The registration will be effective for 3 years.

§46.504 How must an IRB be registered?

Each IRB must be registered electronically through http://ohrp.cit.nih.gov/efile unless an institution or organization lacks the ability to register its IRB(s) electronically. If an institution or organization lacks the ability to register an IRB electronically, it must send its IRB registration information in writing to OHRP.

§46.505 When must IRB registration information be renewed or updated?

(a) Each IRB must renew its registration every 3 years.
(b) The registration information for an IRB must be updated within 90 days after changes occur regarding the contact person who provided the IRB registration information or the IRB chairperson. The updated registration information must be submitted in accordance with §46.504.
(c) Any renewal or update that is submitted to, and accepted by, OHRP begins a new 3-year effective period.
(d) An institution's or organization's decision to disband a registered IRB which it is operating also must be reported to OHRP in writing within 30 days after permanent cessation of the IRB's review of HHS-conducted or -supported research.
Selected Auxiliary Regulations/Policy

DHHS

FDA

Other Selected Agency Information
Office for Human Research Protections (OHRP)

Frequently Asked Questions About Human Research

These FAQs provide guidance that represents OHRP's current thinking on these topics and should be viewed as recommendations, unless specific regulatory requirements are cited. The use of the word "must" in OHRP guidance means that something is required under HHS regulations at 45 CFR part 46. The use of the word "should" in OHRP guidance means that something is recommended or suggested, but not required. An institution may use an alternative approach if the approach satisfies the requirements of the HHS regulations at 45 CFR part 46. OHRP is available to discuss alternative approaches at 240-453-6900 or 866-447-4777.

45 CFR 46 (the Human Research Regulations) FAQs

Assurance Process FAQs
Children: Research with Children FAQs
Exempt Research Determination FAQs
Informed Consent FAQs
Investigator Responsibilities FAQs
IRB Registration Process FAQs
Prisoner Research FAQs
Quality Improvement Activities FAQs

Commonly Used Abbreviations

CFR — Code of Federal Regulations
FDA — Food and Drug Administration
FWA — Federalwide Assurance
HHS — Department of Health and Human Services
IEC — Independent Ethics Committee
IRB — Institutional Review Board
OHRP — Office for Human Research Protections
45 CFR 46 - FAQs:

What is the historical basis for the current human research regulations, 45 CFR part 46?

The history of contemporary human subjects protections began in 1947 with the Nuremberg Code, developed for the Nuremberg Military Tribunal as standards by which to judge the human experimentation conducted by the Nazis. The Code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects.

Similar recommendations were made by the World Medical Association in its Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, first adopted in 1964 and subsequently revised many times.

Basic regulations governing the protection of human subjects in research supported or conducted by HHS (then the Department of Health, Education and Welfare) were first published in 1974. In the United States, a series of highly publicized abuses in research led to the enactment of the 1974 National Research Act (Public Law 93-348), which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the National 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 to assure that such research is conducted in accordance with those principles. In 1978, the Commission published “Ethical Principles and Guidelines for the Protection of Human Subjects of Research,” also known as the Belmont Report, named after the Belmont Conference Center where the Commission met when drafting the report. The Belmont Report identifies three fundamental ethical principles for all human subjects research -- respect for persons, beneficence, and justice.

Based on the Belmont Report and other work of the National Commission, HHS revised and expanded its regulations for the protection of human subjects in the late 1970s and early 1980s. The HHS regulations are codified at 45 CFR part 46, subparts A through D. The statutory authority for the HHS regulations derives from 5 U.S.C. 301; 42 U.S.C. 300v-1(b); and 42 U.S.C. 289.

The regulations found at 45 CFR part 46 are based in large part on the Belmont Report and were written to offer basic protections to human subjects involved in both biomedical and behavioral research conducted or supported by HHS. In 1991, 14 other Federal departments and agencies joined HHS in adopting a uniform set of rules for the protection of human subjects, identical to subpart A of 45 CFR part 46 of the HHS regulations. This uniform set of regulations is the Federal Policy for the Protection of Human Subjects, informally known as the “Common Rule.” In 1995 the Central Intelligence Agency was required by Executive Order to comply with all subparts of the HHS regulations.

What human research issues are addressed in 45 CFR part 46?

HHS regulations at 45 CFR part 46 stipulate substantive and procedural requirements for investigators and institutions engaged in HHS-supported or -conducted research. Specifically, in addition to providing definitions and information about application of the regulations, specific sections of the regulations address the following topics:
- Assuring compliance with the regulations (46.103)
- Institutional Review Board (IRB) membership (46.107)
- IRB functions and operations (46.108)
- IRB review of research (46.109)
- Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research (46.110)
- Criteria for IRB approval of research, including minimizing risk, ensuring confidentiality, and protecting vulnerable populations, (46.111)
- Review by institution (46.112)
- Suspension or termination of IRB approval of research (46.113)
- Cooperative research (46.114)
- IRB records (46.115)
- General requirements for informed consent (46.116)
- Documentation of informed consent (46.117)
- Applications and proposals lacking definite plans for involvement of human subjects (46.118)
- Research undertaken without the intention of involving human subjects (46.119)
- Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency (46.120)
- Use of Federal funds (46.122)
- Early termination of research support: Evaluation of applications and proposals (46.123)
- Conditions (46.124)

Additional protections for specific populations have been adopted by HHS (and other departments and agencies to a lesser extent), as follows:

- **Subpart B**, Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- **Subpart C**, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- **Subpart D**, Additional Protections for Children Involved as Subjects in Research

**How can I find out if the 45 CFR 46 human subject research regulations apply to my research?**

HHS regulations at 45 CFR 46.103(a) require that each institution engaged in human subjects research that is supported or conducted by HHS provide the Office on Human Research Protections with a satisfactory Assurance of Compliance to comply with the regulations, unless the research is exempt under 45 CFR 46.101(b). The assurance identifies policies and procedures for the institution and describes the activities to which the regulations apply.

You should check your institution’s Terms of Assurance to find out whether the regulations apply to your research. In addition, you might want to consult OHRP’s decision charts at: [http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html](http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html).
How does HHS ensure that regulatory requirements for human research are met?

HHS employs many approaches to facilitate compliance with the regulations. First, through a system of IRB registration and assurances, HHS regulations require institutions to commit to compliance with 45 CFR part 46 before initiating participation in HHS-conducted or -supported research involving human subjects. On behalf of the Secretary, HHS, the Office on Human Research Protections (OHRP) approves the terms of these written institutional assurances, which constitute binding commitments.

In essence, OHRP holds accountable and depends on institutional officials, committees, researchers, and other agents of the institution to comply with the institution’s assurance and the regulations.

In carrying out its oversight responsibility, OHRP’s Division of Compliance Oversight monitors compliance through not-for-cause compliance oversight surveillance activities and for-cause compliance oversight evaluations of allegations or indications of noncompliance with the regulations. OHRP has the authority under Title IV of the Public Health Service Act (42 USC 281 et seq.) to investigate complaints about human subject protections in HHS-conducted or -funded research, as well as any other research covered by the institution’s Assurance of Compliance. OHRP also promotes compliance through its Division of Policy and Assurances, which provides policy and guidance documents pertaining to the regulatory requirements in 45 CFR 46.

In addition, through its Division of Education and Development, OHRP provides a multifaceted education program -- including national conferences, research community forums, and a quality improvement program -- all of which enhance understanding of the regulations and what is necessary for compliance.

Do the human research regulations apply to non-U.S. institutions?

Yes, whenever non-U.S. institutions are engaged in non-exempt HHS-supported or -conducted human subjects research, the regulations apply.

Please see: http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html#sectionb.

How does 45 CFR part 46 relate to the Common Rule and human subjects regulations used by non-HHS agencies?

The current US system of protection for human research subjects is heavily influenced by the Belmont Report, written in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report outlines the basic ethical principles in research involving human subjects. In 1981, with this report as foundational background, HHS and the Food and Drug Administration revised, and made as compatible as possible under their respective statutory authorities, their existing human subjects regulations.

The Federal Policy for the Protection of Human Subjects or the “Common Rule” was published in 1991 and codified in separate regulations by 15 Federal departments and agencies, as listed below. The HHS
regulations, 45 CFR part 46, include four subparts: subpart A, also known as the Federal Policy or the “Common Rule”; subpart B, additional protections for pregnant women, human fetuses, and neonates; subpart C, additional protections for prisoners; and subpart D, additional protections for children. Each agency includes in its chapter of the Code of Federal Regulations [CFR] section numbers and language that are identical to those of the HHS codification at 45 CFR part 46, subpart A. For all participating departments and agencies the Common Rule outlines the basic provisions for IRBs, informed consent, and Assurances of Compliance. The list below displays the agencies and departments that have signed onto the Common Rule and their CFR numbers.

- Agency for International Development (22 CFR part 225)
- Consumer Product Safety Commission (16 CFR part 1028)
- Department of Agriculture (7 CFR part 1c)
- Department of Commerce (15 CFR part 27)
- Department of Defense (32 CFR part 219)
- Department of Education (34 CFR part 97 subpart A)
- Department of Energy (10 CFR part 745)
- Department of Health and Human Services (45 CFR part 46 subpart A)
- Department of Housing and Urban Development (24 CFR part 60)
- Department of Justice (28 CFR part 46)
- Department of Veterans Affairs (38 CFR part 16)
- Department of Transportation (49 CFR part 11)
- Environmental Protection Agency (40 CFR part 26)
- National Aeronautics and Space Administration (14 CFR part 1230)
- National Science Foundation (45 CFR part 690)

In addition, the Central Intelligence Agency must comply with all subparts of 45 CFR part 46 under Executive Order 12333.

Several non-HHS federal departments and agencies have additional regulations in place for research involving special populations or for human subjects research in general. Investigators are encouraged to review the regulations of the funding agency to determine whether additional regulations apply. Also, many agencies have not adopted subparts B, C, or D and grantees of those agencies are not necessarily bound by them. Grantees should consult their funding agency for guidance.

How do subparts B, C, and D of the HHS human research regulations at 45 CFR part 46 relate to subpart A?

Subparts B (additional protections for pregnant women, human fetuses, and neonates); C (additional protections for prisoners); and D (additional protections for children) are regulations that supplement subpart A by providing additional protections for vulnerable subject populations. Investigators conducting HHS-supported research in these populations must comply with all of the requirements of subpart A as well as the requirements of the relevant subpart. Institutions may further choose to apply subparts B-D to all research regardless of whether it is HHS-supported. Therefore, investigators should contact their relevant institutional officials to determine which subparts apply to their specific research project.
Assurance Process - FAQs:

What assurance of compliance process for human subject protection is accepted by the Office for Human Research Protections (OHRP) and other Federal agencies?

HHS human subject protection regulations and policies require that any institution engaged in non-exempt human subjects research conducted or supported by HHS must submit a written assurance of compliance to OHRP. The Federalwide Assurance (FWA) is the only type of assurance of compliance accepted and approved by OHRP. FWAs also are approved by the Office for Human Research Protections (OHRP) for federalwide use, which means that other federal departments and agencies that have adopted the Federal Policy for the Protection of Human Subjects (also known as the Common Rule) may rely on the FWA for the research that they conduct or support. Institutions engaging in research conducted or supported by non-HHS federal departments or agencies should consult with the sponsoring department or agency for guidance regarding whether the FWA is appropriate for the research in question.

What is an assurance of compliance with human subject protection regulations?

An assurance of compliance is a written document submitted by an institution (not an Institutional Review Board) that is engaged in non-exempt human subjects research conducted or supported by HHS. Through the assurance of compliance, an institution commits to HHS that it will comply with the requirements set forth in the regulations for the protection of human subjects at 45 CFR part 46. The Federalwide Assurance is the only type of assurance of compliance accepted and approved by OHRP.

When does a research institution need to be covered by an assurance of compliance with human subjects research protections?

All institutions engaged in human subjects research that is not exempt from the regulations, and is conducted or supported by any HHS agency must be covered by an Office for Human Research Protections-approved assurance of compliance (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html). The Federalwide Assurance (FWA) is the only type of assurance of compliance accepted and approved by OHRP.

An institution may extend its FWA to cover a collaborating individual investigator under certain conditions using the sample Individual Investigator Agreement or a comparable agreement developed by the institution.

When is an institution considered to be “engaged in research”?

In general, an institution is considered to be engaged in human subjects research when its employees or agents:

(1) obtain data about living individuals for research purposes through intervention or interaction with them,
(2) obtain individually identifiable private information for research purposes (45 CFR 46.102(d),(f))

(3) obtain the informed consent of human subjects.

Employees and agents, including students, are individuals performing institutionally designated activities and acting on behalf of the institution or exercising institutional authority or responsibility.

In general, an institution is considered to be engaged in human subjects research whenever it receives a direct HHS award to support such research, even if all of the human subjects activities will be performed by agents or employees of another institution. In general, simply informing potential subjects about a research study is not considered engagement in research. Also, providing written information about a research study, including how to contact the investigators for information and enrollment, and seeking and obtaining prospective subjects' permission for investigators to contact them are not considered engagement in research. However, obtaining informed consent from a research participant is considered engagement in research.

[For details, please see OHRP guidance on this topic at: http://www.hhs.gov/ohrp/policy/engage08.html, specifically, Section (B)(4).]

What is a Federalwide Assurance (FWA)?

The Federalwide Assurance (FWA) is the only type of assurance of compliance accepted and approved by OHRP for institutions engaged in non-exempt human subjects research conducted or supported by HHS. Under an FWA, an institution commits to HHS that it will comply with the requirements set forth in 45 CFR part 46, as well as the Terms of Assurance.

FWAs also are approved by OHRP for federalwide use, which means that other federal departments and agencies that have adopted the Federal Policy for the Protection of Human Subjects (also known as the Common Rule) may rely on the FWA for the research that they conduct or support. Institutions engaging in research conducted or supported by non-HHS federal departments or agencies should consult with the sponsoring department or agency for guidance regarding whether the FWA is appropriate for the research in question.

There is a single version of the FWA and the Terms of Assurance for domestic (U.S.) institutions and international (non-U.S.) institutions.

What research does the Federalwide Assurance (FWA) cover?

The FWA covers all non-exempt human subjects research at the submitting institution that is HHS-conducted or supported or funded by any other federal department or agency that has adopted the Common Rule and relies upon the FWA. It is not project specific. Domestic institutions may voluntarily extend their FWA to cover all human subjects research at the submitting institution regardless of the source of support for the particular research activity.
What time period does the Federalwide Assurance (FWA) cover and when does it have to be updated?

The Federalwide Assurance (FWA) is effective for 5 years and must be renewed every 5 years, even if no changes have occurred, in order to maintain an active FWA. The institution must update its FWA within 90 days after changes occur regarding the legal name of the institution, the Human Protections Administrator, or the Signatory Official. Any renewal or update that is submitted electronically, and approved by OHRP, begins a new 5-year effective period.

What are the key features of the Federalwide Assurance (FWA)?

The key features of the Federalwide Assurance (FWA) are the following:

a) The identifying information for the institution filing the FWA, the Human Protections Administrator (or a reliable point of contact) at the institution, and the institutional official signing the FWA;

b) A list of the institution’s legal components that operate under different names that will be covered by the FWA and the city and state or country where the component is located. (legal components are generally defined as parts of your institution that may be viewed as separate organizations, but remain part of the legal entity or institution, for example, ABC University can list its XYZ University Hospital, KLM School of Public Health, and EFG Institute for International Studies as components);

c) A statement of ethical principles to be followed in protecting human subjects of research;

d) An applicability statement indicating that the FWA applies whenever the institution becomes engaged in human subjects research conducted or supported by any United States (U.S.) federal department or agency that has adopted the U.S. Federal Policy for Protection of Human Subjects (known as the Common Rule), unless the research is exempt from Common Rule requirements or a Common Rule agency or department determines the research will be conducted under a separate assurance of compliance. U.S. institutions may voluntarily extend the Common Rule or 45 CFR part 46 to all research conducted by the institution regardless of the source of support;

e) An assurance of compliance indicating that the institution will comply with the Terms of the FWA. An institution outside of the U.S. also must assure that it will comply with one or more procedural standards whenever it engages in research covered by the FWA. A list of 6 such standards is included or an institution can submit another standard for the protection of human subjects that is recognized by the Common Rule departments and agencies. (See Terms of Assurance, section 3(b));

f) The designation of all internal IRBs that will review the research covered by the FWA. If the institution has no internal IRB, it must designate the external IRB that reviews all research covered by the FWA. If the institution relies upon multiple external IRBs, the institution should designate the external IRB that reviews the largest percentage of the research covered by the FWA. All IRBs designated on an institution’s FWA must be registered
Please note that all IRBs reviewing research covered by an institution’s FWA must be registered whether or not they are designated on the institution’s FWA;

\[\text{http://www.hhs.gov/ohrp/assurances/irb/index.html} \] with OHRP before the FWA can be approved.


The signature of an official authorized to represent the institution, identified on the FWA as Signatory Official. The Signatory Official must assure that human subjects research to which the FWA applies is conducted in accordance with the Terms of Assurance. The Signatory Official must electronically sign the FWA using the electronic submission system available through the OHRP website at: \[\text{http://ohrp.cit.nih.gov/efile/} \], unless the institution lacks the ability to submit its FWA electronically. The Signatory Official typically is someone at the level of President, Chief Executive Officer, Chief Operating Officer, Director General, or Chancellor.

**Do international institutions have a separate FWA form or Terms of Assurance?**

No. There is a single version of the FWA and the Terms of Assurance for U.S. and non-U.S. institutions.

**Do international institutions seeking a Federalwide Assurance (FWA) have to comply with 45 CFR part 46?**

OHRP is sometimes asked whether, if an international institution selects a procedural standard under the FWA that has less stringent requirements than 45 CFR part 46, the institution may disregard the more stringent requirements of 45 CFR part 46.

It is current OHRP policy that in the absence of an OHRP determination that a procedural standard affords protections equivalent to the protections provided by 45 CFR part 46, the requirements of 45 CFR part 46 must be applied to all research conducted or supported by HHS.

As described in a July 7, 2006 Federal Register notice (71 FR 38645) it is OHRP’s position that if an international institution selects a procedural standard under its FWA other than 45 CFR part 46, any requirements of 45 CFR part 46 still must be satisfied for non-exempt human subject research that is conducted or supported by HHS.

For example, the International Conference on Harmonization E-6 Guidelines for Good Clinical Practice (ICH-GCP-E6) do not specifically limit use of expedited review for research undergoing continuing review
by the IRB. For research conducted or supported by HHS, if an international institution selected ICH-GCP-E6 as its primary procedural standard on its FWA, the IRB may only use an expedited review procedure to conduct continuing review of HHS-conducted or supported research if the research qualifies for expedited review as provided for under HHS regulations at 45 CFR 46.110.

Please note that the statements above pertain to compliance with the requirements of 45 CFR part 46 for non-exempt human subjects research that is conducted or supported by HHS. If the institution needs guidance regarding implementation of the Common Rule and/or other applicable U.S. federal regulations for research that is not conducted or supported by HHS, the institution should contact appropriate officials at the U.S. federal department or agency conducting or supporting the research.

Are there options other than the Federalwide Assurance (FWA) for obtaining an assurance of compliance to conduct HHS-supported or -conducted research?

No. The FWA is the only type of assurance of compliance accepted and approved by OHRP.

Who is covered by a Federalwide Assurance (FWA)?

Employees and agents of the institution holding an approved FWA are covered whenever they are involved in the conduct of research covered by the FWA. Employees and agents, including students, are individuals performing institutionally designated activities and acting on behalf of the institution or exercising institutional authority or responsibility.

An institution holding an OHRP-approved FWA (hereafter referred to as the assured institution) may extend the applicability of its FWA to cover two types of collaborating individual investigators: collaborating independent investigators and collaborating institutional investigators.

1. A collaborating independent investigator is:
   a. not otherwise an employee or agent of the assured institution;
   b. conducting collaborative research activities outside the facilities of the assured institution; and
   c. not acting as an employee of any institution with respect to his or her involvement in the research being conducted by the assured institution.

2. A collaborating institutional investigator is:
   a. not otherwise an employee or agent of the assured institution;
   b. conducting collaborative research activities outside the facilities of the assured institution;
   c. acting as an employee or agent of an institution that does not hold an OHRP-approved FWA with respect to his or her involvement in the research being conducted by the assured institution; and employed by, or acting as an agent of, an institution that does not hold an OHRP-approved FWA and does not routinely conduct human subjects research.

The extension of an assured institution’s FWA to cover a collaborating individual investigator should be documented using an Individual Investigator Agreement (IIA) or another similar agreement developed by the institution holding the FWA (see [http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.html](http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.html) for OHRP’s guidance on the use of the IIA and the link to the sample IIA document).
If HHS-conducted or -supported human subjects research activities routinely occur at a non-assured institution, the institution should obtain an OHRP-approved FWA, and the IIA (or similar agreements) should not be used. Also, if the non-assured institution is the primary awardee for an HHS-supported award providing support for non-exempt human subjects research, the institution must obtain its own OHRP-approved FWA. If an institution is uncertain about the need for its own FWA, it should consult with OHRP.

**NOTE:** All previous types of sample agreements to cover an independent investigator [i.e., Agreement for Independent Investigators (AII), Non-Institutional Investigator Agreement (NIA), and Unaffiliated Investigator Agreement (UIA)] have been replaced by the sample Individual Investigator Agreement (IIA). Previously executed AIs, NIAs, and UIAs may remain in effect until all applicable research that has already been initiated is completed or until the previous agreement has been replaced by a new Individual Investigator Agreement modeled on the OHRP sample IIA, or by a comparable written agreement developed by an assured institution.

**What are the procedures for submitting a Federalwide Assurance (FWA)?**

Institutions must submit all FWAs (including new submissions, updates, and renewals) electronically using the electronic submission system available through the OHRP website at [http://ohrp.cit.nih.gov/efile/](http://ohrp.cit.nih.gov/efile/), unless an institution lacks the ability submit electronically. If an institution believes it lacks the ability to submit its FWA electronically, please contact OHRP by telephone or email (see [http://www.hhs.gov/ohrp/assurances/contact/index.html](http://www.hhs.gov/ohrp/assurances/contact/index.html)) and explain why the institution cannot submit its FWA electronically.

The FWA application will only be considered complete by OHRP when it is completed in its entirety, signed by the Signatory Official, and dated. Additionally, the IRB(s) designated on the FWA must be registered with OHRP before the FWA can be approved.

The instructions for submitting an FWA (new submission, update, and renewal) may be found at [http://www.hhs.gov/ohrp/assurances/assurances/index.html](http://www.hhs.gov/ohrp/assurances/assurances/index.html).

**Who may sign as the Signatory Official on a Federalwide Assurance (FWA)?**

The FWA Signatory Official should be a high-level institutional official who has the authority to represent the institution named in the Federalwide Assurance (FWA), as well as all the institutional components listed in the FWA. Entities that the Signatory Official is not authorized to represent may not be covered under the FWA. This person is usually the President, Chief Executive Officer, Chief Operating Officer, Director General, or Chancellor.

The intent in requiring that the Signatory Official be a high-level individual is two-fold. First, OHRP encourages institutions to promote a culture of conscience for the ethical conduct of human subjects research at the highest level within the institution. Second, the Signatory Official should be at a level of responsibility that would allow authorization of necessary administrative or legal action should that be required. OHRP recommends that the Signatory Official not be the chair or member of any IRB designated under the FWA.
Where can I find the instructions and forms for submitting a Federalwide Assurance (FWA)?

Links to the instructions and the forms for submitting an FWA may be found on the OHRP website at [http://www.hhs.gov/ohrp/assurances/forms/index.html](http://www.hhs.gov/ohrp/assurances/forms/index.html).

Who can I contact with questions about submitting a Federalwide Assurance (FWA)?

If you have questions about submitting an FWA, you should contact the Assurance Coordinator assigned to your state or international region (see the OHRP website at [http://www.hhs.gov/ohrp/assurances/status/contact/index.html](http://www.hhs.gov/ohrp/assurances/status/contact/index.html)).

How can I track the Office for Human Research Protection's (OHRP) receipt of my Federalwide Assurance (FWA) submission?

You may track the receipt of an FWA on the Office for Human Research Protections website at [http://ohrp.cit.nih.gov/search/](http://ohrp.cit.nih.gov/search/). Here you will find information about when the FWA was received, as well as which Assurance Coordinator is reviewing it and how to contact that person.

How will I know when my institution’s Federalwide Assurance (FWA) is approved?

With electronic submission of your institution’s Federalwide Assurance (FWA), which is required unless your institution lacks the ability to submit its FWA electronically, the Signatory Official, Human Protections Administrator, and the individual who submitted the FWA will receive an automatically generated email when OHRP approves the FWA. A copy of the approved FWA will be attached to that email.

How will the Office for Human Research Protections (OHRP) respond to queries from an FWA institution about human subjects research conducted or supported by a non-HHS department or agency?

When the Office for Human Research Protections (OHRP) receives a request from an FWA institution for guidance regarding implementation of the Common Rule for human subjects research conducted or supported by another department or agency that has adopted the Common Rule, OHRP will direct the requestor to contact appropriate officials at the other department or agency. When the requestor seeking guidance regarding a specific research project does not identify the conducting or supporting department or agency, OHRP will qualify its response with a statement that if the research is supported by another department or agency the requestor should also consult with appropriate officials at the supporting department or agency. If the requestor at the FWA institution and appropriate officials at the conducting or supporting department or agency mutually agree to seek OHRP input on the matter, OHRP staff will be available to provide guidance.
When do institutions collaborating in non-HHS research need to obtain a Federalwide Assurance (FWA)?

If human subjects research conducted or supported by a non-HHS Common Rule department or agency involves collaborating institutions that do not hold an FWA or other applicable OHRP-approved assurance of compliance for federalwide use, OHRP does not require the collaborating institutions to obtain FWAs, but an FWA may be required by the non-HHS department or agency conducting or supporting the human subjects research.

For such situations, while obtaining an FWA would be one option for the collaborating institutions to comply with the assurance of compliance requirement of the Common Rule §__.103(a) [http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.103], obtaining an FWA would not be required by HHS. When requests for guidance on this topic are received by OHRP, OHRP will refer the requestor to appropriate officials at the conducting or supporting Common Rule department or agency for assistance in deciding on an appropriate assurance mechanism.

Will the Office for Human Research Protections forward reports received from FWA-holding institutions to non-HHS federal funding agencies or departments?

The Office for Human Research Protections (OHRP) receives reports from institutions holding a Federalwide Assurance (FWA) of:

(i) unanticipated problems involving risks to subjects or others;

(ii) serious or continuing noncompliance with the Common Rule or the requirements or determinations of the IRB; or

(iii) suspension or termination of IRB approval.

If the human subjects research is conducted or supported by a Common Rule department or agency other than HHS, OHRP will not forward the report(s) to that other agency. However, OHRP will remind the FWA-holding institution in writing of the institution’s responsibility to notify the conducting or supporting department or agency head in accordance with the requirements of §__.103(b)(5) [http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.103] of the Common Rule.

How does the Office for Human Research Protections (OHRP) handle allegations or indications of noncompliance when the research is not HHS-supported or conducted?

When the allegations or indications of noncompliance (complaints) are limited solely to the research activities conducted or supported by another Common Rule department or agency, for Human Research Protections (OHRP) will refer the matter to appropriate officials at the other department or agency for further investigation and action, as appropriate. OHRP’s Division of Compliance Oversight (DCO) will not be involved in the conduct of the investigation unless the relevant department or agency requests OHRP’s
involvement. When the other department or agency completes its investigation without OHRP involvement, a report on the outcome of the investigation should be provided to OHRP.

**How does 45 CFR part 46 relate to the human subjects regulations used by non-HHS federal funding agencies?**

The current U.S. system of protection for human research subjects is heavily influenced by the Belmont Report, written in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report outlines the basic ethical principles in research involving human subjects. In 1981, with this report as foundational background, HHS and FDA revised and made as compatible as possible - under their respective statutory authorities - their existing human subjects regulations. With leadership from HHS, the Federal Policy for the Protection of Human Subjects or the “Common Rule” was published in 1991 and codified in separate regulations by 15 Federal departments and agencies, as listed below (each agency includes in its chapter of the Code of Federal Regulations [CFR] section numbers and language that are identical to those of 45 CFR part 46, subpart A).

- Department of Agriculture (7 CFR part 1c)
- Department of Commerce (15 CFR part 27)
- Department of Defense (32 CFR part 219)
- Department of Education (34 CFR part 97)
- Department of Energy (10 CFR part 745)
- Department of Health and Human Services (45 CFR part 46 subpart A)
- Department of Housing and Urban Development (24 CFR part 60)
- Department of Justice (28 CFR part 46)
- Department of Veterans Affairs (38 CFR part 16)
- Department of Transportation (49 CFR part 11)
- Consumer Product Safety Commission (16 CFR part 1028)
- Environmental Protection Agency (40 CFR part 26)
- Agency for International Development (22 CFR part 225)
- National Aeronautics and Space Administration (14 CFR part 1230)
- National Science Foundation (45 CFR part 690)

In addition, the Central Intelligence Agency must comply with all subparts of 45 CFR part 46 under Executive Order 12333. And, in accordance with the Intelligence Reform and Terrorism Protection Act of 2004 (P.L. 108-458, Section 8306), the Department of Homeland Security adopted policies implementing the protections for human subjects under 45 CFR part 46 for the research that it conducts or supports.

For all participating departments and agencies the Common Rule outlines the basic provisions for IRBs, informed consent, and Assurances of Compliance. HHS has developed additional regulations for the human subjects research it conducts or supports that apply to particular special populations: 45 CFR part 46 subparts B-D apply to research involving pregnant women, human fetuses, and neonates (subpart B), prisoners (subpart C), and children (subpart D).
Several non-HHS federal departments and agencies have additional regulations in place for research involving special populations or for human subjects research in general.

**Do the human research regulations apply to non-U.S. institutions?**

Yes, whenever non-U.S. institutions are engaged in non-exempt HHS-supported or -conducted human subjects research, the HHS human subjects protection regulations, 45 CFR part 46, apply.

Please see: [http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html](http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html)

**Does approval of an institution's assurance of compliance by the Office for Human Research Protections (OHRP) mean that the institution is in full compliance with the Department of Health and Human Services (HHS) Protection of Human Subjects regulations?**

No, OHRP's approval of an institution's assurance of compliance does not mean that OHRP has determined that the institution is complying with the requirements of the HHS Protection of Human Subjects regulations, 45 CFR part 46. It means that an institution has submitted all of the documentation OHRP requires to constitute a commitment by the institution to comply with the requirements of 45 CFR part 46 when its employees or agents engage in non-exempt human subjects research conducted or supported by HHS or other research covered by the assurance of compliance. The Federalwide Assurance is the only type of assurance of compliance accepted and approved by OHRP.

**Research with Children - FAQs:**

**Does research involving children include special requirements?**

Yes, [Subpart D](http://www.hhs.gov/ohrp/policy/faq/index.html) of the HHS regulations at 45 CFR part 46 provides additional protections for children participating in human subjects research. Investigators conducting HHS-supported research must comply with the requirements of subpart D, as well as other subparts. The IRB must determine that all requirements of subparts A and D have been met. If the research involves pregnant minors, then the requirements of [subpart B](http://www.hhs.gov/ohrp/policy/faq/index.html) must be met and if the research involves incarcerated minors then the requirements of [subpart C](http://www.hhs.gov/ohrp/policy/faq/index.html) must be met.

Subpart D’s additional protections include:

a. requiring IRB review of some research activities involving children that would be exempt if the research subjects were adults;

b. use of parental permission and child assent instead of the procedures for obtaining informed consent used for research involving adults;

c. conditions for IRB approval of proposed research activities in three categories depending on the level of risk and other specified features of the proposed research activity;
d. review by the Secretary for research that an IRB finds not approvable under any of the three categories; and,

e. additional conditions for certain research activities involving children who are wards of the State or any other agency, institution, or entity

a. **Altering the Exemption:** Subpart D widens the range of research activities requiring IRB review by reducing the scope of the exemption in 45 CFR 46.101(b)(2) regarding research activities involving education tests, survey or interview procedures, or observation of public behavior, if the subjects are children. The exemption of research activities involving survey and interview procedures is eliminated. The exemption is also narrowed for research involving observation of public behavior, by eliminating the exemption of any research involving observation of public behavior if the investigator will participate in the activities being observed.

b. **Parental Permission and Child Assent:** Subpart D uses parental permission and child assent instead of the procedures for informed consent used for research involving adults. In general, one or both parents or a guardian must be provided with the information ordinarily required for informed consent, so that they may decide whether to allow the child to participate, and children capable of assent must also express their willingness to participate. Subpart D allows for various conditions and waivers of parental permission and child assent, depending on the nature of the research activity and the maturity of the child.

c. **Categories of Approvable Research:** Subpart D requires the reviewing IRB to identify the level of risk, the potential for direct benefits to the subjects, and other specified features of the research during the approval process. Depending on the level of risk and other specified features of the research activity, there are three categories under which the IRB can approve research involving children.

d. **Secretarial Review:** If the IRB does not believe that a proposed research activity fits any of the three categories, but that it does present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB may forward that proposed activity to the HHS Secretary for review under conditions identified in section 407 of the regulations.

e. **Wards:** Subpart D also sets additional conditions for research involving children who are wards of the State or any other agency, institution, or entity if the research is approved under two of the categories of approvable research: it limits the kind of research activities approved under these two categories in which children who are wards can participate, and it requires the appointment of an advocate to act in the best interests of the child.

**How do the human subject research regulations define “children”***?

The human subject research regulations define “children” as follows:

“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 (45 CFR 46.402(a)).

In the United States the legal age of adulthood is a matter of state and local law. This means that who is legally considered a child may vary from state to state; in a large majority of states eighteen years of age is
the legal age of adulthood, but this is not true in every state, locality, or territory. Also, there may be exceptions to who is considered a child and additional laws in places that define emancipated minors. The definition of “children” also takes into account the particular treatments or procedures involved in the proposed research; for example, in some places individuals who are sixteen years of age may legally consent to certain medical treatments, and so if the involvement of human subjects in a proposed research activity consists of these treatments, then they may be considered as adults for that purpose. If a proposed activity includes something for which the subject has not yet reached the legal age of consent, however, that person must be considered a child.

**What categories of research involving children can an Institutional Review Board approve?**

Three of the four categories of human research involving children may be approved by an Institutional Review Board (IRB). The four categories differ from one another according to the level of risk involved, the prospect of direct benefit to the research subjects, and the anticipated research findings. For all four categories, the proposed research activity must satisfy the requirements for parental or guardian permission and child assent. Depending on the category, additional conditions must be met in order for the IRB to approve the research activities. The three categories approvable by an IRB are:

a. **Section 404** of the regulations allows the IRB to approve research if the IRB finds that the risks of the research are no more than minimal.

b. **Section 405** of the regulations allows the IRB to approve research if 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;
   - the risk is justified by the anticipated benefit to the subjects; and,
   - the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

c. **Section 406** allows the IRB to approve research if 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 that is not likely to contribute to the well-being of the child;
   - the risk represents a minor increase over minimal risk;
   - 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; and,
   - 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.

The fourth category of approvable research involving children is identified in **Section 407**, and requires the IRB to make certain findings and refer the proposed research activity to the Secretary of HHS for further review and approval.
Classifying a particular activity into one of these categories involves, among other things, determining whether the proposed research involves “minimal risk” to the subjects. The regulations rely on the definition of “minimal risk” provided in Subpart A of the regulations, as follows:

**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 (45 CFR 46.102(i)).

Determining that a research activity presents no more than minimal risk involves comparing the possible harms or discomforts experienced in normal daily life or during routine physical or psychological examinations or tests with the possible harms or discomforts that will be faced by subjects as a consequence of research participation. The nature of the harms or discomforts (e.g., physical, psychological, legal) should be considered, as well as the chances that they will occur and the seriousness of their impact if they were to happen. Depending on what kind of experience(s) are involved in participation in a specific research activity, it may be easier to compare the anticipated experience of participation in research to the possible harms or discomforts of daily life, or to the possible harms or discomforts of a routine physical or psychological examination or test. Including measures to prevent or decrease the likelihood of harm or discomfort from the research may affect whether the proposed research activity involves no more than minimal risk.

**What research involving children may an Institutional Review Board refer to the HHS Secretary for special review under 45 CFR 46.407?**

The regulations at 45 CFR 46.407 allow the Institutional Review Board (IRB) to refer HHS-conducted or -funded research to the HHS Secretary for consideration if the IRB finds that the research does not meet the conditions for approval under the other three categories of research involving children. If an institution’s IRB does not believe the proposed research meets the requirements of 45 CFR 46.404, 46.405, or 46.406 of subpart D, but finds and documents 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 (in accordance with HHS regulations at 45 CFR 46.407(a)), the IRB or other appropriate institutional official may submit the protocol and supporting materials to the Office for Human Research Protections (OHRP) for HHS consideration under the provisions of 45 CFR 46.407(b). Before submitting a protocol to OHRP, the IRB must determine that, in addition to meeting the requirements of 45 CFR 46.407(a) and other applicable sections of subpart D, the proposed research also meets all of the requirements of 45 CFR part 46, subpart A, except those requirements modified by Subpart D.

After receiving recommendations from a panel of experts and following an opportunity for public comment, the Secretary may approve the research under either one of two conditions:

1) The Secretary finds that the research is actually approvable under one of the first three categories of research, despite the IRB’s finding to the contrary; or

2) the Secretary concurs with the IRB’s findings that the research is not allowable under the other three categories and determines that the research presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting children’s health or welfare, and, in addition, determines that the
research will be conducted in accordance with sound ethical principles and that adequate provisions are made for soliciting the assent of children and permission of their parents or guardians as discussed in 46.408.

The Secretary may conditionally approve research under 46.407 providing specific stipulations are met.


**When should an Institutional Review Board (IRB) or institution request a “407” review for research involving children as subjects?**

Once an IRB determines that a protocol does not meet the requirements of 46.404, 46.405, or 46.406 for approval of research, but does meet the requirements for review under 45 CFR 46.407(a), the institution or the Institutional Review Board may request that the Office for Human Research Protections (OHRP), on behalf of the Secretary, HHS, conduct a 46.407 review.

**What materials must be submitted to the Office for Human Research Protections with a request for a 407 review for research involving children?**

For OHRP to determine whether a 407 review for research involving children should proceed, the institution must submit the following documents/information to the Office for Human Research Protections (OHRP) in both written and electronic (if available) forms:

a. IRB documentation of required findings under 45 CFR 46.407 that the proposed research does not meet the requirements of 46.404, 46.405, or 46.406, but presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
b. Institution name, institution assurance number, and IRB name.
c. Institutional contact’s name, title, phone number, fax number, mailing address, and email address.
d. Title of protocol, and name of principal investigator(s).
e. HHS application number and name of funding agency.
f. Relevant HHS grant application or proposal.
g. Most current version of protocol and grant application submitted to and reviewed by the IRB and modified by the principal investigator if required by the IRB.
h. Most current version of parental permission/assent documents submitted to and reviewed by the IRB and modified by the principal investigator if required by the IRB.
i. Relevant IRB minutes and correspondence.

Hard copy versions of the materials should be sent to:

Division of Policy and Assurances
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
OHRP will provide the submitting institution with instructions for transmitting documents electronically. See OHRP’s guidance on the 407 review process at http://www.hhs.gov/ohrp/policy/populations/guidance_407process.html.

**Are the exemptions different for research involving children?**

One of the six exemptions of research involving human subjects is narrowed in scope by Subpart D’s additional protections for research involving children. The other five exemptions apply to research involving children as human subjects in the same way that they apply to research involving adults.

The narrowed exemption is the exemption at 45 CFR 46.101(b)(2), which generally applies to research involving educational tests, interviews or survey procedures or observation of public behavior, if the data are recorded without individual identifiers, or if disclosure of the recorded responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to their financial standing, employability, or reputation. Where children will be involved as research subjects, however, the use of survey or interview procedures is eliminated from this exemption, and so is research involving the observation of public behavior if the investigators participate in the activity being observed.

In other words, the only research activities involving children that may fall under this exemption are those involving educational tests or observation of public behavior where the investigators do not participate in the activity being observed. To be exempt, these activities must also meet the condition that the data are recorded without individual identifiers, or the condition that disclosure of the recorded responses would not place the subjects at risk of criminal or civil liability or be damaging to their financial standing, employability, or reputation. Otherwise, all the requirements of the human subjects regulations apply.

**What is parental permission in the context of research involving children?**

By definition, children are unable to provide informed consent to participate in research, although they might be able to give their assent. The IRB should determine that unless parental permission can be waived adequate provisions are made for soliciting the permission of the parent(s) or legal guardian(s). The regulations define “permission” at 46.402(c) as the “agreement of parent(s) or guardian to the participation of their child or ward in research.” The term “parent” means a “child's biological or adoptive parent.” The term “guardian” means “an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.”

**Can parental or guardian permission for research involving children be waived?**

Yes, under certain circumstances. An Institutional Review Board (IRB) may waive the requirements for obtaining parental or guardian permission if it makes and documents the findings under either 45 CFR 46.116(c) or (d).

In addition to the provisions for waiver contained in 46.116(c) and (d), if the IRB determines that a research protocol is designed to study conditions in children or 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 parental permission requirements provided that an appropriate mechanism is in place to protect the children, and provided that the waiver is not inconsistent with federal, state, or local law (45 CFR 46.408(c)). The choice of an appropriate substitute mechanism (for example, appointing a child advocate or an assent monitor) for protecting children participating in research would depend on the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and the child’s age, maturity, status, and condition (45 CFR 46.408(c)).

**How should parental permission for research involving children be documented?**

Permission by parents or guardians shall be documented in accordance with and to the extent required by 46.117 of subpart A of 45 CFR part 46. Essentially, parental permission should be documented in a manner similar to that used to document informed consent. An Institutional Review Board (IRB) may find that waiver of documentation of informed consent is appropriate under the HHS regulations at 46.117.

**Do both parents need to provide permission for their child to participate in research?**

It depends. In general, permission should be obtained from both parents before a child is enrolled in research. However, the Institutional Review Board (IRB) may find that the permission of one parent is sufficient for research to be conducted under 46.404 or 46.405. When research is to be conducted under 46.406 and 46.407 permission must be obtained from both parents, 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.

**What is child assent, and how do the requirements vary with the age of the research subjects?**

“Assent” is defined by the regulations as follows:

“Assent” means a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. (45 CFR 46.402(b)).

This means the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way. When judging whether children are capable of assent, the Institutional Review Board (IRB) is charged with taking into account the ages, maturity, and psychological state of the children involved. The IRB has the discretion to judge children’s capacity to assent for all of the children to be involved in a proposed research activity, or on an individual basis.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to
be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.”

When does child assent have to be obtained for research and can it be waived?

The Institutional Review Board (IRB) is responsible for deciding whether child assent is required in proposed research activities. The IRB should require child assent unless it can be appropriately waived, or if the child is not capable of providing assent.

The regulations at 45 CFR 46.408(a) identify three types of circumstances where the IRB may determine that waiver of children’s assent is appropriate:

1. if the capability of some or all of the children is so limited that they cannot reasonably be consulted;
2. if the intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research.
3. if the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at either 45 CFR 46.116(c) or 45 CFR 46.116(d).

How should child assent for research participation be documented?

The HHS regulations do not require documentation of assent. The Institutional Review Board (IRB) has the discretion to determine the appropriate manner, if any, of documenting child assent. Based on such considerations as the child’s age, maturity, and degree of literacy, the IRB should decide what form of documentation, if any, is most appropriate. If adolescents are involved in research where a consent form would have been used if the subjects were adults, it would generally be appropriate to use a similar form to document an adolescent’s assent.

If young children are involved who are as yet unable to read, documentation should take a form that is appropriate for the purpose of recording that assent took place. The IRB may also decide that documentation of assent is not warranted.

Do parental permission and child assent for research involving children have to occur at the same time or in any particular order?

The HHS regulations do not specify the order in which parental or guardian permission and child assent should be sought. Therefore, Institutional Review Boards (IRB) have the discretion to determine the appropriate order given the research and the context in which it will be conducted.

In general, parental or guardian permission should be sought before seeking the assent of a child, particularly in more than minimal risk research, unless the requirement for obtaining parental or guardian permission can
be waived. There might be some cases, however, involving minimal risk research, where it would be reasonable to seek child assent prior to seeking parental permission.

For example, a school-based study of minimal risk (e.g., investigating children’s responses to music), could be posed to children in the school setting. Children could be asked if they wanted to participate and if so, sent home with a request for parental or guardian permission. In all cases, except when the requirement for obtaining parental or guardian permission can be waived, parental or guardian permission, even if sought after child assent is provided, is required before the child can be enrolled in the study.

**What happens when there is disagreement between a child and his/her parents about research participation?**

If a child is capable of assent and the Institutional Review Board (IRB) requires that assent be sought, it must be obtained before the child can participate in the research activity. Thus, if the child dissents from participating in research, even if his or her parents or guardian have granted permission, the child’s decision prevails.

However, the regulations state at 45 CFR 46.408(a) that the IRB may waive the assent requirements if the intervention or procedure involved in the research holds out the prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of research. Conversely, if a child assents to participate in research, and parental permission has not been waived by the IRB, the permission of the parents or guardian is also required before the child can be enrolled in the research.

**If by law a child is able to consent to treatment without parental permission, can they also consent to participate in research related to that treatment?**

HHS regulations at 45 CFR 46.402(a) define “children” as “persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.” If research on a specific treatment involves solely treatments or procedures for which minors can give consent outside the research context (under applicable state and local laws, for example, research on sexually transmitted diseases or pregnancy), such individuals would not meet the definition of children as defined at 45 CFR 46.402(a). Thus, subpart D would not apply to the research and parental permission (or waiver thereof) is not a consideration for these minors. Under these circumstances, minors may provide their own informed consent.

**What happens if a child reaches the legal age of consent while enrolled in a study?**

The Office for Human Research Protections (OHRP) notes that informed consent should be viewed as an ongoing process throughout the duration of a research project. When a child who was enrolled in research with parental or guardian permission subsequently reaches the legal age of consent to the procedures involved in ongoing research, the subject’s participation in the research is no longer regulated by the requirements of 45 CFR part 46.408 regarding parental or guardian permission and subject assent.
Unless the Institutional Review Board (IRB) determines that the requirements for obtaining informed consent can be waived, the investigators should seek and obtain the legally effective informed consent, as described in 45 CFR 46.116, for the now-adult subject for any ongoing interactions or interventions with the subjects. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject. However, the IRB could approve a waiver of informed consent under 45 CFR 46.116(d), if the IRB finds and documents that the required conditions are met.

Similarly, if the research does not involve any ongoing interactions or interventions with the subjects, but continues to meet the regulatory definition of “human subjects research” (for example, it involves the continued analysis of specimens or data for which the subject’s identity is readily identifiable to the investigator(s)), then it would be necessary for the investigator(s) to seek and obtain the legally effective informed consent of the now-adult subjects. The IRB may consider, if appropriate, a waiver under 45 CFR 46.116(d) of the requirements for obtaining informed consent in order for the subjects to continue their participation in the research.

**Are there special regulatory requirements for research involving children as subjects who are also wards?**

The HHS regulations at 45 CFR part 46, subpart D provide additional protections for children who are also wards of the State or any other agency, institution, or entity. These special protections for wards apply to two categories of research:

- research approved by an IRB under 45 CFR 46.406; or
- research approved in accordance with the requirements of 45 CFR 46.407 that requires a special level of HHS review beyond that provided by the Institutional Review Board (IRB).

As set out in 45 CFR 46.409, before children who are wards of the State or any other agency, institution, or entity can be included in either of the two categories of research referenced above, the research must meet the following conditions:

- the research must be either related to the children’s status as wards; or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards; and
- the IRB must 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, and must 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. The advocate should represent the individual child subject’s interests throughout the child’s participation in the research. The HHS regulations further require that the advocate not be 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.
When must an advocate be appointed to oversee a child’s enrollment in research?

HHS regulations at 45 CFR 46.409 require appointment of an advocate for each child who is a ward of the State or any other agency, institution, or entity, for the following two categories of research:

a. research approved by an Institutional Review Board (IRB) under 45 CFR 46.406; or
b. research approved under 45 CFR 407 that requires a special level of HHS review beyond that provided by the IRB.

What is the role of an advocate in research involving children?

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child throughout the duration of the child’s participation in the research. This includes ensuring that to the extent possible, the child understands what will be required of him or her during the research, and that if capable, the child provides his or her assent to participate.

Acting in the best interests of the child could include evaluating the ongoing impact of the research study on the child. The advocate should represent the individual child subject’s interests throughout the child’s participation in the research. This added protection is intended to ensure that the ward, who is particularly vulnerable, is not exploited, coerced, or subjected to undue influence or harm in the course of the research. HHS regulations further require that the advocate not be associated in any way (except in the role of advocate or member of the Institutional Review Board (IRB)) with the research, the investigator(s), or the guardian organization.

Who may be advocates for children involved in research that are wards and how should they be appointed?

Each institution is likely to rely on a different process for appointing an advocate. In some cases it might be a member of the Institutional Review Board (IRB), a representative from an institution’s health advocacy or ombudsman’s office, or a case worker, social worker, or counselor responsible for the child’s rights and welfare.

In some cases, state law or local practice might dictate who is responsible for appointing the advocate. In any case, the appointment should be made by a party or individual with no interest in or affiliation with the research being conducted. Investigators and IRBs should consult with their institution to determine the policies in procedures in place locally. IRBs should review and approve the process for appointing advocates.
Exempt Research Determination - FAQs:

Who may determine that research is exempt?

The regulations do not specify who at an institution may determine that research is exempt under 45 CFR 46.101(b). However, OHRP recommends that, because of the potential for conflict of interest, investigators not be given the authority to make an independent determination that human subjects research is exempt. (For more on this issue, see also Must there be review by someone other than the investigator before a research study is determined to be exempt?). Institutions should implement exemption policies that most effectively address the local setting and programs of research. OHRP recognizes that this may result in a variety of configurations of exemption authority, any of which are acceptable assuming compliance with applicable regulations.

In developing policies and procedures addressing exemption, OHRP recommends that institutions consider the following:

- Persons making an exemption determination should have access to sufficient information to make a correct determination. Evaluation tools and resources may take a variety of forms, including but not restricted to: checklists, Standard Operating Procedures, or specialized training for individuals authorized by the institution to make an exemption determination.
- When an exemption determination is made, the specific exemption category or categories should be included in the record and this information should be available for oversight and audit purposes.
- Institutional policies and procedures should identify clearly who is responsible for making exemption decisions. This may be done in a variety of ways, including delegation by name, role, or position.
- Institutions should make policy and procedure information addressing exemption determination readily accessible to investigators and others involved in the conduct and administration of human subjects research.
- Regarding the possibility of exemption determinations being made without review by someone other than the investigator, please also see "Must there be review by someone other than the investigator before a research study is determined to be exempt?"

OHRP notes that the HHS retains final authority as to whether a particular human subjects research study conducted or supported by HHS is exempt from the HHS regulations (45 CFR 46.101(c)).

Must there be review by someone other than the investigator before a research study is determined to be exempt?

No, the regulations do not require that someone other than the investigator be involved in making a determination that a research study is exempt. What they do require is that there be accurate determinations so that non-exempt research ends up being reviewed by an IRB. Because of the potential for conflict of interest in this situation, OHRP's long-standing recommendation is that investigators not be given the authority to make an independent determination that human subjects research is exempt.
OHRP recognizes that some institutions will wish to take advantage of the regulatory flexibility so that exemption determinations can be made in a manner that minimally delays research, while at the same time not diminishing human subject protections. While an institutional policy that allowed investigators to make their own exemption determinations, without additional protections, would likely risk inaccurate determinations, institutions may be able to craft policies that build in protections which lead to accurate determinations by appropriately dealing with investigator conflicts of interest and lack of detailed knowledge of the regulations.

For example, an institution might craft a checklist for certain exemption categories, with questions that are easily answered "yes" or "no" by an investigator, with certain answers leading to a clear conclusion that the study is exempt. The institution might allow a researcher to immediately begin a study after having completed such a checklist and filed it, together with accompanying documents, with an appropriate institutional office, without waiting for or requiring any prior review of that filing. Similarly, a web-based form might be created that served the same purpose, allowing the researcher to begin the research immediately after submitting the required information using the web form. In both instances, the key issue would be whether these procedures lead to correct determinations that studies are exempt.

OHRP notes that the HHS retains final authority as to whether a particular human subjects research study conducted or supported by HHS is exempt from the HHS regulations (45 CFR 46.101(c)).

What should investigators do when considering changes to an exempt study that could make it nonexempt?

Investigators should consult with the appropriate institutional authority whenever questions arise about whether planned changes to an exempt study might make that study nonexempt human subjects research. OHRP recommends that institutions have policies in place to define how proposed changes to exempt research will be evaluated. The person(s) authorized to make this determination should have access to sufficient information to make a correct determination. In addition, the institution should ensure the appropriate communication of such a policy to all investigators.

Informed Consent - FAQs:

What is informed consent and when, why, and how must it be obtained?

The HHS regulations at 45 CFR part 46 for the protection of human subjects in research require that an investigator obtain the legally effective informed consent of the subject or the subject’s legally authorized representative, unless (1) the research is exempt under 45 CFR 46.101(b); (2) the IRB finds and documents that informed consent can be waived (45 CFR 46.116(c) or (d)); or (3) the IRB finds and documents that the research meets the requirements of the HHS Secretarial waiver under 45 CFR 46.101(i) that permits a waiver of the general requirements for obtaining informed consent in a limited class of research in emergency settings. When informed consent is required, it must be sought prospectively, and documented to the extent
required under HHS regulations at 45 CFR 46.117. [Food and Drug Administration (FDA) regulations at 21 CFR part 50 may also apply if the research involves a clinical investigation regulated by FDA.]

The requirement to obtain the legally effective informed consent of individuals before involving them in research is one of the central protections provided for under the HHS regulations at 45 CFR part 46. This requirement is founded on the principle of respect for persons, one of the three ethical principles governing human subjects research described in the Belmont Report. The principle of respect for persons requires that individuals be treated as autonomous agents and that the rights and welfare of persons with diminished autonomy be appropriately protected. The Belmont Report states that an autonomous agent is “an individual capable of deliberation about personal goals and of acting under the direction of such deliberation.” Respect for persons requires that prospective research subjects “be given the opportunity to choose what shall or shall not happen to them” and thus necessitates adequate standards for informed consent.

The informed consent process involves three key features: (1) disclosing to potential research subjects information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the research. Informed consent must be legally effective and prospectively obtained. HHS regulations at 45 CFR 46.116 and 45 CFR 46.117 describe the informed consent requirements.

The informed consent process is the critical communication link between the prospective human subject and an investigator, beginning with the initial approach of an investigator to the potential subject (e.g., through a flyer, brochure, or any advertisement regarding the research study) and continuing until the completion of the research study. For the purposes of the HHS regulations at 45 CFR part 46, “investigators” are individuals who conduct human subjects research projects, including individuals directly involved in seeking the voluntary informed consent of potential subjects. Investigators can include physicians, scientists, nurses, administrative staff, teachers, and students, among others.

The informed consent process should be an active process of sharing information between the investigator and the prospective subject. The exchange of information between the investigator and prospective subjects can occur via one or more of the following modes of communication, among others: face-to-face contact; mail; telephone; video; or fax. Prospective subjects should be provided with ample opportunity to ask questions and seek clarification from the investigator. The prospective subjects should be in a position to freely decide whether to initially enroll in the research, or later, to withdraw or continue participating in the research. The informed consent process should ensure that all critical information about a study is completely disclosed, and that prospective subjects or their legally authorized representatives adequately understand the research so that they can make informed choices.

The procedures used in seeking and obtaining informed consent should be designed to communicate with the subject population in terms that they can understand. Information about a research project must be presented in such a way that enables each person to voluntarily decide whether or not to participate as a research subject. Thus, the information must be conveyed in language understandable to those being asked to participate as subjects in the research (45 CFR 46.116).
For most research, informed consent is documented using a written document that provides key information regarding the research. The consent form is intended, in part, to provide information for the potential subject’s current and future reference and to document the interaction between the subject and the investigator. However, even if a signed consent form is required, it alone does not constitute an adequate consent process. The informed consent process is an ongoing exchange of information between the investigator and the subject and could include, for example, use of question and answer sessions, community meetings, and videotape presentations. In all circumstances, however, individuals should be provided with an opportunity to have their questions and concerns addressed on an individual basis.

The consent process and its documentation should be revised when deficiencies in its accuracy or completeness are noted, when new information about reasonably foreseeable risks and potential benefits becomes available, or when other additional information becomes known that will improve the consent process. Such revisions must be reviewed and approved by an IRB prior to the revised consent being utilized except when necessary to eliminate apparent immediate hazards to subjects (45 CFR 46.103(b)(4)).

Is it possible to obtain legally effective informed consent to research in an urgent or emergency care setting?

Yes, in certain circumstances it is possible to obtain legally effective informed consent in an urgent or emergency care setting. For a particular research study, the answer depends on (1) the expected medical condition of the prospective subject population; (2) the nature of the research; (3) whether there is sufficient time for the potential subjects or their legally authorized representatives to consider participation; and (4) whether the circumstances for obtaining informed consent appropriately minimize the possibility of coercion or undue influence. The Institutional Review Board (IRB) and investigator(s) would have to consider several variables. For example, what is the likely health and emotional condition of the patient population being considered for the proposed research (e.g., conscious but receiving emergency care, undergoing preparation prior to surgery)? What is the likely ability of this population during the consent process to process information, ask questions, and consider the risk involved? What is the timing of the consent process and is it so close to the receipt of care that the patient might blur the distinction between treatment and research?

Because individuals receiving urgent or emergent medical care frequently may be vulnerable to coercion or undue influence, even if temporarily, additional protections may be required to ensure the subject's consent to participate in research is truly voluntary and sought under circumstances that minimize the possibility of coercion or undue influence (45 CFR 46.111(b), 45 CFR 46.116). In addition, in some cases, it might be possible to obtain consent from a legally authorized representative (e.g., in the case of decisionally incapacitated individuals). In certain emergency circumstances, the Secretarial waiver of informed consent under 45 CFR 46.101(i) may be applicable. It should be noted that if the research is regulated by FDA, the Secretarial waiver permits the research to be conducted under a comparable provision.

What are the basic elements of informed consent?

The basic required elements of informed consent can be found in the HHS regulations at 45 CFR 46.116(a). OHRP also has a tips sheet for informed consent available at http://www.hhs.gov/ohrp/policy/ictips.html.

The regulations require that the following information must be conveyed to each subject:

- 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;
  1. a description of any reasonably foreseeable risks or discomforts to the subject;
  2. a description of any benefits to the subject or to others which may reasonably be expected from the research;
  3. a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
  4. a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
  5. 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;
  6. 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
  7. a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional elements are described at 45 CFR 46.116(b)

What additional information might be appropriate to provide during the consent process?

When determined to be appropriate by the Institutional Review Board (IRB), subjects must be provided with one or more of the following additional elements of information during the informed consent process (see 45 CFR 46.116(b)):

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.

It is up to the IRB to determine in a particular instance whether some or all of the above additional elements must be included as part of the informed consent process for a particular study. The IRB should make this determination based on the nature of the research and its knowledge of the local research context. If the IRB determines that additional elements are appropriate to the research study, this additional information should be considered just as essential as the eight basic elements of informed consent described in the HHS regulations at 45 CFR 46.116(a).

Furthermore, an IRB may require that additional information beyond the basic and additional elements be given to subjects during the informed consent process, when in the IRB’s judgment the additional information would meaningfully add to the protection of the rights and welfare of the subjects 45 CFR 46.109(b).

Can consent or parental permission ever be “passive” or “implied”?

Terms such as “passive” or “implied” consent are not referenced in the HHS regulations. However, OHRP is aware that these terms are sometimes used by investigators or IRBs to describe a process in which consent or parental permission requirements have been altered or waived, or for which the requirement to document consent or parental permission has been waived.

HHS regulations at 45 CFR 46.116 state that no investigator may involve a human being as a subject unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative. However, under conditions specified in the regulations at 45 CFR 46.116(c) or (d) an IRB may approve a consent procedure that does not include, or that alters some or all of the elements of informed consent set forth in 45 CFR 46.116. In some cases, an IRB also can waive the requirement to obtain consent (45 CFR 46.116(c) and (d)). In addition, under conditions specified in the regulations at 45 CFR 46.117, an IRB may also waive the requirement for documentation of informed consent. (Note that the regulations at 45 CFR 46.408(c) also permit an IRB to waive parental permission.)

For example, a researcher conducting a survey (that does not qualify for an exemption under 45 CFR 46.101(b) mails a survey questionnaire to a random sample of adults. The survey materials clearly state that by responding to the questions and mailing the survey back, the recipients have agreed to participate in the research. However, the materials accompanying the questionnaire do not include all of the elements of consent listed at 45 CFR 46.116(a) and do not require that the subject sign a consent form. If the IRB has approved this alteration of the consent process and has waived the need for documentation of consent, then such procedures are permissible under the regulations. By sending back a completed survey the recipient has implied that he or she consents to participate but has not signed an informed consent document. Although some might call this “implied informed consent,” OHRP would consider this to be a permissible informed consent process if the IRB has approved the informed consent alteration and waived the requirement for documentation of informed consent.
The term “passive consent” is sometimes used in research with children to describe situations in which the investigator can assume that a parent is permitting a child to participate. For example, researchers collecting survey and behavioral data from children at school provide parents with information regarding the study by mail and ask the parent(s) to return a form if they do not want their child to participate. Sometimes this practice is referred to as an opt out procedure, which is not consistent with the regulatory requirement for seeking and obtaining parental permission. If the IRB determines that the conditions for waiver of parental permission can be met, then the IRB could waive the requirement for parental permission under 45 CFR 46.408(c) or 45 CFR 46.116(c) or (d). Even though not required by the regulations, an IRB may require that parents be given the opportunity to refuse permission even when the IRB has waived the regulatory requirement to obtain parental permission.

What does it mean to minimize the possibility of coercion or undue influence?

The HHS regulations state that “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” (45 CFR 46.116). This requirement applies to all nonexempt human subjects research not eligible for a waiver of the consent requirements.

Coercion occurs when an overt or implicit threat of harm is intentionally presented by one person to another in order to obtain compliance. For example, an investigator might tell a prospective subject that he or she will lose access to needed health services if he or she does not participate in the research.

Undue influence, by contrast, often occurs through an offer of an excessive or inappropriate reward or other overture in order to obtain compliance. For example, an investigator might promise psychology students extra credit if they participate in the research. If that is the only way a student can earn extra credit, then the investigator is unduly influencing potential subjects. If, however, she offers comparable non-research alternatives for earning extra credit, the possibility of undue influence is minimized.

In addition to undue influence that can arise with the offering of rewards, undue influence also can be subtle. For example, patients might feel obligated to participate in research if their physician is also the investigator, or students might feel pressure to participate in research if everyone else in the class is doing so. Because influence is contextual, and undue influence is likely to depend on an individual’s situation, it is often difficult for IRBs to draw a bright line delimiting undue influence. It is up to the IRB to use its discretion in determining which circumstances give rise to undue influence. For example, an IRB might consider whether the informed consent process will take place at an appropriate time and in an appropriate setting, and whether the prospective subject may feel pressured into acting quickly or be discouraged from seeking advice from others.

Because of their relative nature and lack of clear-cut standards on the boundaries of inappropriate and appropriate forms of influence, investigators and IRBs must be vigilant about minimizing the possibility for coercion and undue influence. Reasonable assessments can be made to minimize the likelihood of undue influence or coercion occurring. For example, IRBs may restrict levels of financial or nonfinancial incentives for participation and should carefully review the information to be disclosed to potential subjects to ensure
that the incentives and how they will be provided are clearly described. Known benefits should be stated accurately but not exaggerated, and potential or uncertain benefits should be stated as such, with clear language indicating how much is known about the uncertainty or likelihood of these potential benefits.

The regulatory requirements for IRB review and approval also specify the need for the IRB -- in order to approve research covered by the HHS regulations -- to ensure that “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” (45 CFR 46.111(b)). Thus, inducements that would ordinarily be acceptable in some populations may become undue influences for these vulnerable subject groups.

**When does compensating subjects undermine informed consent or parental permission?**

The HHS regulations require that “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” (45 CFR 46.116). Paying research subjects in exchange for their participation is a common and, in general, acceptable practice. However, difficult questions must be addressed by the IRB. For example, how much money should research subjects receive, and for what should subjects receive payment -- their time, inconvenience, discomfort, or some other consideration -- IRBs must be sensitive to whether any aspect of the proposed remuneration will be an undue influence, thus interfering with the potential subjects’ ability to give voluntary informed consent.

Remuneration for participation in research should be just and fair. However, the specifics of each protocol will influence how those determinations are made. Both researchers and IRBs need to be familiar with the study population and the context of the research in order to make reasonable judgments about how compensation might affect participation. Wherever the remuneration is set, it will influence the decisions of some more than others. In particular, it will be more important to those for whom it will make a significant financial difference. Thus, IRBs should be cautious that payments are not so high that they create an “undue influence” or offer undue inducement that could compromise a prospective subject’s examination and evaluation of the risks or affect the voluntariness of his or her choices.

Information submitted to IRBs should indicate and justify proposed levels and purposes of remuneration, which also should be clearly stated in the accompanying consent forms.

Some institutions have adopted policies regarding the recruitment and payment of volunteers. IRBs and investigators should ensure that the consent process includes a detailed account of the terms of payment, including a description of the conditions under which a subject would receive partial or no payment (e.g., what will happen if he or she withdraws part way through the research or the investigator removes a subject from the study for medical or noncompliance reasons).

Finally, in studies of considerable duration or that involve multiple interactions or interventions, OHRP recommends that payment be prorated for the time of participation in the study rather than delayed until
study completion, because the latter could unduly influence a subject’s decision to exercise his or her right to withdraw at any time. For example, if the study is conducted over a period of 6 months, there might be a monthly or bi-monthly payment. Or, if the study involves 12 sessions, there might be payment after every two sessions.

The above principles would apply to remuneration offered to parents whose children are prospective subjects.

[Note: The previous version of the response to this FAQ included the following sentences. “In no case should remuneration be viewed as a way of offsetting risks; that is, it should not be considered a benefit to be weighed against study risks. The level of remuneration should not be so high as to cause a prospective subject to accept risks that he or she would not accept in the absence of the remuneration.” The first sentence has been struck because this FAQ focuses on potential undue influence in the consent process (45 CFR 46.116) rather than on IRB considerations under 45 CFR 46.111. However, OHRP continues to assert that IRBs should not consider remuneration as a way of offsetting risks. The second sentence has been deleted to clarify that remuneration to subjects may include compensation for risks associated with their participation in research and that compensation may be an acceptable motive for agreeing to participate in research. In addition, the previous version contained the following sentence, which has been struck because it is focused on IRB considerations under 45 CFR 46. 111 rather than informed consent, and was misplaced in this FAQ: “IRBs may need to request of the investigator some plan for monitoring subject recruitment to ensure that such inducements do not result in inequitable subject recruitment (e.g., recruiting only economically disadvantaged individuals).”]

Can non-financial enrollment incentives constitute undue influence?

Yes, in certain circumstances. Non-monetary incentives (e.g., extra credit for students, access to services or programs) also can create undue influence on a potential subject’s decision about research participation. Informed consent always must be voluntary (45 CFR 46.116).

IRBs should ensure that non-financial incentives are not so great as to diminish the voluntariness of consent or cloud someone’s appreciation of risks or potential benefits that might be gained from participating in a study (45 CFR 46.116). Moreover, it must be clear that choosing to not participate will not adversely affect an individual’s relationship with the institution or its staff or the provision of services in any way (e.g., loss of credits or access to programs) (45 CFR 46.116(a)(8)).

Overt coercion (e.g., threatening loss of services or access to programs to which the potential subjects are otherwise entitled) is never appropriate. However, it might be permissible to provide incentives to participate that do not constitute undue influence. Using enrollment incentives to recruit subjects may be ethically permissible as long as the IRB has determined that, although they may be a factor in a subject’s decision to participate, they have not served to unduly influence the subject to participate. To make this determination, IRBs should know who the subject population will be, what incentives are being offered, and the conditions under which the offer will be made.
What constitutes coercion or undue influence when students are involved in research in a college or university setting?

The regulations require that the investigator seek consent only under circumstances that minimize the possibility of coercion or undue influence (45 CFR 46.116). The Office for Human Research Protections (OHRP) recommends that institutions have policies in place that clarify for students and faculty that any participation of students in research must be voluntary. Reasonable levels of extra credit or rewards may be offered for participating in research. If extra credit or rewards are offered for participation, students must be provided with and informed of non-research alternatives involving comparable time and effort to obtain the extra credit in order for the possibility of undue influence to be minimized. However, if participation in research is a course requirement, students must be informed of non-research alternatives involving comparable time and effort to fulfill those requirements in order for the possibility of undue influence to be minimized. Moreover, students must not be penalized for refusing to participate in research (45 CFR 46.116(a)(8)).

In addition, some research institutions use a so-called “student subject pool” to identify students who might be willing to participate in research, even when the exact nature of the research to be conducted has not yet been determined. Extra credits or other rewards are often offered as an incentive to encourage participation. Students who sign up for such pools have not legally consented to participate in a research study since they have not been provided with sufficient information concerning the exact study in which they would participate. Thus, signing up to be in a subject pool is only a first and preliminary step by which individuals can indicate their willingness to be considered for research participation. The student must also provide informed consent, unless the consent requirement is waived by an IRB once he or she is being considered for a specific study (45 CFR 46.116). Furthermore, individuals in the pool must be free to decline participation in any available research projects without penalty (45 CFR 46.116(a)(8)).

What constitutes coercion or undue influence when employees are the subjects of research?

The issues involving employees as research subjects are essentially identical to those involving students as research subjects: that is, investigators and IRBs must be cautious about the potential for coercion or undue influence and the need to protect confidentiality.

Employee participation raises questions about the ability of employees to exercise free choice, for example, because of the possibility that a decision to participate could affect performance evaluations or job advancement, even if it is only the employee’s perception that this is the case. In the case of coercion, refusal to participate might result in a loss of benefits (e.g., salary increases, time off). In the case of undue influence, a decision to participate could result in a job promotion. Employees are likely to view their employers as authority figures to whom they must show deference, which could undermine the freedom of their choice.
Should the initial consent or parental permission procedure ever be repeated or supplemented?

Yes, in some circumstances. The HHS regulations require that an investigator obtain legally effective informed consent from subjects or a legally authorized representative before the subjects may be involved in research (45 CFR 46.116), unless this requirement has been waived by an IRB. Likewise, for research involving children, permission of the potential subjects' parents or guardians must be obtained (45 CFR 46.408(c)), unless an IRB has waived this requirement. Ensuring an adequate consent or parental permission process may require repeating or supplementing the initial consent procedure. The regulations also stipulate that “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 minimizes the possibility of coercion or undue influence” (45 CFR 46.116). This requirement also might necessitate repeating or supplementing the initial consent procedure.

Informed consent and parental permission should be viewed as an ongoing process. The regulations do not explicitly describe all of the circumstances that might require repeating or supplementing the informed consent process. However, they do require that potential subjects be provided, when appropriate, with 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” (45 CFR 46.116(b)(5)). Thus, to ensure that consent remains legally effective -- for example, if the protocol design or risks have changed, or if a substantial period of time has elapsed between the time consent was obtained and the study begins -- it might be necessary to ensure that subjects still want to participate in the research. For example, the prospective subject may no longer be interested in participating, may no longer meet the eligibility criteria, may no longer find the risks acceptable, or may no longer have the time to complete all study-related activities.

The IRB must review and approve any changes in the approved consent procedure, including alterations of the content, as described in the elements listed at 45 CFR 46.116, or in its timing, and may consider whether there is a need to reiterate the process (45 CFR 46.103(b)(4)). The IRB should take into account whether the changes could potentially affect a subject’s understanding of the nature of the study or potentially affect a subject’s willingness to participate. If so, such changes need to be made in the informed consent document. Even without significant changes to a protocol or informed consent document, periodic reiteration or affirmation of consent is often a good idea, especially if the study takes place over a long period of time or is particularly complex. Minor changes, such as correcting nonsubstantive typographical errors in the consent document, would not generally rise to a level requiring repeating the consent process.

How far in advance of research participation can consent be obtained?

The HHS regulations at 45 CFR part 46 do not specify how far in advance of study entry a subject can provide consent. The amount of time required by a subject to make a decision would presumably depend on the nature of the study, taking into account, among other factors, the degree of risk, potential benefits, alternatives, and desire to consult with family members or others. However, if a prolonged period of time elapses from the date of consent to the date of entry into the study even if there have been no changes in the study design or no new significant findings affecting the study it might be prudent to review the information contained in the consent form with the subject prior to initiating any research procedures with the subject.
Can records or databases be reviewed to identify potential subjects without obtaining informed consent or parental permission?

Yes, under certain circumstances. Although the HHS regulations do not specifically reference this type of activity, sometimes referred to as “preparatory to research,” such an activity must be reviewed and approved by an IRB in accordance with HHS regulations at 45 CFR 46.109(a) when:

1. The activity involves human subjects research, as defined by the regulations at 45 CFR 46.102(f);
2. The research does not meet the criteria for exemption under HHS regulations at 45 CFR 46.101(b).

In general, informed consent of the subjects, or parental permission for children involved in research, must be sought and documented in accordance with, and to the extent required by, HHS regulations at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116”>45 CFR 46.116 and 45 CFR 46.117 respectively.

However, an IRB may approve a consent or parental permission procedure that does not include, or that alters, some or all of the elements of informed consent, or may waive the requirements to obtain informed consent (45 CFR 46.116(c) or (d)). In order to permit investigators to obtain and record identifiable private information for the purposes of identifying potential subjects, OHRP expects that IRBs routinely will waive the requirement for informed consent for such activities. In assessing the level of risk to determine whether a waiver of informed consent or parental permission is permissible for the identification of potential subjects, the IRB need only consider the risk of investigators accessing the subjects’ identifiable private information, not the risks of the research in toto.

How can the consent and parental permission processes be designed to facilitate understanding?

The procedures used in obtaining informed consent and parental permission should be designed to inform the subject population or the parents of the subject population about the research in terms that they can understand. Therefore, informed consent and parental permission language and its documentation in the accompanying forms (especially explanation of the study’s purpose, duration, experimental procedures, alternatives, risks, and benefits) should be provided in language that is understandable and culturally sensitive to those being asked to participate or provide permission for their child’s participation.

If the prospective subjects include, for example, persons whose primary language is not English, or populations with low literacy levels, the IRB should take special care to ensure that both oral presentations and consent or permission forms are comprehensible to all subjects or the parents of subjects who are children. Subjects who do not speak English should be presented with a consent or permission document written in a language understandable to them. OHRP strongly encourages the use of such a document whenever possible. (See OHRP guidance on this topic at http://www.hhs.gov/ohrp/policy/ic-non-e.html; for information about requirements for child assent, see FAQs regarding research with children.)
In general, ordinary language should replace technical terms (e.g., upper extremities are better referred to as arms, venipuncture as taking blood from your arm with a needle, and so forth).

Some IRBs find that their lay members (e.g., community or non-scientist members) are particularly helpful in suggesting necessary modifications to language. Others ask members of the proposed subject population (e.g., clinic patients) to review consent or permission forms and indicate which parts they do not understand.

**Can an electronic signature be used to document consent or parental permission?**

Yes, under certain circumstances. First, the investigator and the IRB need to be aware of relevant laws pertaining to electronic signatures in the jurisdiction where the research is going to be conducted.

Unless the IRB waives the requirement for the investigator to obtain a signed consent or permission form based on the HHS regulations at 45 CFR 46.117(c), a written consent or permission form, which may be an electronic version, must be given to and signed by the subjects or the subjects' legally authorized representatives or the parents of subjects who are children. Some form of the consent document must be made available to the subjects or the parents of subjects who are children in a format they can retain. OHRP would allow electronic signature of the document if such signatures are legally valid within the jurisdiction where the research is to be conducted.

OHRP does not mandate a specific method of electronic signature. Rather, OHRP permits IRBs to adopt such technologies for use as long as the IRB has considered applicable issues such as how the electronic signature is being created, if the signature can be shown to be legitimate, and if the consent or permission document can be produced in hard copy for review by the potential subject. One method of allowable electronic signatures in some jurisdictions is the use of a secure system for electronic or digital signature that provides an encrypted identifiable “signature.” If properly obtained, an electronic signature can be considered an “original” for the purposes of recordkeeping.

**Is a faxed copy of the signed consent or parental permission form acceptable to document informed consent?**

Yes, if it is more convenient for the subjects or parents of children who are subjects to fax a signed copy of the consent or permission form to the investigator, the research subjects or parents may fax the signed form. The subjects or parents need not provide the investigator with the original signed consent or parental permission documents.

**Who must sign the informed consent or parental permission document?**

When a written consent or parental permission form is used that embodies some or all of the elements of informed consent required by the regulations at 45 CFR 46.116, the regulations only require that the informed consent or parental permission document be signed by the subjects or the subjects’ legally authorized representatives or by the parents of children who are subjects (45 CFR 46.117(a)) and 45 CFR 46.408(d)). Only in situations where a short form is used, stating that the elements of informed consent required by 45 CFR 46.116 have been presented orally to the subject or the subject’s legally authorized
representative or to the parent(s) of a child who is a subject, are there additional requirements for signatures (45 CFR 46.117(b)(2)).

For the consent or parental permission process using the short form, the regulations state that there must be a witness to the oral presentation, who then signs both the short form and a copy of the IRB-approved written summary of what is to be said to the subject or the subject's legally authorized representative or to the parent(s) of a child who is a subject. The subject or the subject’s legally authorized representative or the parent(s) must sign the short form, and the person actually obtaining the consent must sign the copy of the summary (45 CFR 46.117(b)(2)). Thus, three types of persons are involved in this specific consent process -- the subject or legally authorized representative or parent(s) of a child who is a subject, the person obtaining consent, and the witness.

**Do signatures on consent forms have to be dated?**

Although the HHS regulations at 45 CFR 46.117 do not require the consent form to be dated at the time it is signed, OHRP recommends that it be dated so that the IRB and others can document that informed consent was obtained prior to a subject’s participation in the research.

**Who can be a legally authorized representative (LAR) for the purpose of providing consent on behalf of a prospective subject?**

Legally authorized representative (LAR) 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 (45 CFR 46.102(c)). The regulations state that “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” (45 CFR 46.116). The issue as to who can be an LAR is determined by the laws of the jurisdiction in which the research is conducted (e.g., local or state law). Some states have statutes, regulations, or common law that specifically address consent by someone other than the subject for participation in research. Most states have no law specifically addressing the issue of consent in the research context. In these states, law that addresses who is authorized to give consent on behalf of another person to specific medical procedures or generally to medical treatment may be relevant if the research involves those medical procedures or medical treatment.

When the laws of the jurisdiction in which the research is being conducted provide a reasonable basis for authorizing an individual to consent on behalf of a prospective subject to their participation in the research procedure(s), OHRP would consider such an individual to be an LAR as defined by HHS regulations at 45 CFR 46.102(c). IRBs may wish to consult with legal counsel when deciding who can serve as an LAR for subjects of proposed research.

**When may a legally authorized representative provide consent on behalf of an adult with diminished decision-making capacity?**

In answering this question, the HHS regulations at 45 CFR part 46 should be consulted in addition to the laws of the jurisdiction in which the research is conducted. As a general matter, if an adult lacks capacity to
consent, for example, as a result of trauma, mental retardation, some forms of mental illness, or dementia - whether temporary, progressive, or permanent - only a legally authorized representative for that adult can give consent for participation in the research, unless the requirement to obtain informed consent is waived by the IRB in accordance with the requirements at 45 CFR 46.116(c)(d), or in accordance with the provisions for emergency waiver, which are permitted under the authority of the HHS Secretary at 45 CFR 46.101(i).

(See the Federal Register notice of this waiver at: http://www.hhs.gov/ohrp/documents/100296.pdf.) Should the subject regain or develop the capacity to consent, then his or her consent must be obtained for any further research, as the consent of the legally authorized representative is no longer valid.

What should be considered in seeking informed consent from individuals with diminished decision-making capacity?

The HHS regulations are silent on the consent procedures specific to subjects with impaired decision-making capacity, for example, as a result of trauma, mental retardation, some forms of mental illness, or dementia, whether temporary, progressive, or permanent. The regulations do require that the IRB ensure that “additional safeguards have been included in the study to protect the rights and welfare” of all subjects that are “likely to be vulnerable to coercion or undue influence.” The regulations include “mentally disabled persons” in this category (45 CFR 46.111(b)).

In research involving adult subjects with mental illnesses or cognitive impairments, the IRB and investigator(s) must be knowledgeable about the condition and any level of impairment that is likely to be present in the subject population. The regulations do speak to the fact that the IRB must possess “the professional competence necessary to review specific research activities” (45 CFR 46.107(a)). This is achieved either by having members with the appropriate experience and expertise or inviting consultants with competence in the special area to assist in the review of issues that require expertise beyond or in addition to that available on the IRB (45 CFR 46.107(a) and (f)). Ensuring such expertise on the IRB improves its ability to make determinations about subject recruitment, enrollment, and informed consent requirements that best match the needs of the subjects.

In some research, such as longitudinal studies involving progressive disorders or aging populations, enrolled subjects may be competent to consent on their own behalf at the outset, yet may experience effects of progressive or intermittent disorders that lead to decisional impairment during the course of the study. In these situations IRBs and investigators should consider the need to discuss with the prospective subjects whether they should designate someone to serve as a legally authorized representative at the outset of the study, consistent with all applicable laws. Even if a subject has consented on his or her own accord, a designated representative would be ready to step in as the legally authorized representative if the subject’s ability to assess his or her own needs and interests becomes compromised during the study.

What are the requirements for assent and parental permission in research with children?

The IRB must determine, to the extent required by 45 CFR 46.116, 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 -- as well as the permission of the parents (45 CFR 46.408). Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research (45 CFR 46.402(c)).

By regulatory definition, 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” (45 CFR 46.402(a)). In the United States the legal age of adulthood is a matter of state and local law. This means that who is legally considered a child may vary from state to state; in a large majority of states 18 years of age is the legal age of adulthood, but this is not true in every state, locality, or territory. State law also may address specific circumstances in which a person younger than the age of adulthood is legally authorized to consent to medical procedures: for example, some states allow children younger than the legal age of adulthood to consent to the provision of contraceptive services. Certain states provide a mechanism for the emancipation of minors, through which a child younger than the legal age of adulthood may gain certain civil rights, which might include the legal ability to consent to research participation.

The definition of children also takes into account the particular interventions or interactions involved in the proposed research (e.g., surveys, blood tests). For example, in some places individuals who are 16 years of age may legally consent to certain clinical interventions or interactions. If the involvement of human subjects in a proposed research activity consists of these interventions or interactions, then those individuals may be considered as adults for that purpose. If a proposed activity includes an intervention or interaction for which the subject has not yet reached the legal age of consent, however, that person must be considered a child.

Under 45 CFR 408(b) the IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 or 45 CFR 46.405. Where research is conducted under 45 CFR 46.406 or 45 CFR 46.407, permission must be obtained from both parents 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.

Although the regulations state that children are unable to provide legally effective informed consent to participate in research, some might be able to give their assent. Assent means a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent (45 CFR 46.402(b)).

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted regarding assent, 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 certain circumstances in accord with 45 CFR 46.116 and 45 CFR 46.408(a).

May the requirement for obtaining informed consent or parental permission be altered or waived?

Waiver or alteration of the requirements for obtaining informed consent from adult subjects can occur under any of the following three provisions:
1. Public benefit or service programs: an IRB may approve a consent procedure that alters some or all of the elements of informed consent, or waive the requirement to obtain informed consent under HHS regulations at 45 CFR 46.116(c), provided that the IRB finds and documents that both of the following conditions are met:
   a. the research could not practicably be carried out without the waiver or alteration; and
   b. 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.

2. Research in general: an IRB may waive or alter the requirement of informed consent under 45 CFR 46.116(d), provided that the IRB finds and documents that all of the following four conditions are met:
   a. the research involves no more than minimal risk to the subjects;
   b. the waiver or alteration will not adversely affect the rights and welfare of the subjects;
   c. the research could not practicably be carried out without the waiver or alteration; and
   d. whenever appropriate, the subjects will be provided with additional pertinent information after participation.

3. Research in emergency settings: an IRB may also waive the requirement for obtaining informed consent if it finds and documents that the research meets the requirements of the HHS Secretarial waiver under 45 CFR 46.101(i) that permits a waiver of the general requirements for obtaining informed consent in a limited class of research in emergency settings (PDF) (23KB).

For research involving children, an IRB may waive the requirements for obtaining parental or guardian permission under any of the following four provisions:

1. The IRB makes and documents the required findings under 45 CFR 46.116(c) as described above.
2. The IRB makes and documents the required findings under 45 CFR 46.116(d) as described above.
3. The IRB determines that a research protocol is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), and the following 2 additional criteria are also met:
   a. an appropriate mechanism is in place to protect the children, and
   b. the waiver is not inconsistent with federal, state, or local law (45 CFR 46.408(c)). The choice of an appropriate substitute mechanism (for example, appointing a child advocate or an assent monitor) for protecting children participating in research would depend on the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and the child’s age, maturity, status, and condition (45 CFR 46.408(c)). Note that an IRB may waive the requirement for obtaining parental or guardian permission under 45 CFR 46.408(c) even if the research involves more than minimal risk to the child subjects.
4. The IRB finds and documents that the research meets the requirements of the HHS Secretarial waiver under 45 CFR 46.101(i) that permits a waiver of the general requirements for obtaining informed consent in a limited class of research in emergency settings (PDF) (23KB).

What is the definition of guardian in the context of obtaining consent for research involving children?

The term guardian means “an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care” (45 CFR 46.402(e)) The role of a guardian in the context of research involving a child who is a ward is to provide permission, in lieu of a child’s biological or adoptive parents, for the ward to participate in the research (45 CFR 46.402(c)). For a more extensive discussion see FAQs on Research with Children.

What happens if a child reaches the legal age of consent while enrolled in a study?

The Office of Human Research Protections notes that informed consent should be viewed as an ongoing process throughout the duration of a research project. When a child who was enrolled in research with parental or guardian permission subsequently reaches the legal age of consent to the procedures involved in ongoing research, the subject’s participation in the research is no longer regulated by the requirements of 45 CFR part 46.408 regarding parental or guardian permission and subject assent.

Unless the IRB determines that the requirements for obtaining informed consent can be waived, the investigators should seek and obtain the legally effective informed consent, as described in 45 CFR 46.116, for the now-adult subject for any ongoing interactions or interventions with the subjects. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject. However, the IRB could approve a waiver of informed consent under 45 CFR 46.116(d), if the IRB finds and documents that the required conditions are met.

Similarly, if the research does not involve any ongoing interactions or interventions with the subjects, but continues to meet the regulatory definition of “human subjects research” (e.g., it involves the continued analysis of specimens or data for which the subject’s identity is readily identifiable to the investigator(s)), then it would be necessary for the investigator(s) to seek and obtain the legally effective informed consent of the now-adult subjects. The IRB may consider, if appropriate, a waiver under 45 CFR 46.116(d) of the requirements for obtaining informed consent in order for the subjects to continue their participation in the research.

What is a waiver or alteration of informed consent or parental permission?

The HHS regulations allow the IRB to waive the requirement for obtaining informed consent or parental permission or to approve a consent procedure that leaves out or alters some or all of the elements of informed consent otherwise required under 45 CFR 46.116(a) and (b).

Waiving the requirement for obtaining informed consent or parental permission means that the IRB has determined that investigators need not obtain the subjects’ informed consent to participate in research. For example, some research about natural behavior may require that subjects be unaware that the research is
taking place. Such research can only be approved by the IRB if the research meets the criteria for a waiver of informed consent under HHS regulations and for approving research according to 45 CFR 46.111.

An IRB may approve research for which some or all of the elements of informed consent at 45 CFR 46.116 (a) and (b) have been altered, or for which some elements have been left out. For example, some research designs require that subjects be left unaware of the particular purpose of the research, because the subjects’ responses might be biased if they know in advance what the investigators are seeking. Such research designs do not preclude offering potential subjects some information about the research and giving them the opportunity to decide whether to participate. The IRB may approve such research in which investigators will leave out or alter elements of informed consent, so long as the research meets the criteria for approving research in 45 CFR 46.111, and the research meets the criteria specified in the HHS regulations for leaving out or altering those elements.

**What are the regulatory bases for waiving or altering some or all of the required elements of informed consent or parental permission?**

The conditions under which an IRB may waive the requirement for obtaining informed consent or parental permission or may approve a consent procedure that leaves out or alters some or all of the elements of informed consent derive from four sources in the HHS regulations.

1. At 45 CFR 46.116(c), the regulations identify when IRBs may waive or approve an alteration of informed consent in some research examining state or local public benefit or service programs, or certain features of those programs.
2. At 45 CFR 46.116(d) the regulations identify when IRBs may waive or approve an alteration of informed consent in research that meets four specified criteria.
3. At 45 CFR 46.408(c), the regulations identify when IRBs may approve waiver of parental permission in certain research involving children.
4. Under the provisions of 45 CFR 46.101(i), the Secretary, HHS, has waived the general requirements for obtaining informed consent in a limited class of research in emergency settings.

**What are the criteria under 45 CFR 46.116(c) for waiving or altering some or all of the required elements of informed consent or parental permission?**

Under 45 CFR 46.116(c), an IRB may waive the requirement for obtaining informed consent or parental permission or approve a consent or parental permission procedure that leaves out or alters some or all of the elements of informed consent, provided that the IRB finds and documents that the following two criteria are satisfied:

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:
   1. public benefit or service programs;
   2. procedures for obtaining benefits or services under those programs;
   3. possible changes in or alternatives to those programs or procedures; or
4. possible changes in methods or levels of payment for benefits or services under those programs; 45 CFR 46.116(c)(1).

Note that this criterion means that only public benefit or service program research activities that are under state or local authority meet this criterion; similar research conducted under federal authority would not qualify here and is treated elsewhere in the regulations. Research conducted by or subject to the approval of only a private entity also would not qualify.

1. the research could not practicably be carried out without the waiver or alteration (45 CFR 46.116(c)(2)).

This criterion means that the practical circumstances of the research are such that the research is not feasible if the informed consent of the subjects must be obtained. For example, a study of identifiable private information about program benefit recipients using 20-year-old records might meet this criterion, if current contact information for those recipients is not available.

What are the criteria under 45 CFR 46.116(d) for waiving or altering some or all of the required elements of informed consent or parental permission?

Under 45 CFR 46.116(d) the IRB may waive the requirement for obtaining informed consent or approve a consent procedure that leaves out or alters some or all of the elements of informed consent, provided that the IRB finds and documents that all of the following four criteria are met:

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.

Is it possible to waive the informed consent requirement when conducting research in an emergency setting?

In 1996, the HHS Secretary announced, under 45 CFR 46.101(i), a waiver of the applicability of the regulatory requirement for obtaining and documenting informed consent for a strictly limited class of research, that is, research that may be carried out in human subjects who are in need of emergency therapy and for whom, because of the subjects’ medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be obtained. This waiver applies to research involving adults or children, but does not apply to research involving pregnant women, human fetuses, neonates of uncertain viability, and nonviable neonates, or prisoners.

For more detailed information on the Emergency Research Consent Waiver, see OHRP’s guidance at: http://www.hhs.gov/ohrp/policy/hsdc97-01.html. It should be noted that FDA also has a comparable provision for a waiver of informed consent for emergency research at 21 CFR 50.24.
When may the requirement for documentation of informed consent or parental permission be waived or altered?

When an Institutional Review Board (IRB) has not waived the requirement for seeking prospective informed consent of the subjects or the parental permission of children who are subjects, under the HHS regulations at 45 CFR 46.117(c), it 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 (e.g., drawing a blood sample, or asking shoppers in a mall about the ambient lighting or temperature).

Some subjects might refuse a copy of the consent form once signed out of concern that their possession of the form could compromise their privacy. This is fully consistent with the idea behind one of the bases for a waiver of the requirements for documentation of informed consent - that harm would result to the subject if his/her identity were compromised by the documentation itself. The investigator may document that the subject refused a copy of the informed consent document and still include the subject in the study.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects or the parents of children who are subjects with a written statement regarding the research.

Can parental or guardian permission for research involving children be waived?

Yes, under certain circumstances. An IRB may waive the requirements for obtaining parental or guardian permission if either of the following two conditions is met:

1. The IRB makes and documents the required findings under either 45 CFR 46.116(c) or (d); or
2. The IRB determines that a research protocol is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), and the following 2 additional criteria are also met:
   a. An appropriate mechanism is in place to protect the children, and
   b. The waiver is not inconsistent with federal, state, or local law (45 CFR 46.408(c)).

The choice of an appropriate substitute mechanism (for example, appointing a child advocate or an assent monitor) for protecting children participating in research would depend on the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and the child’s age, maturity, status, and condition (45 CFR 46.408(c)).
Note that an IRB may waive the requirement for obtaining parental or guardian permission under 45 CFR 46.408(c) even if the research involves more than minimal risk to the child subjects.

**Is child assent always required when research involves children?**

No, the IRB is responsible for deciding whether child assent is required in proposed research activities. Assent means a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent (45 CFR 46.402(b)). Child assent is required, except in the following three circumstances described at 45 CFR 46.408(a):

1. the capability of some or all of the children is so limited that they cannot reasonably be consulted;
2. the intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research;
3. the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at either 45 CFR 46.116(c) or 45 CFR 46.116(d).

**How should child assent be documented?**

The HHS regulations do not require documentation of assent. The IRB has the discretion to determine the appropriate manner, if any, of documenting child assent. Based on such considerations as the child’s age, maturity, and degree of literacy, the IRB should decide what form of documentation, if any, is most appropriate. If adolescents are involved in research where a consent form would have been used if the subjects were adults, it would generally be appropriate to use a similar form to document an adolescent’s assent.

If young children are involved who are as yet unable to read, documentation should take a form that is appropriate for the purpose of recording that assent took place. The IRB may also decide that documentation of assent is not warranted.

**What is the meaning of “legally effective informed consent?”**

Informed consent is legally effective if it is both obtained from the subject or the subject’s legally authorized representative and documented in a manner that is consistent with the HHS protection of human subjects regulations and with applicable laws of the jurisdiction in which the research is conducted. In general terms, the regulations stipulate that an investigator should seek consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence. The information provided should be in language that is understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language.
It is important to note that the informed consent requirements in the regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed for consent to be legally effective (45 CFR 46.116(e)).

Investigator Responsibilities - FAQs:

Do the human research regulations apply to non-U.S. institutions?

Yes, whenever non-U.S. institutions are engaged in non-exempt HHS-supported or -conducted human subjects research, the regulations apply. Please see: http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html#sectionb.

Who are “investigators”?

The HHS regulations at 45 CFR part 46 use the term “investigator” to refer to an individual performing various tasks related to the conduct of human subjects research activities, such as obtaining informed consent from subjects, interacting with subjects, and communicating with the IRB. For the purposes of the HHS regulations, OHRP interprets an “investigator” to be any individual who is involved in conducting human subjects research studies. Such involvement would include:

- obtaining information about living individuals by intervening or interacting with them for research purposes;
- obtaining identifiable private information about living individuals for research purposes;
- obtaining the voluntary informed consent of individuals to be subjects in research; and
- studying, interpreting, or analyzing identifiable private information or data for research purposes.

Investigators can include physicians, scientists, nurses, administrative staff, teachers, and students, among others. Some research studies are conducted by more than one investigator, and usually one investigator is designated the “principal investigator” with overall responsibilities for the study. In every human subjects research study, investigators have certain responsibilities regarding the ethical treatment of human subjects.

Must investigators obtain IRB approval before involving human subjects in nonexempt research?

Yes, investigators are responsible for obtaining IRB approval before beginning any nonexempt human subjects research (45 CFR 46.109(a) and (d)). Investigators are responsible for providing the IRB with sufficient information and related materials about the research (e.g., grant applications, research protocols, sample consent documents) so that the IRB can fulfill its regulatory obligations, including making the required determinations under 45 CFR 46.111 and, if applicable, subparts B, C and D. Investigators should follow institutional policies and procedures for IRB review that are required by HHS regulations at 45 CFR 46.103(b)(4).
What are investigators’ responsibilities during the conduct of an approved research study?

Investigators play a crucial role in protecting the rights and welfare of human subjects and are responsible for carrying out sound ethical research consistent with research plans approved by an IRB. Along with meeting the specific requirements of a particular research study, investigators are responsible for ongoing requirements in the conduct of approved research that include, in summary:

- obtaining and documenting informed consent of subjects or subjects’ legally authorized representatives prior to the subjects’ participation in the research, unless these requirements have been waived by the IRB (45 CFR 46.116; 45 CFR 46.117);
- obtaining prior approval from the IRB for any modifications of the previously approved research, including modifications to the informed consent process and document, except those necessary to eliminate apparent immediate hazards to subjects (45 CFR 46.103(b)(4)); and
- ensuring that progress reports and requests for continuing review and approval are submitted to the IRB in accordance with the policies, procedures, and actions of the IRB as referenced in the institution’s OHRP-approved Federalwide assurance (45 CFR 46.103(b)(4), 45 CFR 46.109(e), 45 CFR 46.115(a)(1)). In certain circumstances, investigators also would be responsible for meeting the following additional regulatory requirements:
  - providing to the IRB prompt reports of any unanticipated problems involving risks to subjects or others (45 CFR 46.103(b)(5));
  - providing to the IRB prompt reports of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB (45 CFR 46.103(b)(5)); and
  - keeping certain records as required by the HHS regulations for at least three years after completion of the study (45 CFR 46.115(b)).

Are investigators responsible for obtaining and documenting informed consent?

Yes, investigators are responsible for obtaining and documenting the informed consent of research subjects or their legally authorized representatives, unless the IRB approves a waiver of informed consent, or a waiver of documentation of informed consent, respectively (45 CFR 46.116, 45 CFR 46.117). Investigators must give a copy of the informed consent document to each research subject (or the subject’s legally authorized representative), and keep the signed original or a copy of it for their records (45 CFR 46.117(a); 45 CFR 46.115(b)).

When the documentation requirement is waived, the IRB may require investigators to provide subjects with a written statement regarding the research (45 CFR 46.117(c)).

(For information about parental permission and assent, see the FAQs related to subpart D of 45 CFR part 46.)

What should investigators do if they want to revise an IRB-approved research study?

If investigators wish to modify an ongoing IRB-approved research study, they must submit a request to the IRB and receive IRB approval before implementing the proposed modification, unless the change is designed
to eliminate an apparent immediate hazard to subjects (45 CFR 46.103(b)(4)). If the investigators change the research in order to eliminate apparent immediate hazards to subjects without prior IRB approval, they should report those changes promptly to the IRB. The HHS protection of human subjects regulations allow for expedited review and approval of requests for minor changes in previously approved studies (45 CFR 46.110(b)(2)).

What should investigators do when considering changes to an exempt study that could make it nonexempt?

Investigators should consult with the appropriate institutional authority whenever questions arise about whether planned changes to an exempt study might make that study nonexempt human subjects research. OHRP recommends that institutions have policies in place that designate the individual or entity authorized to determine whether human subjects research qualifies for exemption under HHS regulations at 45 CFR 46.101(b). OHRP recommends that investigators not be given the authority to make an independent determination that human subjects research is exempt. The person(s) authorized to make the determination should be knowledgeable about the human subject protection regulations. In addition, the institution should ensure the appropriate communication of such a policy to all investigators.

Are investigators responsible for obtaining continuing review of research?

Yes, investigators are responsible for fulfilling requirements associated with continuing review in time for the IRB to carry out review prior to the expiration date of the current IRB approval. Continuing review of research and approval of research studies is required so long as the research study is ongoing, that is, until research-related interactions and interventions with human subjects or the obtaining and analysis of identifiable private information described in the IRB-approved research plan have been completed. Investigators are responsible for submitting sufficient materials and information for the IRB to meet its regulatory obligations, and should follow the institutional policies and procedures for continuing IRB review of research that are required by HHS regulations at 45 CFR 46.103(b)(4) and referenced in the institution's OHRP-approved Federalwide assurance.


What should investigators do if IRB approval expires?

If IRB approval of a specific study expires before continuing review and approval occur, investigators must stop all research activities involving human subjects related to that study (45 CFR 46.103(b)), except where they judge that it is in the best interests of already enrolled subjects to continue to participate. When investigators make this judgment, they must promptly notify the IRB (45 CFR 46.103(b)(5)).

When the IRB reviews the investigator’s decision, it may decide whether it is in the best interests of already enrolled subjects to continue to participate in the research by considering the best interests of subjects either one at a time or as a group. If an IRB determines that it is not in the best interests of already enrolled subjects to continue to participate, investigators must stop all human subjects research activities, including
intervening or interacting with subjects, or obtaining or analyzing identifiable private information about human subjects (45 CFR 46.103(b)). Investigators may resume the human subjects research activity once continuing review and approval by the IRB has occurred.

What are investigators’ responsibilities once a study is completed?

If all research-related interventions or interactions with human subjects have been completed, and all data collection and analysis of identifiable private information described in the IRB-approved research plan have been finished, then the human subjects research study has been completed. When a human subjects research study has been completed, the investigators no longer are required to obtain continuing review and approval of that study by the IRB. The investigators should follow any applicable institutional policies and procedures for notifying the IRB of the study's completion.

Once a study has been completed, investigators may keep the data they collected, including identifiable private data, if consistent with the IRB-approved research plan. Investigators should continue to honor any confidentiality protections of the data.

Investigators also should honor any other commitments that were agreed to as part of the approved research, for example, providing information about the study results to research subjects, or honoring commitments for compensation to research subjects for research participation.

What records should investigators keep, and for how long?

The HHS protection of human subjects regulations require institutions to retain records of IRB activities and certain other records frequently held by investigators for at least three years after completion of the research (45 CFR 46.115(b)). In addition, other regulations may apply and require retention of these records for a longer period of time. Documentation of the informed consent of the subjects - either the signed informed consent form or the short form and the written research summary - are records related to conducted research that are typically held by investigators and must be retained for at least three years after completion of the research, unless the IRB waived the requirement for informed consent or the requirement for documentation of informed consent (45 CFR 46.117).

If investigators have been designated to retain certain records (e.g., informed consent documents signed by subjects) on behalf of the institution as required by the HHS regulations at 45 CFR 46.115(b), they must retain the records in some form. Such records may be preserved in hardcopy, electronic or other media form and must be accessible for inspection and copying by authorized representatives of HHS at reasonable times and in a reasonable manner (45 CFR 46.115(b)). Retention of multiple copies of each record is not required. Investigators should follow the institution’s policies and procedures for retaining records. If investigators who have been designated to retain records on behalf of the institution leave that institution, the investigators and the institution should identify the successor responsible for maintaining those institutional records, either at the original institution or wherever the records are relocated, for the period of time required under HHS regulations at 45 CFR 46.115(b).
Other regulations or policies may apply to the retention of records, including study data

**Must investigators obtain training in the protection of human subjects?**

The HHS regulations for the protection of human subjects ([45 CFR part 46](http://www.hhs.gov/ohrp/policy/faq/index.html)) do not require investigators to obtain training in the protection of human subjects in research. However, an institution holding an OHRP-approved Federalwide Assurance (FWA) is responsible for ensuring that its investigators conducting HHS-conducted or -supported human subjects research understand and act in accordance with the requirements of the HHS regulations for the protection of human subjects. Therefore, as stated in the **Terms of the FWA**, OHRP strongly recommends that institutions and their designated IRBs establish training and oversight mechanisms (appropriate to the nature and volume of their research) to ensure that investigators maintain continuing knowledge of, and comply with, the following:

- relevant ethical principles;
- relevant federal regulations;
- written IRB procedures;
- OHRP guidance;
- other applicable guidance;
- state and local laws; and
- institutional policies for the protection of human subjects.

Furthermore, OHRP recommends that investigators complete appropriate institutional educational training before conducting human subjects research.

In some cases, other federal requirements regarding training for investigators must be met, such as the National Institute of Health’s (NIH) requirement for the training of key personnel in NIH-sponsored or -conducted human subjects research.

**Return to top**

**IRB Registration Process - FAQs:**

**What IRBs must be registered?**

The HHS regulations at 45 CFR part 46, subpart E, require all IRBs to register with HHS if they will review human subjects research conducted or supported by HHS and are to be designated under an assurance of compliance approved for federalwide use (i.e, an FWA) by OHRP.

**When must an IRB be registered?**

An IRB must be registered before it can be designated under an OHRP-approved FWA. IRB registration becomes effective when reviewed and accepted by OHRP. The registration is effective for 3 years.
How must an IRB be registered?

Each IRB must be registered electronically through http://ohrp.cit.nih.gov/efile/ unless an institution or organization lacks the ability to register its IRB electronically. If an institution or organization believes it lacks the ability to register an IRB electronically, it should contact OHRP by telephone or email (see http://www.hhs.gov/ohrp/assurances/status/contact/index.html) and explain why it is unable to register its IRB electronically. Any institution or organization that is unable to register electronically after consultation with OHRP must send its IRB registration information in writing to OHRP by fax at (240) 453-8202, by email as a pdf scanned document, or mail it to the Office for Human Research Protections, U.S. Department of Health and Human Services, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852.

Where can I find the IRB registration instructions and registration form?

Links to the instructions and the form for submitting an IRB registration can be found on the OHRP website at http://www.hhs.gov/ohrp/assurances/forms/index.html. Additional instructions for electronic submission of a new IRB registration or for updating or renewing the registration of an IRB already registered with OHRP can be found at http://ohrp.cit.nih.gov/efile/.

Who can I contact with questions about an IRB registration?

If you have questions about submitting an IRB registration, you should contact an IRB Coordinator listed at http://www.hhs.gov/ohrp/assurances/status/contact/index.html.

How can I track receipt of my IRB registration submission?

You can track the receipt of an IRB registration submission on the OHRP website at http://ohrp.cit.nih.gov/search/. Here you will find information about when the IRB registration was received, which IRB Coordinator is reviewing it, and how to contact that person.

How will I know when my IRB registration has been reviewed and accepted?

Once the OHRP has reviewed and accepted the registration, the contact person that provided the registration information, the senior officer or head official of the institution or organization and the IRB chairperson(s) will receive an automatically generated e-mail informing them of the IRB registration. A copy of the reviewed and accepted registration is also attached to the email. Of course, this is dependent upon correct e-mail addresses being provided for these individuals. All OHRP reviewed and accepted IRB registrations - both new registrations and updates/renewals - are listed on the OHRP website http://ohrp.cit.nih.gov/search/.

When must an IRB registration be renewed or updated?

Each IRB must renew its registration every three years. An IRB registration also must be updated within 90 days after changes occur regarding the contact person who provided the IRB registration information and/or the IRB chairperson. The updated registration information must be submitted electronically unless an
institution or organization believes it lacks the ability to register its IRB electronically. If an institution or organization believes it lacks the ability to register an IRB electronically, it should contact OHRP by telephone or email (see http://www.hhs.gov/ohrp/assurances/status/contact/index.html) and explain why it is unable to register its IRB electronically. Any institution or organization that is unable to register electronically after consultation with OHRP must send its IRB registration information in writing to OHRP by fax at (240) 453-8202, by email as a pdf scanned document, or mail it to the:

    Office for Human Research Protections
    U.S. Department of Health and Human Services
    1101 Wootton Parkway, Suite 200
    Rockville, MD 20852.

Any renewal or update that is submitted to, and accepted by, OHRP begins a new 3-year effective period.

An institution’s or organization’s decision to disband a registered IRB that it is operating also must be reported to OHRP in writing within 30 days after permanent cessation of the IRB’s review of HHS-conducted or –supported research.

What are the requirements for providing information on the number of protocols being reviewed by the IRB?

The HHS regulations at 45 CFR 46.502 (e) require institutions or organizations to provide the approximate number of all active protocols and approximate number of active protocols conducted or supported by HHS when registering an IRB. For the purpose of these requirements, an “active protocol” is any protocol for which the IRB conducted an initial or a continuing review at a convened meeting or under an expedited review procedure during the preceding twelve months.

If the IRB reviews protocols regulated by both OHRP and the Food and Drug Administration (FDA), the institution or organization also must provide the approximate number of active protocols involving FDA-regulated products and 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.

What are the requirements for providing information on the number of full time equivalent positions?

The HHS regulations at 45 CFR 46.502 (f) require institutions or organizations to provide information on the number of full time equivalent positions devoted to the IRB’s administrative activities when registering an IRB.

What are the requirements for IRB membership?

The requirements for IRB membership are addressed in the HHS regulations at 45 CFR 46.107[Note: 45 CFR 46.304 requires a specialized IRB composition when research involving prisoners is being reviewed, including the presence of a prisoner representative].
An IRB must:

i. have at least five members with varying backgrounds to promote complete and adequate review of the research activities commonly conducted by the institution;

ii. make every nondiscriminatory effort to ensure that the membership is not composed of entirely men or entirely women;

iii. include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas;

iv. 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; and

v. not allow any member to participate in the initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. Please see the regulations at 45 CFR 46.107 for complete information on all of the required qualifications to properly compose an IRB.

How do I determine the various categories of members for the IRB roster?

The following are some general guidelines to assist you in composing the IRB membership roster.

Scientist/Nonscientist - Members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline should be considered a scientist, while members whose training, background, and occupation would incline them to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline should be considered a nonscientist. In addition, the IRB must have members with sufficient knowledge of the specific scientific discipline(s) relevant to the research that it reviews.

Affiliation - An employee or agent of the organization registering the IRB (or a member of that person’s immediate family) is considered affiliated. Affiliated members include, but are not limited to, individuals who are: part-time employees; current students; members of any governing panel or board of the institution; paid or unpaid consultants; healthcare providers holding credentials to practice at the institution; and volunteers working at the institution on business unrelated to the IRB. An individual that has no affiliation with the organization registering the IRB, other than as an IRB member, is considered unaffiliated with the entity operating the IRB. Unaffiliated members may include people whose only association with the institution is that of a patient, subject, or former student at that institution. Paying unaffiliated members for their services would not make the member “otherwise affiliated” as stated in the regulations, or cause the member to have a conflicting interest.

Alternate Members – The HHS regulations at 45 CFR part 46 do not address the designation of alternate IRB members. However, for many years, the OHRP has permitted organizations submitting IRB registrations to OHRP to identify alternate members for primary members. When reviewing rosters that include alternate members OHRP assumes that, in general, with respect to the capacity in which the primary IRB member was intended to serve, each alternate IRB member has experience, expertise, background, professional
competence, and knowledge comparable to that of the primary IRB member whom the alternate would replace. The minutes of an IRB meeting should document the attendance of all primary and alternate IRB members who attended any part of the IRB meeting. If both a primary IRB member and his or her alternate(s) attend the same IRB meeting, OHRP assumes that the primary member is acting as the official voting member of the IRB for review of research protocols, unless the minutes clearly indicate otherwise. A designated alternate IRB member for a primary IRB member may substitute for the primary IRB member for an entire meeting or at any time during a meeting. Substitution during a meeting commonly occurs when the primary member is (a) absent from the room for part of the meeting, or (b) recused from review of certain research protocols because the primary IRB member has a conflicting interest with respect to a specific research protocol. Whenever this occurs, the minutes of the IRB meeting should indicate clearly that the alternate IRB member has replaced the designated primary IRB member. OHRP recommends that the reason for the substitution of the alternate IRB member also should be documented in the minutes.

**Does a FWA have to be updated if an institution later relies on an IRB not included in the original FWA submission?**

Yes, if that IRB is an internal IRB, because all internal IRBs that review research covered by the institution’s FWA must be designated on that FWA. In addition, if the institution has no internal IRBs and has designated one external IRB, but decides to rely on a second external IRB that will review the largest percentage of research covered by its FWA, the institution must update its FWA to replace the first external IRB with the second IRB.

Reliance on an external IRB, i.e. an IRB of another institution or organization, or an independent IRB, must be documented by a written agreement that is available for review by the OHRP upon request.

OHRP’s sample IRB Authorization Agreement may be used for this purpose (see [http://www.hhs.gov/ohrp/assurances/forms/iprotsup.rtf](http://www.hhs.gov/ohrp/assurances/forms/iprotsup.rtf)) or the parties involved may develop their own agreement.

**Does registration mean that an IRB is in full compliance with the HHS regulations, 45 CFR part 46, or is otherwise meeting a particular standard of competence or expertise?**

No, IRB registration is not a form of accreditation or certification by the HHS. An IRB that reviews human subjects research conducted or supported by HHS, and that is designated under an assurance of compliance approved for federalwide use by the OHRP under 45 CFR 46.103(a), must be registered with OHRP. However, the fact that an IRB is registered with OHRP does not mean that OHRP has determined that the IRB reviews research in accordance with the requirements of the HHS Protection of Human Subjects regulations, and does not mean that the IRB has the appropriate competence or expertise to review a particular research project.
Prisoner Research - FAQs:

Are there additional regulatory considerations for research involving prisoners?

Yes, in addition to the requirements of subpart A, subpart C of the HHS regulations at 45 CFR part 46 identifies more requirements for research involving prisoners. In summary, the major additional considerations are:

- the exemptions that generally apply to certain types of research involving human subjects do not apply to research involving prisoners (45 CFR 46.101, footnote 1);
- in order to approve research involving prisoners, the IRB must find that the proposed research falls into one of the permissible categories of research, and make six other findings;
- the institution must certify to OHRP that an IRB has reviewed the proposal and made seven required findings, and receive OHRP authorization prior to initiating any research involving prisoners; (45 CFR 46.305(c))
- the IRB must include a prisoner or prisoner representative, (45 CFR 46.304(b)) and meet a membership requirement concerning the number of IRB members not associated with a prison involved in the research; (45 CFR 46.304(a))
- Secretarial waiver of informed consent in certain emergency research is not applicable to research involving prisoners (61 FR 51531, October 2, 1996)

How do the regulations define “prisoner”?

The regulations define “prisoner” as follows:

“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 (45 CFR 46.303(c)).

Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.

Common examples of the application of the regulatory definition of prisoner are as follows:

- Individuals who are detained in a residential facility for court-ordered substance abuse treatment as a form of sentencing or alternative to incarceration are prisoners; however, individuals who are receiving non-residential court-ordered substance abuse treatment and are residing in the community are not prisoners.
- Individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to a criminal prosecution or incarceration are prisoners; however, individuals who have been voluntarily admitted to an institution for treatment of a psychiatric illness, or who have been
When is an institution “engaged” in research involving prisoners?

In general, an institution is considered engaged in a particular human subjects research proposal involving prisoners when its employees or agents, for the purposes of the research proposal, obtain:

(1) data about the prisoner subjects through intervention or interaction with them; or

(2) identifiable private information about the prisoner subjects.

Some examples of activities that would make an institution engaged in human subjects research involving prisoners are:

(1) seeking the informed consent of prisoners to be subjects in research;

(2) using, studying or analyzing, for research purposes, identifiable private information about prisoners, or identifiable specimens obtained from prisoners; and

(3) surveying prisoners for a research study.

In addition, institutions generally become engaged in research involving prisoners if they are the primary awardee of HHS funds to conduct such research, even where all activities involving prisoner subjects are carried out by agents or employees of another institution.

Do the exemptions apply to research involving prisoners?

No, none of the exemption categories in the HHS regulations for research involving human subjects at 45 CFR 46.101(b) apply to research involving prisoners (45 CFR 46.101(i), Footnote 1)

What are the categories for permissible research involving prisoners?

Research involving prisoners is permissible only if the research involves one or more of four permissible categories, or if the research meets the criteria described in an HHS Secretarial waiver that applies to certain epidemiological research (68 FR 36929, June 20, 2003):
• The first two categories are (i) the study of the possible causes, effects, and processes of incarceration, and of criminal behavior, and (ii) the study of prisons as institutional structures or of prisoners as incarcerated persons. Research in these two categories is permissible only if the study presents no more than minimal risk, and no more than inconvenience to the subjects (45 CFR 46.306(a)(2)).

• The third category (iii) is research on conditions particularly affecting prisoners as a class; the regulations list as examples 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 addition, and sexual assaults. Research in this category may proceed only after the HHS Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and has published notice in the Federal Register of his or her intent to approve the research (45 CFR 46.306(a)(2)).

• The fourth category (iv) is research on practices, either innovative or accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In this category, if the IRB-approved proposal is a study in which some prisoners will be assigned to a control group and these prisoners may not benefit from their participation in research, such research may proceed only after the HHS Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and has published notice in the Federal Register of his or her intent to approve the research (45 CFR 46.306(a)(2)). OHRP interprets control groups which may not benefit from research to include a control group receiving standard of care that the prisoners would otherwise receive, services as usual, or a placebo.

• The HHS Secretarial waiver for certain epidemiological research conducted or supported by HHS functions as a fifth category of permissible research. The criteria for this category are that the research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease. The institution still must review the research under subpart C and certify to OHRP that an appropriately constituted IRB has reviewed the proposal and made all other required findings under HHS regulations at 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. All of the other requirements of subpart C apply to research in this category.

**Does research involving prisoners not conducted or supported by HHS require Secretarial consultation?**

No, research proposals in category (iii) or (iv) that are not conducted or supported by HHS do not require a Secretarial consultation, nor do they require certification to OHRP.

**What are the certification requirements for research involving prisoners?**

For any HHS-conducted or -supported research involving prisoners, the institution(s) engaged in the research must certify to the Secretary (through OHRP) that the IRB reviewed the research and made seven findings as required by the regulations (45 CFR 46.305(c) and 46.306(a)(1)). The certification request must be forwarded to OHRP. OHRP then will determine whether the proposed research involves one of the categories of research permissible under 45 CFR 46.306(a)(2), and if so which one. Following its review of
the certification, OHRP will send the institution a letter authorizing the involvement of prisoners in the proposed research, if OHRP determines that the research involves one of the permissible categories.

OHRP (on behalf of the Secretary of HHS) will consult with appropriate experts with respect to certain research that falls under paragraphs (iii) and (iv) of 45 CFR 46.306(a)(2). When applicable, OHRP (on behalf of the Secretary of HHS) also will publish a notice of intent to approve such research in the Federal Register. Research involving prisoners may proceed only after receipt of the OHRP authorization letter.

If OHRP determines that the proposed research does not involve one of the permissible categories, it will state in the letter to the institution that such research involving prisoners cannot proceed.

**What materials and information should be sent to OHRP for certification of research involving prisoners?**

The institution's certification must indicate that the IRB reviewed the research under subpart C and made the seven findings as required by the regulations (45 CFR 46.305(a)).

Under its authority at 45 CFR 46.115(b), OHRP also requires the responsible institution to submit a copy of the research proposal so OHRP can determine whether the proposed research involves one of the categories of research permissible under 45 CFR 46.306(a)(2), and if so, which one. The term “research proposal” includes:

- the IRB-approved protocol; any relevant HHS grant application or proposal;
- any IRB application forms required by the IRB;
- and any other information requested or required by the IRB to be considered during initial IRB review.

OHRP also encourages the institution to include the following information in its prisoner research certification letter to facilitate processing:

- the OHRP Federalwide Assurance (FWA) number;
- the IRB registration number for the designated IRB; and
- the date(s) of IRB meeting(s) in which the protocol was considered, including a brief chronology that encompasses:
  - the date of initial IRB review; and
  - the date of subpart C review, if not done at the time of initial IRB review.

**What happens if an IRB chooses the wrong category of research involving prisoners in its certification to OHRP?**

If OHRP's review of the certification materials leads to the conclusion that the IRB incorrectly applied the categories of permissible research to the research protocol under consideration, OHRP has the authority to re-categorize the study to the appropriate category. OHRP will inform the institution of this action by letter. If
the research does not fit any of the permissible categories of research, OHRP will inform the institution that the research cannot involve prisoners.

**Does research involving prisoners not conducted or supported by HHS require certification?**

No, if research is not HHS-conducted or -supported, the institution does not need to submit any certification to OHRP, regardless of whether the institution has chosen to extend the applicability of its FWA and subpart C to all research.

**If a study involving prisoners previously authorized by OHRP is amended, does the institution need to recertify?**

Usually not. OHRP should be notified only if there is a fundamental change in the research that alters the applicability of the approved category under 45 CFR 46.306.

**If multiple institutions are engaged in the same research study involving prisoners, do all institutions need to certify to OHRP?**

Each institution engaged in a multicenter research study involving prisoners must certify to OHRP in accordance with the requirements of HHS regulations at 45 CFR 46.305(c) and 46.306(a)(1), unless (a) an institution relied upon the review of an IRB operated by another institution engaged in the research; and (b) that IRB or the other institution certified to OHRP on behalf of both institutions.

**What conditions must be met for an IRB to approve research involving prisoners?**

Along with the requirements of subpart A, an IRB must make the following seven additional findings required by the regulations in order to review and approve research involving prisoners:

1. The research under review represents one of the categories of research permissible under 45 CFR 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 receiving such advantages in the limited-choice prison environment 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 the IRB with written justification for following some other procedures, control subjects must be selected randomly from the group of available prisoners that meet the characteristics needed for that particular research proposal;
5. The information is presented in language that 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 IRB finds there may be a need for follow-up examination or care of participants after the
end of their participation, adequate provision has been made for such examination or care, taking into
account the varying lengths of individual prisoners' sentences, and for informing participants of this
fact (45 CFR 46.305(a)).

OHRP notes that in order to make some of these seven findings and meet the requirements of subpart A of 45
CFR part 46, the IRB must be familiar with the specific conditions in the local prison(s) or jail site(s) that are
pertinent to subject protections, before approving the proposal for the local site (45 CFR 46.107(a)).

**What are the IRB composition requirements for review of research involving prisoners?**

In addition to satisfying the requirements of 45 CFR 46.107, when an IRB reviews a proposal involving
prisoners as subjects, the composition of the IRB must satisfy the following regulatory requirements at 45
CFR 46.304(a) and (b):

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

The IRB must meet these composition requirements for all types of review by the convened IRB, including
initial review, continuing review, and review of amendments.

OHRP recommends that a prisoner representative have a close working knowledge and understanding and
appreciation of prison conditions from the prisoner's perspective.

**How should institutions list prisoner or prisoner representative members on their IRB registration
roster?**

Institutions registering IRBs with members who are prisoners or prisoner representatives should follow the
instructions on the OHRP website for registering IRBs. If the IRB frequently reviews research involving
prisoner research, the IRB registration should identify each IRB member who is a prisoner or prisoner
representative simply by inserting a note in the Comment section for that member. If the IRB infrequently
reviews prisoner research, OHRP suggests the following alternatives when submitting an IRB registration:

- Register two IRBs, annotating the name of the IRB with the prisoner representative, for example
  “Prisoner Research.” This roster would only be invoked and used to determine quorum when the IRB is
  reviewing a study covered by subpart C of 45 CFR part 46. The assurance should list both IRBs; or
- Register one IRB with the prisoner representative and add a "Comment" to the IRB roster identifying the voting member who is the prisoner representative and stipulating that the prisoner representative will only count towards quorum when he or she is in attendance and reviewing studies covered by subpart C.

Can research involving prisoners be approved under expedited review?

Yes, however, because of the vulnerability of prisoners, OHRP recommends that all research involving prisoners be reviewed by the convened IRB. If the research is reviewed under the expedited review procedure, OHRP recommends that the IRB member(s) reviewing the research include a prisoner or prisoner representative. OHRP's website includes guidance on the use of expedited review procedures and the list of expedited review categories.

How do the regulations define “minimal risk” for research involving prisoners?

For research involving prisoners, the regulations at subpart C of 45 CFR part 46 define “minimal risk” as follows:

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 (45 CFR 46.303(d)).

The wording of the subpart C definition differs in several ways from the definition of “minimal risk” in subpart A of 45 CFR part 46, which applies generally to research involving human subjects. The differences are:

- The subpart C definition refers to “physical or psychological harm” rather than “harm or discomfort” as in subpart A.
- The subpart C definition compares the probability and magnitude of harm in the research to the probability and magnitude of those harms normally encountered in daily life, or in “routine medical, dental, or psychological examinations,” rather than in daily life or “routine physical or psychological examinations or tests” as in subpart A.
- The subpart C definition identifies “healthy persons” as the comparison group against which the risks of the research should be measured, rather than leaving the comparison group unspecified, as in subpart A. OHRP interprets the term “healthy persons” in this definition as referring to healthy persons who are not prisoners.

Can informed consent be waived or altered in research involving prisoners?

Yes, so long as the appropriately constituted IRB reviews the research and makes the appropriate findings regarding the waiver or alteration of informed consent requirements, research involving prisoners may be approved with a waiver or alteration of informed consent. However, even if informed consent is waived or altered, subpart C of 45 CFR part 46 still requires that the subjects be clearly informed in advance that
participation in the research will have no effect on their parole, if such notification is relevant. (45 CFR 46.305(a)(6)).

Note that prisoners cannot be involved in emergency research where the requirement for informed consent has been waived by the Secretary under the authority of 45 CFR 46.101(i).

What happens if a human subject becomes a prisoner during the course of a research study?

If a human subject involved in ongoing research becomes a prisoner during the course of the study, and the relevant research proposal was not reviewed and approved by the IRB in accordance with the requirements for research involving prisoners under subpart C of 45 CFR part 46, the investigator must promptly notify the IRB. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must be suspended immediately, except as noted below. Upon receipt of the investigator's report that a previously enrolled research subject has become a prisoner, if the investigator wishes to have the prisoner subject continue to participate in the research, the IRB must promptly re-review the proposal in accordance with the requirements of subpart C, and the institution(s) engaged in the research involving the prisoner subject must send a certification to OHRP and wait for a letter of authorization in reply. Otherwise, the prisoner subject must stop participating in the research, except as noted below.

OHRP allows one important exception to the requirement that all research interactions or interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until the regulatory requirements for research involving prisoners are met. In special circumstances in which the investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the subject may continue to participate in the research until the requirements of subpart C are satisfied. The investigator must promptly notify the IRB of this occurrence, so that the IRB can re-review the study. Note that in these circumstances, some of the findings required by 45 CFR 46.305(a) may not be applicable; for example, the finding required under 45 CFR 46.305(a)(4) regarding the selection of subjects within the prison may not be applicable, if the subject was recruited outside of an incarcerated context. The IRB should document findings of non-applicability accordingly.

Can subpart C be applied to research in anticipation of some subjects being or becoming prisoners?

Yes, if investigators anticipate that some of the subjects in a planned research study population are likely to be prisoners or become prisoners during the course of the study (for example, subjects in substance abuse treatment studies) the IRB may review the research prospectively for prisoner involvement in accordance with the requirements of subpart C of 45 CFR part 46. When an IRB reviews a research proposal in which the subjects are not prisoners, but in anticipation of the likelihood that some of the subjects will become prisoners during the course of the research, some of the seven findings required by 45 CFR 46.305(a) may not be applicable. As examples, if subjects are not recruited from within a prison, the finding under 45 CFR 46.305(a)(4) would not be applicable; and, if there is no particular parole board involved yet, the finding under 45 CFR 46.305(a)(6) would not be applicable. The IRB should document these findings accordingly, and must certify the research to OHRP. The IRB must wait for OHRP to authorize the research study prior to initiating any interaction or intervention with, or obtaining identifiable private information about, prisoners.
IRBs should use their discretion in deciding whether to apply the additional requirements of subpart C to research in anticipation of some subjects being or becoming prisoners. In some cases, the involvement of subjects who may be prisoners or become prisoners can be anticipated in ways that make the additional protections of subpart C meaningful. In other cases there may be insufficient information available at that time to make the seven findings required by 45 CFR 46.305(a) (for example, the IRB may not know the specific penal institutions where subjects will be prisoners and therefore will lack important information about the local research context), and the IRB may have to wait until more specific information becomes available. In these instances, the IRB would need to conduct the subpart C review after research subject(s) have become incarcerated.

Return to top

Quality Improvement Activities - FAQs:

How does HHS view quality improvement activities in relation to the regulations for human research subject protections?

Protecting human subjects during research activities is critical and has been at the forefront of HHS activities for decades. In addition, HHS is committed to taking every appropriate opportunity to measure and improve the quality of care for patients. These two important goals typically do not intersect, since most quality improvement efforts are not research subject to the HHS protection of human subjects regulations. However, in some cases quality improvement activities are designed to accomplish a research purpose as well as the purpose of improving the quality of care, and in these cases the regulations for the protection of subjects in research (45 CFR part 46) may apply.

To determine whether these regulations apply to a particular quality improvement activity, the following questions should be addressed in order:

1. does the activity involve research (45 CFR 46.102(d));

2. does the research activity involve human subjects (45 CFR 46.102(f));

3. does the human subjects research qualify for an exemption (45 CFR 46.101(b)); and

4. is the non-exempt human subjects research conducted or supported by HHS or otherwise covered by an applicable FWA approved by OHRP.

For those quality improvement activities that are subject to these regulations, the regulations provide great flexibility in how the regulated community can comply. Other laws or regulations may apply to quality improvement activities independent of whether the HHS regulations for the protection of human subjects in research apply.
Do the HHS regulations for the protection of human subjects in research (45 CFR part 46) apply to quality improvement activities conducted by one or more institutions whose purposes are limited to: (a) implementing a practice to improve the quality of patient care, and (b) collecting patient or provider data regarding the implementation of the practice for clinical, practical, or administrative purposes?

No, such activities do not satisfy the definition of “research” under 45 CFR 46.102(d), which is “…a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge…” Therefore the HHS regulations for the protection of human subjects do not apply to such quality improvement activities, and there is no requirement under these regulations for such activities to undergo review by an IRB, or for these activities to be conducted with provider or patient informed consent.

Examples of implementing a practice and collecting patient or provider data for non-research clinical or administrative purposes include:

- A radiology clinic uses a database to help monitor and forecast radiation dosimetry. This practice has been demonstrated to reduce over-exposure incidents in patients having multiple procedures. Patient data are collected from medical records and entered into the database. The database is later analyzed to determine if over-exposures have decreased as expected.
- A group of affiliated hospitals implements a procedure known to reduce pharmacy prescription error rates, and collects prescription information from medical charts to assess adherence to the procedure and determine whether medication error rates have decreased as expected.
- A clinic increasingly utilized by geriatric patients implements a widely accepted capacity assessment as part of routine standard of care in order to identify patients requiring special services and staff expertise. The clinic expects to audit patient charts in order to see if the assessments are performed with appropriate patients, and will implement additional in-service training of clinic staff regarding the use of the capacity assessment in geriatric patients if it finds that the assessments are not being administered routinely.

Do quality improvement activities fall under the HHS regulations for the protection of human subjects in research (45 CFR part 46) if their purposes are limited to: (a) delivering healthcare, and (b) measuring and reporting provider performance data for clinical, practical, or administrative uses?

No, such quality improvement activities do not satisfy the definition of “research” under 45 CFR 46.102(d), which is “…a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge…” Therefore the HHS regulations for the protection of human subjects do not apply to such quality improvement activities, and there is no requirement under these regulations for such activities to undergo review by an IRB, or for these activities to be conducted with provider or patient informed consent.

The clinical, practical, or administrative uses for such performance measurements and reporting could include, for example, helping the public make more informed choices regarding health care providers by...
communicating data regarding physician-specific surgical recovery data or infection rates. Other practical or administrative uses of such data might be to enable insurance companies or health maintenance organizations to make higher performing sites preferred providers, or to allow other third parties to create incentives rewarding better performance.

**Can I analyze data that are not individually identifiable, such as medication databases stripped of individual patient identifiers, for research purposes without having to apply the HHS protection of human subjects regulations?**

Yes, whether or not these activities are research, they do not involve “human subjects.” The regulation defines a “human subject” as “a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information….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.” Thus, if the research project includes the analysis of data for which the investigators cannot readily ascertain the identity of the subjects and the investigators did not obtain the data through an interaction or intervention with living individuals for the purposes of the research, the analyses do not involve human subjects and do not have to comply with the HHS protection of human subjects regulations.


**Are there types of quality improvement efforts that are considered to be research that are subject to HHS human subjects regulations?**

Yes, in certain cases, a quality improvement project may constitute non-exempt human subjects research conducted or supported by HHS or otherwise covered by an applicable FWA. For example, if a project involves introducing an untested clinical intervention for purposes which include not only improving the quality of care but also collecting information about patient outcomes for the purpose of establishing scientific evidence to determine how well the intervention achieves its intended results, that quality improvement project may also constitute nonexempt human subjects research under the HHS regulations.

**If I plan to carry out a quality improvement project and publish the results, does the intent to publish make my quality improvement project fit the regulatory definition of research?**

No, the intent to publish is an insufficient criterion for determining whether a quality improvement activity involves research. The regulatory definition under 45 CFR 46.102(d) is “Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” Planning to publish an account of a quality improvement project does not necessarily mean that the project fits the definition of research; people seek to publish descriptions of nonresearch activities for a variety of reasons, if they believe others may be interested in learning about those activities. Conversely, a quality improvement project may involve research even if there is no intent to publish the results.
Does a quality improvement project that involves research need to be reviewed by an IRB?

Yes, in some cases. IRB review is needed if the research involves human subjects, is not exempt, and is conducted or supported by HHS or otherwise covered by an applicable FWA.


Does IRB review of a quality improvement project that is also non-exempt human subjects research always need to be carried out at a convened IRB meeting?

No, if the human subjects research activity involves no more than minimal risk and fits one or more of the categories of research eligible for expedited review, the IRB chair or another member designated by the IRB chair may conduct the review.

The categories of research eligible for expedited review are available at: http://www.hhs.gov/ohrp/policy/expedited98.html.

If a quality improvement project involves non-exempt research with human subjects, do I always need to obtain informed consent from all subjects (patients and/or providers) involved in the research?

No, the HHS regulations protecting human subjects allow an IRB to waive the requirements for obtaining informed consent of the subjects of the research when

(a) the risk to the subjects is minimal,

(b) subjects’ rights and welfare will not be adversely affected by the waiver,

(c) conducting the research without the waiver is not practicable, and

(d) if appropriate, subjects are provided with additional pertinent information after their participation (45 CFR 46.116(d)).

Other applicable regulations or laws may require the informed consent of individuals in such projects independent of the HHS regulations for the protection of human subjects in research.

If a quality improvement project is human subjects research requiring IRB review, do I need to obtain separate IRB approval from every institution engaged in the project?

No, not if certain conditions are met. The HHS protection of human subjects regulations allow one IRB to review and approve research that will be conducted at multiple institutions. An institution has the option of relying upon IRB review from another institution by designating that IRB on its FWA and submitting the revised FWA to OHRP, and having an IRB Authorization Agreement with the other institution.

Division of Compliance Oversight  
Office for Human Research Protections (OHRP)  
OHRP Compliance Oversight Activities: Determinations of Noncompliance  
02/04/2009

This document provides a list of determinations of noncompliance that OHRP has made in compliance oversight determination letters over the last several years.

A. INITIAL AND CONTINUING REVIEW

1. Research Conducted without IRB Review and/or Approval
2. Failure of IRB to Review HHS Grant Applications
3. IRB Lacks Sufficient Information to Make Determinations Required for Approval of Research
4. Inadequate IRB Review at Convened Meetings
5. Members Present at Convened IRB Meetings Lacked the Expertise to Make Determinations Required for Approval of Research
6. Approval of Research Not Approved by the IRB
7. Contingent Approval of Research with Substantive Changes and no Additional Review by the Convened IRB
8. IRB Meeting Convened without Quorum (No Nonscientist Present)
9. IRB Meeting Convened without Quorum (Lack of a Majority)
10. IRB Members with Conflicting Interest Participated in IRB Review of Research
11. Inadequate Continuing Review
12. Failure to Conduct Continuing Review at Least Once per Year
13. Continuing Review for Follow up in Research Protocols

B. EXPEDITED REVIEW PROCEDURES

16. Failure to Advise IRB Members of Expedited Approvals
17. Expedited Review Conducted by Someone Other than an IRB Member

C. REPORTING OF UNANTICIPATED PROBLEMS, NONCOMPLIANCE, SUSPENSIONS, AND TERMINATIONS

18. Failure to Report Unanticipated Problems, Noncompliance, Suspensions, and Terminations to IRB, Institutional Officials, and OHRP

D. IRB REVIEW OF PROTOCOL CHANGES

20. Inadequate IRB Review and/or Approval of Protocol Changes
E. APPLICATION OF EXEMPTIONS

(21) Inappropriate Application of Exempt Categories of Research
(22) Inappropriate Application of Exemption 4
(23) Inappropriate Application of Exemption 2 for Research Involving Children

F. INFORMED CONSENT

(24) Failure of the Investigator to Obtain the Legally Effective Informed Consent of Subjects or of the IRB to Appropriately Waive the Requirements to Obtain Informed Consent
(25) Failure to Document Informed Consent or of the IRB to Appropriately Waive the Requirements to Document Informed Consent
(26) Failure to Provide a Copy of the Informed Consent Document (ICD) to the Subject or the Subject’s Legally Authorized Representative
(27) Inadequate ICD for Specific Research/Lack of Basic Elements
(28) Inadequate ICD for Specific Research/Lack of Additional Elements
(29) ICD Language too Complex
(30) Exculpatory Language in ICDs
(31) Enrollment Procedures did not Minimize Possibility of Coercion or Undue Influence

G. IRB MEMBERSHIP, EXPERTISE, STAFF, SUPPORT, AND WORKLOAD

(32) Failure To Have An Unaffiliated IRB Member
(33) Lack of Prisoner/Prisoner Representative for IRB Review of Research Involving Prisoners
(34) IRB Chairperson and Members Lack Sufficient Understanding of HHS Regulations
(35) Designation of an Additional IRB under a Federalwide Assurance (FWA) without Prior OHRP Approval
(36) Inadequate IRB Resources
(37) Overburdened IRB
(38) Lack of IRB Professional Competence to Review Specific Research Activities

H. IRB DOCUMENTATION, FINDINGS, AND PROCEDURES

(39) Lack of Appropriate Written IRB Policies and Procedures
(40) Failure of an Institution Engaged In HHS-Conducted or –Supported Research to Hold an OHRP-Approved Assurance
(41) Inadequate IRB Records
(42) Inadequate IRB Minutes
(43) Poorly Maintained IRB Files
(44) Failure of IRB to Determine That Criteria for IRB Approval Are Satisfied
Failure of IRB to Make Required Findings When Reviewing Research Involving Children

Failure of IRB to Make Required Findings When Reviewing Research Involving Prisoners

Failure of IRB to Make and Document Required Findings for Waiver of Informed Consent

Failure to Make Required Findings for IRB Waiver of a Signed Informed Consent Document

Inadequate Retention of IRB Records

Failure to Notify Investigators/Institution of IRB Actions

I. OTHER

Failure of Signatory Official to Fulfill Obligations

A. INITIAL AND CONTINUING REVIEW

(1) Research Conducted without IRB Review and/or Approval.

In accordance with HHS regulations at 45 CFR 46.103(b) and 46.109(a), the IRB must review and approve all non-exempt human subject research covered by an assurance before the research can be conducted. We have determined that certain non-exempt human subjects research was conducted without IRB review and/or approval.

(2) Failure of IRB to Review HHS Grant Applications.

HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each application or proposal for research covered by the assurance has been reviewed and approved by an IRB designated under the institution’s federalwide assurance. We have determined that the IRB consistently failed to review the grant application for proposed research for which the institution is the primary awardee. (see “IRB Review of Applications for HHS Support” http://www.dhhs.gov/ohrp/humansubjects/guidance/aplrev.htm)

(3) IRB Lacks Sufficient Information to Make Determinations Required for Approval of Research.

We have determined that the IRB, when reviewing protocol applications, lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, the IRB reviewed insufficient information regarding (a) risks to subjects and how they are minimized; (b) subject recruitment and enrollment procedures; (c) the equitable selection of subjects; (d) provisions to protect the privacy of subjects and maintain the confidentiality of data; and
(e) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable.

(4) **Inadequate IRB Review at Convened Meetings.**

In accordance with HHS regulations at 45 CFR 46.108(b), review of proposed research must be conducted by the IRB 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, except where expedited review is appropriate under HHS regulations at 45 CFR 46.110(b). We have determined that little substantive review took place at convened meetings. Protocols undergoing initial/continuing review and protocol amendments undergoing review were neither individually presented nor discussed at a convened meeting of the IRB. Furthermore, we have noted little evidence that IRB approval of research was consistently based on consideration of the determinations required under HHS regulations at 45 CFR 46.111. Specifically, the IRB appeared not to have considered systematically and rigorously such issues as risks to subjects and how they are minimized, equitable selection of subjects and subject recruitment, privacy and confidentiality protections, and additional safeguards for subjects likely to be vulnerable to coercion or undue influence.

(5) **Members Present at Convened IRB Meetings Lacked the Expertise to Make Determinations Required for Approval of Research.**

HHS regulations at 45 CFR 46.107(a) provide, among other things, that 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. In addition, the regulations provide that the IRB be sufficiently qualified through the experience and expertise of its members to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects and 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 convened IRB, when reviewing protocol applications, must have sufficient expertise among the members present at the meeting to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. We have determined that the members of the IRB present at convened meetings did not have the background and expertise necessary to review the research being proposed.

(6) **Approval of Research Not Approved by the IRB.**

HHS regulations at 45 CFR 46.113 require that the IRB 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. In addition, HHS regulations at 45 CFR 46.112 provide that non-exempt human subjects research that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, such officials may not approve non-exempt human subjects research if it has not been approved by an IRB.
We have determined that the IRB voted to suspend research, and that an institutional official rescinded or delayed that suspension, in violation of HHS regulations at 45 CFR 46.113 and 112.

(7) **Contingent Approval of Research with Substantive Changes and no Additional Review by the Convened IRB.**

We have determined that the IRB frequently approved research contingent upon substantive modifications or clarifications that were directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111 without requiring additional review by the convened IRB. We have noted that when the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that the IRB needs in order to make the determinations required by the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research must be deferred, pending subsequent review by the convened IRB of responsive material, unless the research is eligible for review under an expedited review procedure.

(8) **IRB Meeting Convened without Quorum (No Nonscientist Present).**

HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, research be reviewed 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 a nonscientific area (hereinafter referred to as “nonscientist”). We have determined that the IRB failed to meet this requirement for certain IRB meetings. Thus, any actions taken at these meetings that required a quorum were not valid under the HHS regulations at 45 CFR part 46. We have emphasized that should the quorum fail during a meeting (e.g., those with conflicts being excused, early departures, absence of a nonscientist member), the IRB may not take further actions or votes that require a quorum unless the quorum is restored.

(9) **IRB Meeting Convened without Quorum (Lack of a Majority).**

HHS regulations at 45 CFR 46.108 require that, except when an expedited review procedure is used, the IRB review proposed research at convened meetings at which a majority of the members of the IRB are present. We have determined that the IRB failed to meet this requirement for certain IRB meetings. Thus, any actions taken at these meeting that required a quorum were not valid under the HHS regulations at 45 CFR part 46. We have emphasized that should the quorum fail during a meeting (e.g., those with conflicts being excused, early departures, absence of a nonscientist member), the IRB may not take further actions or votes that require a quorum unless the quorum can be restored.
IRB Members with Conflicting Interest Participated in IRB Review of Research.

HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB’s initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB. We have determined that IRB members inappropriately participated in the initial and continuing review of protocols for which they had a conflicting interest, for example, by voting on protocols on which they were investigators.

Inadequate Continuing Review.

Continuing review of research must be substantive and meaningful. HHS regulations describe at 45 CFR 46.111 (and at subparts B, C, and D of 45 CFR part 46 when applicable) the criteria that must be satisfied in order for the IRB to approve research. These criteria must be satisfied when the IRB conducts continuing review of research either at a convened meeting or under an expedited review procedure. These criteria include, among other things, determinations by the IRB regarding risks, potential benefits, informed consent, and additional safeguards for subjects likely to be vulnerable to coercion or undue influence.

We have determined that continuing review of research by the IRB was not substantive and meaningful.

Failure to Conduct Continuing Review at Least Once per Year.

HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk, but not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB chairperson or another IRB member designated by the chairperson, continuing review must occur no later than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date the IRB chairperson or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

We have determined that the IRB failed to conduct continuing review of research at least once per year and that in some cases the IRB has granted extensions beyond the expiration date of IRB approval.

Continuing Review for Follow up of Subjects in Research Protocols.

HHS regulations at 45 CFR 46.109(e) state that 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. HHS regulations at 45 CFR 46.102(f) define human subject as a living individual about whom an investigator (whether professional or student)
conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. Even where (i) the research is permanently closed to the enrollment of new subjects; and (ii) all subjects have completed all research-related interventions, continuing review is required as long as the research remains active for long-term follow-up of subjects and continues to involve non-exempt human subjects research. Furthermore, continuing IRB review of research is required where the remaining research activities are limited to data analysis of individually identifiable private information (see 63 FR 60364-60367, category (8)). We have determined that continuing review did not occur in protocols involving follow-up activities.

B. EXPEDITED REVIEW PROCEDURES

(14) Inappropriate Use of Expedited Review Procedures for Initial or Continuing IRB Review.

HHS regulations at 45 CFR 46.108(b) require that the IRB 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, except where expedited review is appropriate under HHS regulations at 45 CFR 46.110. HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures for initial or continuing review to specific research categories published in the Federal Register at 63 FR 60364--60367 (see [link](http://www.dhhs.gov/ohrp/humansubjects/guidance/expedited98.htm)) when the research is determined to involve no more than minimal risk. We have determined that:

(a) The IRB inappropriately applied expedited review to research that involved minimal risk but did not appear in the categories of research published in the Federal Register.

(b) The IRB inappropriately applied expedited review to research that involved greater than minimal risk.


HHS regulations at 45 CFR 46.108(b) require that the IRB 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, except where expedited review is appropriate under HHS regulations at 45 CFR 46.110. HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes in previously approved research during the period for which approval is authorized. We have determined that the IRB has employed expedited procedures to review changes that were more than minor.
(16) **Failure to Advise IRB Members of Expedited Approvals.**

HHS regulations at 45 CFR 46.110(c) require that all IRB members be advised of research proposals which have been approved under an expedited review procedure. We have determined that all IRB members were not advised of (a) research protocols approved at time of initial or continuing review under an expedited review procedure, or (b) minor changes in research protocols approved under an expedited review procedure.

(17) **Expedited Review Conducted by Someone Other than an IRB Member.**

HHS regulations at 45 CFR 46.110(b) state that 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 the members of the IRB. We have determined that an individual who was not a member of the IRB approved human subject research purportedly under an expedited review procedure, in violation of HHS regulations at 45 CFR 46.103(b), 45 CFR 46.109(a) and 45 CFR 46.110(b).

C. **REPORTING OF UNANTICIPATED PROBLEMS, NONCOMPLIANCE, SUSPENSIONS, AND TERMINATIONS**

(18) **Failure to Report Unanticipated Problems, Noncompliance, Suspensions, and Terminations, to IRB, Institutional Officials, and OHRP.**

We have determined that unanticipated problems involving risks to subjects or others or serious or continuing noncompliance or suspensions or terminations of IRB approval were not reported to appropriate institutional officials or the IRB or OHRP or the head of the sponsoring Federal department or agency as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

D. **IRB REVIEW OF PROTOCOL CHANGES**

(19) **Changes to Research Initiated Without IRB Review and Approval.**

HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. We have found no documentation that the IRB reviewed and approved protocol changes prior to initiation or we determine that certain protocol changes were initiated without IRB approval and/or approval, in circumstances where the changes were not necessary to eliminate apparent immediate hazards to the subjects.

(20) **Inadequate IRB Review and/or Approval of Protocol Changes.**

HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has
already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. We have determined that the IRB’s procedures for reviewing protocol modifications was inadequate. In some cases, the IRB chairperson or designated IRB reviewer from among the IRB members approved such modifications in the absence of a complete description of the proposed changes.

We note that when reviewing proposed changes to research, the IRB must also receive sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111 and, when applicable, under subparts B, C, and D of 45 CFR part 46, although we did not cite these regulatory provisions when making this determination in the past.

E. APPLICATION OF EXEMPTIONS

(21) Inappropriate Application of Exempt Categories of Research.

HHS regulations at 45 CFR 46.101(b) delineate six specific categories of research that are exempt from the requirements of 45 CFR part 46. We have determined that the institution applied an exemption to research activities that exceed these categories.

(22) Inappropriate Application of Exemption 4.

HHS regulations at 45 CFR 46.101(b)(4) exempt research that only involves the collection or study of existing data, documents, records, pathologic specimens, or diagnostic specimens provided specified conditions are met. We have noted that such materials must already exist at the time the research is proposed. We have determined instances where this exemption was applied to research involving data, documents, pathologic specimens, or diagnostic specimens that were not existing at the time the research was proposed.

(23) Inappropriate Application of Exemption 2 for Research Involving Children.

HHS regulations at 45 CFR 46.401(b) stipulate that the exemption at 45 CFR 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by 45 CFR part 46, subpart D (Additional Protections for Children Involved as Subjects in Research), except for research involving observation of public behavior when the investigators do not participate in the activities being observed. We have determined that exemption 2 was inappropriately applied to survey and observational research involving children.

F. INFORMED CONSENT

(24) Failure of the Investigator to Obtain the Legally Effective Informed Consent of Subjects or of the IRB to Appropriately Waive the Requirements to Obtain Informed Consent.
HHS regulations at 45 CFR 45.116 state that no investigator may involve a human being as a subject in research covered by the regulations unless (a) the investigator has obtained the legally effective informed consent of the subjects or the subject’s legally authorized representative, or (b) the IRB has waived the requirements to obtain informed consent in accordance with 45 CFR 46.116(c) or (d), or in accordance with the provisions for waiver of informed consent for research in emergent settings published in the Federal Register, Vol. 61, pp. 51531-51533. We have determined that the investigator initiated human subject research without obtaining legally effective informed consent of subjects and without the IRB appropriately waiving these requirements.

(25) Failure to Document Informed Consent or of the IRB to Appropriately Waive the Requirement to Document Informed Consent.

HHS regulations at 45 CFR 46.117(a) require that informed consent be documented by the use of a written consent form approved by the IRB and that is signed by the subject, or the subject’s legally authorized representative, unless the IRB waives this requirement in accordance with 45 CFR 46.117(c). We have determined that informed consent was not documented by a written consent form signed by the subject(s) for this research and there was no IRB waiver of this requirement.

(26) Failure to Provide a Copy of the Informed Consent Document (ICD) to the Subject or the Subject’s Legally Authorized Representative.

HHS regulations at 45 CFR 46.117(a) require that informed consent 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 unless the requirement for documentation of informed consent has been waived by the IRB in accordance with HHS regulations at 45 CFR 46.117(c). The regulations further require that a copy of the informed consent document shall be given to the person signing the form. We have determined that a copy of the informed consent document was not provided to the person signing the informed consent form.

(27) Inadequate ICD for Specific Research/Lack of Basic Elements.

HHS regulations at 45 CFR 46.116(a) require that when seeking informed consent specific information shall be provided to each subject unless the IRB approves a consent procedure which does not include, or which alters, some or all of the required basic elements of informed consent provided in accordance with 45 CFR 46.116 (c) or (d). We have determined that the informed consent documents reviewed and approved by the IRB failed to include and/or adequately address the following basic elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): (i) A statement that the study involves research; (ii) an explanation of the purposes of the research; (iii) the expected duration of the subject’s participation; and (iv) a complete description of the
procedures to be followed, and identification of any procedures which are experimental.

(b) Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts.

(c) Section 46.116(a)(3): A description of any benefits to the subject or others that may reasonably be expected from the research.

(d) Section 46.116(a)(4): A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(e) Section 46.116(a)(5): A statement describing the extent to which confidentiality of records identifying the subject will be maintained.

(f) Section 46.116(a)(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.

(g) Section 46.116(a)(7): An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights (should include someone other than the investigator), and whom to contact in the event of a research-related injury to the subject.

(h) Section 46.116(a)(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.

Moreover, we found no documentation that the IRB approved a consent procedure which did not include, or which altered, some of the required basic elements of informed consent noted above in accordance with 45 CFR 46.116(c) or (d).

(28) Inadequate ICD for Specific Research/Lack of Additional Elements.

HHS regulations at 45 CFR 46.116(b) require that, when appropriate, additional elements of information shall be provided to subjects. We have determined that the following additional elements of informed consent should have been included in the informed consent documents under HHS regulations at 45 CFR 46.116(b):

(a) Section 46.116(b)(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;

(b) Section 46.116(b)(2): Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent.

(c) Section 46.116(b)(3): Any additional costs to the subject that may result from participation in the research;

(d) Section 46.116(b)(4): The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject.
(e) Section 46.116(b)(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.

(f) Section 46.116(b)(6): The approximate number of subjects involved in the study.

Moreover, we found no documentation that the IRB approved a consent procedure which did not include, or which altered, some of the required additional elements noted above in accordance with 45 CFR 46.116(c) or (d).

(29) ICD Language too Complex.

HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject’s legally authorized representative. We have determined that the informed consent information provided to subjects would not be understandable to some subjects.

(30) Exculpatory Language in ICDs.

HHS regulations at 45 CFR 46.116 prohibit the inclusion of any exculpatory language in informed consent through which the subject is made to waive, or appear to waive, any of the subject's legal rights. We have determined certain language in the IRB-approved informed consent documents was exculpatory.

(31) Enrollment Procedures did not Minimize Possibility of Coercion or Undue Influence.

HHS regulations at 45 CFR 46.116 require that investigators seek the legally effective informed consent of subjects under circumstances that minimize the possibility of coercion or undue influence. We have determined that informed consent was not sought from prospective subjects under circumstances that minimized the possibility of coercion or undue influence.

G. IRB MEMBERSHIP, EXPERTISE, STAFF, SUPPORT, AND WORKLOAD

(32) Failure To Have An Unaffiliated IRB Member.

HHS regulations at 45 CFR 46.107(d) require that each IRB 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. We have determined that the IRB did not include any such member.

(33) Lack of Prisoner/Prisoner Representative for IRB Review of Research Involving Prisoners.
HHS regulations at 45 CFR 46.304 require that at least one member of an IRB that reviews research involving prisoners 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 IRB only one IRB need satisfy this requirement. When the convened IRB reviews research involving prisoners (including initial review, continuing review, review of protocol modifications, and review of unanticipated problems involving risks to subjects or others), the prisoner or prisoner representative must be present as a voting member. We have determined that the IRB failed to meet this requirement when reviewing research projects involving prisoners.

(34) **IRB Chairperson and Members Lack Sufficient Understanding of HHS Regulations.**

HHS regulations at 45 CFR 46.107(a) provide, among other things, that the IRB shall be sufficiently qualified through the experience and expertise of its members to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects and 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. We have determined that the IRB chairperson and/or IRB members lacked a detailed understanding of the specific requirements of the HHS regulations for the protection of human subjects. As a result, IRB determinations sometimes deviated from these requirements.

(35) **Designation of an Additional IRB under an FWA without Prior OHRP Approval.**

HHS regulations at 45 CFR 46.103(b) state, in part, that assurances applicable to federally supported or conducted research shall include designation of one or more IRBs established in accordance with the requirements of the regulations, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

Designation of additional IRBs under an FWA requires prior notification of and approval by OHRP. We have determined that the institution established an additional IRB that reviews research covered by its FWA without such approval.

(36) **Inadequate IRB Resources.**

HHS regulations at 45 CFR 46.103(b)(2) require that institutions provide meeting space and sufficient staff to support the IRB’s review and recordkeeping duties. We have determined that the IRB lacked sufficient meeting space and/or staff to support the IRB’s review and recordkeeping duties.

(37) **Lack of IRB Knowledge of Local Research Context.**

HHS regulations at 45 CFR 46.107(a) require, among other things, that the IRB be (a) sufficiently qualified through 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; and (b) able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. Institutions have a responsibility to ensure that all IRBs designated under an OHRP-approved Assurance possess sufficient knowledge of the local research context to satisfy these requirements. We have determined that the IRB did not have the background and expertise to review the above-referenced research based on its failure to include members with sufficient understanding of the cultural conditions, including the social, economic, and political status, of the subject population.

We note that the IRB also must have sufficient background and expertise regarding the local research context in order to make the determinations required for approval of research as described within HHS regulations at 45 CFR 46.111 and applicable subparts, although we did not cite this regulatory provision when making this determination in the past.

(38) Lack of IRB Professional Competence to Review Specific Research Activities.

HHS regulations at 45 CFR 46.107(a) require, among other things, that the IRB possess the professional competence necessary to review specific research activities. We have determined that the IRB did not possess the professional competence necessary to review specific research activities.

We note that the IRB also must have sufficient professional competence in order to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111, although we did not cite this regulatory provision when making this determination in the past. We also note that under HHS regulations at 45 CFR 46.107(f) an IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which are beyond or in addition to that available on the IRB and IRB’s cited for this determination did not seek to invite individuals with competence in relevant special areas, although this was not noted when the determinations were originally made by OHRP.

H. IRB DOCUMENTATION, FINDINGS, AND PROCEDURES

(39) Lack of Appropriate Written IRB Procedures.

We have determined that the institution did not have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow for conducting its initial review of research.
(b) The procedures which the IRB will follow for conducting its continuing review of research.
(c) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.

(d) The procedures which the IRB will follow for determining which projects require review more often than annually.

(e) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(f) The procedures which the IRB will follow 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.

(g) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

(40) Failure of an Institution Engaged In HHS-Conducted or –Supported Research to Hold an OHRP-Approved FWA.

HHS regulations at 45 CFR 46.103(a) require that each institution “engaged” in human subjects research provide OHRP with a satisfactory assurance to comply with the regulations, unless the research is exempt under 45 CFR 46.101(b). (Please see OHRP guidance at http://www.dhhs.gov/ohrp/humansubjects/guidance/engage08.pdf)

In general, an institution is considered engaged in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research [45 CFR 46.102(d),(f)].

We have determined that the institution was engaged in human subject research under a particular project and the institution was not covered by an OHRP-approved FWA for this research. If the project in question is ongoing, we have noted that involvement of the unassured institution in non-exempt human subject research activities under the specified HHS award must be suspended until OHRP approved an FWA, unless it is determined that it is in subjects’ best interest to continue.

(41) Inadequate IRB Records.

We have determined that IRB records fail to include all the documentation required by HHS regulations at 45 CFR 46.115(a).
(42) **Inadequate IRB Minutes.**

HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings 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. We have determined that minutes of IRB meetings failed to meet these requirements.

(43) **Poorly Maintained IRB Files.**

HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. We found that in numerous instances among the IRB files examined by OHRP, it was difficult to reconstruct a complete history of all IRB actions related to the review and approval of the protocol. In some instances, we could not determine what the IRB actually approved.

(44) **Failure of IRB to Determine That Criteria for IRB Approval Are Satisfied.**

HHS regulations at 45 CFR 46.111 delineate the criteria that must be satisfied in order for an IRB to approve research covered by the regulations. We have determined that for certain research the IRB failed to determine that the following requirements were satisfied:

(a) Risks to subjects are minimized.
(b) 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.
(c) Selection of subjects is equitable.
(d) Informed consent will be sought from each prospective subject or the subject’s legally authorized representative.
(e) Informed consent will be appropriately documented.
(f) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
(g) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
(h) When some or all of the subjects 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 vulnerable subjects.
(45) **Failure of IRB to Make Required Findings When Reviewing Research Involving Children.**

HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. We have determined that the IRB did not make the required findings when reviewing research involving children.

(46) **Failure of IRB to Make Required Findings When Reviewing Research Involving Prisoners.**

HHS regulations at 45 CFR 46.305-306 require specific findings on the part of the IRB for approval of research involving prisoners.

(a) We have determined that the IRB failed to make the required findings when reviewing such research.

(b) We have determined that the IRB approved research involving prisoners even though the research failed to satisfy subpart C criteria.

(47) **Failure of IRB to Make and Document Required Findings for Waiver of Informed Consent.**

HHS regulations at 45 CFR 46.116(c) and (d) require that the IRB find and document specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. We have determined that the IRB failed to satisfy these requirements.

(48) **Failure to Make Required Findings for IRB Waiver of a Signed Informed Consent Document.**

HHS regulations at 45 CFR 46.117(c) requires specific findings on the part of the IRB for waiver of the requirements for the investigator to obtain a signed consent form from all subjects. We have determined that the IRB failed to make the required findings when approving such waivers.

(49) **Inadequate Retention of IRB Records.**

HHS regulations at 45 CFR 46.115(b) require that IRB records be retained for at least 3 years, and records relating to research which is conducted be retained for at least 3 years after completion of the research. All records must be accessible for inspection and copying by authorized representatives of HHS at reasonable times and in a reasonable manner. We have determined that the institution failed to retain IRB records OR records relating to research for at least 3 years after completion of the research at that study site.
(50) **Failure to Notify Investigators/Institution of IRB Actions.**

HHS regulations at 45 CFR 46.109(d) require that an IRB 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. We have determined that the IRB did not notify investigators and the institution in writing of its decision to approve or disapprove proposed research or of modifications required to secure IRB approval of the research.

I. **OTHER**

(51) **Failure of Signatory Official to Fulfill Obligations.**

HHS regulations at 45 CFR 46.103(c) require that an institution’s assurance of compliance with the regulations for the protection of human subjects shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by the regulations. We have determined that the Signatory Official failed to fulfill his or her obligations imposed by the HHS regulations for the protection of human subjects and the institution’s FWA.

We note that HHS regulations at 45 CFR 46.103(a) require that 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 the regulations, although we did not cite this regulatory provision when making this determination in the past. Similarly, Public Law 99-158 Sec. 491(a) requires that the Secretary shall by regulation require that each entity which applies for a grant, contract, or cooperative agreement under this Act for any project or program which involves the conduct of biomedical or behavioral research involving human subjects submit in or with its application for such grant, contract, or cooperative agreement assurances satisfactory to the Secretary.
Title 21--Food and Drugs

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 312--INVESTIGATIONAL NEW DRUG APPLICATION

Subpart A_General Provisions

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>312.1</td>
<td>Scope.</td>
</tr>
<tr>
<td>312.2</td>
<td>Applicability.</td>
</tr>
<tr>
<td>312.3</td>
<td>Definitions and interpretations.</td>
</tr>
<tr>
<td>312.6</td>
<td>Labeling of an investigational new drug.</td>
</tr>
<tr>
<td>312.7</td>
<td>Promotion of investigational drugs.</td>
</tr>
<tr>
<td>312.8</td>
<td>Charging for investigational drugs under an IND.</td>
</tr>
<tr>
<td>312.10</td>
<td>Waivers.</td>
</tr>
</tbody>
</table>

Subpart B_Investigational New Drug Application (IND)

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>312.20</td>
<td>Requirement for an IND.</td>
</tr>
<tr>
<td>312.21</td>
<td>Phases of an investigation.</td>
</tr>
<tr>
<td>312.22</td>
<td>General principles of the IND submission.</td>
</tr>
<tr>
<td>312.23</td>
<td>IND content and format.</td>
</tr>
<tr>
<td>312.30</td>
<td>Protocol amendments.</td>
</tr>
<tr>
<td>312.31</td>
<td>Information amendments.</td>
</tr>
<tr>
<td>312.32</td>
<td>IND safety reporting.</td>
</tr>
<tr>
<td>312.33</td>
<td>Annual reports.</td>
</tr>
<tr>
<td>312.38</td>
<td>Withdrawal of an IND.</td>
</tr>
</tbody>
</table>

Subpart C_Administrative Actions

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>312.40</td>
<td>General requirements for use of an investigational new drug in a clinical investigation.</td>
</tr>
<tr>
<td>312.41</td>
<td>Comment and advice on an IND.</td>
</tr>
<tr>
<td>312.42</td>
<td>Clinical holds and requests for modification.</td>
</tr>
<tr>
<td>312.44</td>
<td>Termination.</td>
</tr>
<tr>
<td>312.45</td>
<td>Inactive status.</td>
</tr>
</tbody>
</table>
312.47 Meetings.
312.48 Dispute resolution.

**Subpart D_Responsibilities of Sponsors and Investigators**

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>312.50</td>
<td>General responsibilities of sponsors.</td>
</tr>
<tr>
<td>312.52</td>
<td>Transfer of obligations to a contract research organization.</td>
</tr>
<tr>
<td>312.53</td>
<td>Selecting investigators and monitors.</td>
</tr>
<tr>
<td>312.54</td>
<td>Emergency research under 50.24 of this chapter.</td>
</tr>
<tr>
<td>312.55</td>
<td>Informing investigators.</td>
</tr>
<tr>
<td>312.56</td>
<td>Review of ongoing investigations.</td>
</tr>
<tr>
<td>312.57</td>
<td>Recordkeeping and record retention.</td>
</tr>
<tr>
<td>312.58</td>
<td>Inspection of sponsor's records and reports.</td>
</tr>
<tr>
<td>312.59</td>
<td>Disposition of unused supply of investigational drug.</td>
</tr>
<tr>
<td>312.60</td>
<td>General responsibilities of investigators.</td>
</tr>
<tr>
<td>312.61</td>
<td>Control of the investigational drug.</td>
</tr>
<tr>
<td>312.62</td>
<td>Investigator recordkeeping and record retention.</td>
</tr>
<tr>
<td>312.64</td>
<td>Investigator reports.</td>
</tr>
<tr>
<td>312.66</td>
<td>Assurance of IRB review.</td>
</tr>
<tr>
<td>312.68</td>
<td>Inspection of investigator's records and reports.</td>
</tr>
<tr>
<td>312.69</td>
<td>Handling of controlled substances.</td>
</tr>
<tr>
<td>312.70</td>
<td>Disqualification of a clinical investigator.</td>
</tr>
</tbody>
</table>

**Subpart E_Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses**

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>312.80</td>
<td>Purpose.</td>
</tr>
<tr>
<td>312.81</td>
<td>Scope.</td>
</tr>
<tr>
<td>312.82</td>
<td>Early consultation.</td>
</tr>
<tr>
<td>312.83</td>
<td>Treatment protocols.</td>
</tr>
<tr>
<td>312.84</td>
<td>Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.</td>
</tr>
<tr>
<td>312.85</td>
<td>Phase 4 studies.</td>
</tr>
<tr>
<td>312.86</td>
<td>Focused FDA regulatory research.</td>
</tr>
<tr>
<td>312.87</td>
<td>Active monitoring of conduct and evaluation of clinical trials.</td>
</tr>
<tr>
<td>312.88</td>
<td>Safeguards for patient safety.</td>
</tr>
</tbody>
</table>
### Subpart F_Miscellaneous

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>312.110</td>
<td>Import and export requirements.</td>
</tr>
<tr>
<td>312.120</td>
<td>Foreign clinical studies not conducted under an IND.</td>
</tr>
<tr>
<td>312.130</td>
<td>Availability for public disclosure of data and information in an IND.</td>
</tr>
<tr>
<td>312.140</td>
<td>Address for correspondence.</td>
</tr>
<tr>
<td>312.145</td>
<td>Guidance documents.</td>
</tr>
</tbody>
</table>

### Subpart G_Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>312.60</td>
<td>Drugs for investigational use in laboratory research animals or in vitro tests.</td>
</tr>
</tbody>
</table>

### Subpart H_Reserved

### Subpart I_Expanded Access to Investigational Drugs for Treatment Use

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>312.300</td>
<td>General.</td>
</tr>
<tr>
<td>312.305</td>
<td>Requirements for all expanded access uses.</td>
</tr>
<tr>
<td>312.310</td>
<td>Individual patients, including for emergency use.</td>
</tr>
<tr>
<td>312.315</td>
<td>Intermediate-size patient populations.</td>
</tr>
<tr>
<td>312.320</td>
<td>Treatment IND or treatment protocol.</td>
</tr>
</tbody>
</table>

### Subpart A--General Provisions

#### Sec. 312.1 Scope.

(a) This part contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's). An investigational new drug for which an IND is in effect in accordance with this part is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.

(b) References in this part to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.
Sec. 312.2 Applicability.

(a) Applicability. Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).

(b) Exemptions. (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:
   (i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
   (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
   (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
   (iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
   (v) The investigation is conducted in compliance with the requirements of 312.7.

(2) (i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and it is shipped in compliance with 312.160.

(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (a) blood grouping serum; (b) reagent red blood cells; and (c) anti-human globulin.

(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with 312.160.

(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

(6) A clinical investigation involving an exception from informed consent under 50.24 of this chapter is not exempt from the requirements of this part.

(c) Bioavailability studies. The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of 320.31.

(d) Unlabeled indication. This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.

(e) Guidance. FDA may, on its own initiative, issue guidance on the applicability of this part to particular investigational uses of drugs. On request, FDA will advise on the applicability of this part to a planned clinical investigation.

Sec. 312.3 Definitions and interpretations.

(a) The definitions and interpretations of terms contained in section 201 of the Act apply to those terms when used in this part:

(b) The following definitions of terms also apply to this part:


*Clinical investigation* means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

*Contract research organization* means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

*FDA* means the Food and Drug Administration.

*IND* means an investigational new drug application. For purposes of this part, "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug."

*Independent ethics committee (IEC)* means a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection. An institutional review board (IRB), as defined in 56.102(g) of this chapter and subject to the requirements of part 56 of this chapter, is one type of IEC.

*Investigational new drug* means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

*Investigator* means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.

*Marketing application* means an application for a new drug submitted under section 505(b) of the act or a biologics license application for a biological product submitted under the Public Health Service Act.

*Sponsor* means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private
organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

_Sponsor-Investigator_ means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

_Subject_ means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.


### Sec. 312.6 Labeling of an investigational new drug.

(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

(c) The appropriate FDA Center Director, according to the procedures set forth in 201.26 or 610.68 of this chapter, may grant an exception or alternative to the provision in paragraph (a) of this section, to the extent that this provision is not explicitly required by statute, for specified lots, batches, or other units of a human drug product that is or will be included in the Strategic National Stockpile.


### Sec. 312.7 Promotion of investigational drugs.

(a) _Promotion of an investigational new drug._ A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is being investigated or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

(b) _Commercial distribution of an investigational new drug._ A sponsor or investigator shall not commercially distribute or test market an investigational new drug.
(c) Prolonging an investigation. A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.


Sec. 312.8 Charging for investigational drugs under an IND.

(a) General criteria for charging. (1) A sponsor must meet the applicable requirements in paragraph (b) of this section for charging in a clinical trial or paragraph (c) of this section for charging for expanded access to an investigational drug for treatment use under subpart I of this part, except that sponsors need not fulfill the requirements in this section to charge for an approved drug obtained from another entity not affiliated with the sponsor for use as part of the clinical trial evaluation (e.g., in a clinical trial of a new use of the approved drug, for use of the approved drug as an active control).

(2) A sponsor must justify the amount to be charged in accordance with paragraph (d) of this section.

(3) A sponsor must obtain prior written authorization from FDA to charge for an investigational drug.

(4) FDA will withdraw authorization to charge if it determines that charging is interfering with the development of a drug for marketing approval or that the criteria for the authorization are no longer being met.

(b) Charging in a clinical trial --(1) Charging for a sponsor's drug. A sponsor who wishes to charge for its investigational drug, including investigational use of its approved drug, must:

(i) Provide evidence that the drug has a potential clinical benefit that, if demonstrated in the clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation, or prevention of a disease or condition;

(ii) Demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval of a drug, or would support a significant change in the labeling of an approved drug (e.g., new indication, inclusion of comparative safety information); and

(iii) Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor. The cost may be extraordinary due to manufacturing complexity, scarcity of a natural resource, the large quantity of drug needed (e.g., due to the size or duration of the trial), or some combination of these or other extraordinary circumstances (e.g., resources available to a sponsor).

(2) Duration of charging in a clinical trial. Unless FDA specifies a shorter period, charging may continue for the length of the clinical trial.

(c) Charging for expanded access to investigational drug for treatment use. (1) A sponsor who wishes to charge for expanded access to an investigational drug for treatment use under subpart I of this part must provide reasonable assurance that charging will not interfere with developing the drug for marketing approval.

(2) For expanded access under 312.320 (treatment IND or treatment protocol), such assurance must include:
(i) Evidence of sufficient enrollment in any ongoing clinical trial(s) needed for marketing approval to reasonably assure FDA that the trial(s) will be successfully completed as planned;

(ii) Evidence of adequate progress in the development of the drug for marketing approval; and

(iii) Information submitted under the general investigational plan (312.23(a)(3)(iv)) specifying the drug development milestones the sponsor plans to meet in the next year.

(3) The authorization to charge is limited to the number of patients authorized to receive the drug under the treatment use, if there is a limitation.

(4) Unless FDA specifies a shorter period, charging for expanded access to an investigational drug for treatment use under subpart I of this part may continue for 1 year from the time of FDA authorization. A sponsor may request that FDA reauthorize charging for additional periods.

(d) Costs recoverable when charging for an investigational drug. (1) A sponsor may recover only the direct costs of making its investigational drug available.

(i) Direct costs are costs incurred by a sponsor that can be specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery. Direct costs include costs per unit to manufacture the drug (e.g., raw materials, labor, and nonreusable supplies and equipment used to manufacture the quantity of drug needed for the use for which charging is authorized) or costs to acquire the drug from another manufacturing source, and direct costs to ship and handle (e.g., store) the drug.

(ii) Indirect costs include costs incurred primarily to produce the drug for commercial sale (e.g., costs for facilities and equipment used to manufacture the supply of investigational drug, but that are primarily intended to produce large quantities of drug for eventual commercial sale) and research and development, administrative, labor, or other costs that would be incurred even if the clinical trial or treatment use for which charging is authorized did not occur.

(3) For expanded access to an investigational drug for treatment use under 312.315 (intermediate-size patient populations) and 312.320 (treatment IND or treatment protocol), in addition to the direct costs described in paragraph (d)(1)(i) of this section, a sponsor may recover the costs of monitoring the expanded access IND or protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access IND.

(4) To support its calculation for cost recovery, a sponsor must provide supporting documentation to show that the calculation is consistent with the requirements of paragraphs (d)(1) and, if applicable, (d)(2) of this section. The documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculations.

[74 FR 40899, Aug. 13, 2009]
(1) An explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved;
(2) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or
(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds that the sponsor's noncompliance would not pose a significant and unreasonable risk to human subjects of the investigation and that one of the following is met:
(1) The sponsor's compliance with the requirement is unnecessary for the agency to evaluate the application, or compliance cannot be achieved;
(2) The sponsor's proposed alternative satisfies the requirement; or
(3) The applicant's submission otherwise justifies a waiver.


Subpart B—Investigational New Drug Application (IND)

Sec. 312.20 Requirement for an IND.

(a) A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to 312.2(a).
(b) A sponsor shall not begin a clinical investigation subject to 312.2(a) until the investigation is subject to an IND which is in effect in accordance with 312.40.
(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization from FDA. FDA shall provide a written determination 30 days after FDA receives the IND or earlier.


Sec. 312.21 Phases of an investigation.

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap. These three phases of an investigation are as follows:

(a) Phase 1. (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total
number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

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

(c) Phase 3. Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

Sec. 312.22 General principles of the IND submission.

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

(d) The IND format set forth in 312.23 should be followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed for a commercially sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format, but ordinarily may, if authorized by the manufacturer, refer to the
manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

Sec. 312.23 IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

(1) Cover sheet (Form FDA-1571). A cover sheet for the application containing the following:

(i) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.

(ii) Identification of the phase or phases of the clinical investigation to be conducted.

(iii) A commitment not to begin clinical investigations until an IND covering the investigations is in effect.

(iv) A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research activity in accordance with the requirements of part 56.

(v) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

(vi) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.

(vii) The name(s) and title(s) of the person(s) responsible under 312.32 for review and evaluation of information relevant to the safety of the drug.

(viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer--in lieu of a listing of the specific obligations transferred--may be submitted.

(ix) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(2) A table of contents.

(3) Introductory statement and general investigational plan. (i) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

(ii) A brief summary of previous human experience with the drug, with reference to other IND's if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s).
(iii) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (a) The rationale for the drug or the research study; (b) the indication(s) to be studied; (c) the general approach to be followed in evaluating the drug; (d) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate); (e) the estimated number of patients to be given the drug in those studies; and (f) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

(4) [Reserved]

(5) Investigator's brochure. If required under 312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

(6) Protocols. (i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with 312.30(a).) In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation--an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose--and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(a) A statement of the objectives and purpose of the study.
The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(c) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

(d) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

(e) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

(f) A description of the observations and measurements to be made to fulfill the objectives of the study.

(g) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

(7) Chemistry, manufacturing, and control information. (i) As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(iii) As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

(iv) Reflecting the distinctions described in this paragraph (a)(7), and based on the phase(s) to be studied, the submission is required to contain the following:
(a) **Drug substance.** A description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies. Reference to the current edition of the United States Pharmacopeia--National Formulary may satisfy relevant requirements in this paragraph.

(b) **Drug product.** A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug product manufacturer; a brief general description of the manufacturing and packaging procedure as appropriate for the product; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product; and information sufficient to assure the product's stability during the planned clinical studies. Reference to the current edition of the United States Pharmacopeia--National Formulary may satisfy certain requirements in this paragraph.

(c) A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.

(d) **Labeling.** A copy of all labels and labeling to be provided to each investigator.

(e) **Environmental analysis requirements.** A claim for categorical exclusion under 25.30 or 25.31 or an environmental assessment under 25.40.

(8) **Pharmacology and toxicology information.** Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i) **Pharmacology and drug disposition.** A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) **Toxicology.** (a) An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular.
mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(b) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

(iii)For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58, a statement that the study was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(9) Previous human experience with the investigational drug. A summary of previous human experience known to the applicant, if any, with the investigational drug. The information is required to include the following:

(i) If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. If the drug has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(ii) If the drug is a combination of drugs previously investigated or marketed, the information required under paragraph (a)(9)(i) of this section should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

(iii) If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

(10) Additional information. In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i) Drug dependence and abuse potential. If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii) Radioactive drugs. If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii) Pediatric studies. Plans for assessing pediatric safety and effectiveness.

(iv) Other information. A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

(11) Relevant information. If requested by FDA, any other relevant information needed for review of the application.
Sec. 312.30 Protocol amendments.

Once an IND is in effect, a sponsor shall amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application. This section sets forth the provisions under which new protocols may be submitted and changes in previously submitted protocols may be made. Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent as set forth in 50.24 of this chapter, the sponsor shall submit a separate IND for such investigation.

(a) New protocol. Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to FDA a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met: (1) The sponsor has submitted the protocol to FDA for its review; and (2) the protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of part 56. The sponsor may comply with these two conditions in either order.

(b) Changes in a protocol. (1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:
(i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

(ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

(iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(2) (i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:

(a) The sponsor has submitted the change to FDA for its review; and

(b) The change has been approved by the IRB with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.

(ii) Notwithstanding paragraph (b)(2)(i) of this section, a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 56.104(c).

(c) New investigator. A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under 312.315 or 312.320. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

(d) Content and format. A protocol amendment is required to be prominently identified as such (i.e. , "Protocol Amendment: New Protocol", "Protocol Amendment: Change in Protocol", or "Protocol Amendment: New Investigator"), and to contain the following:

(1) (i) In the case of a new protocol, a copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols.

(ii) In the case of a change in protocol, a brief description of the change and reference (date and number) to the submission that contained the protocol.

(iii) In the case of a new investigator, the investigator's name, the qualifications to conduct the investigation, reference to the previously submitted protocol, and all additional information about the investigator's study as is required under 312.23(a)(6)(iii)(b).

(2) Reference, if necessary, to specific technical information in the IND or in a concurrently submitted information amendment to the IND that the sponsor relies on to support any clinically significant change in the new or amended protocol. If the reference is made to supporting information already in the IND, the sponsor shall identify by name, reference number, volume, and page number the location of the information.

(3) If the sponsor desires FDA to comment on the submission, a request for such comment and the specific questions FDA's response should address.

(e) When submitted. A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several
submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.


Sec. 312.31 Information amendments.

(a) Requirement for information amendment. A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:
   (1) New toxicology, chemistry, or other technical information; or
   (2) A report regarding the discontinuance of a clinical investigation.

(b) Content and format of an information amendment. An information amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: Chemistry, Manufacturing, and Control", "Information Amendment: Pharmacology-Toxicology", "Information Amendment: Clinical"), and to contain the following:
   (1) A statement of the nature and purpose of the amendment.
   (2) An organized submission of the data in a format appropriate for scientific review.
   (3) If the sponsor desires FDA to comment on an information amendment, a request for such comment.

(c) When submitted. Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more than every 30 days.


Sec. 312.32 IND safety reporting.

(a) Definitions. The following definitions of terms apply to this section:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of
existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious 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 in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**Suspected adverse reaction** means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

**Unexpected adverse event or unexpected suspected adverse reaction.** An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

(b) **Review of safety information.** The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

(c) (1)**IND safety reports.** The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.
(i) **Serious and unexpected suspected adverse reaction.** The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

(B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

(ii) **Findings from other studies.** The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

(iii) **Findings from animal or in vitro testing.** The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

(iv) **Increased rate of occurrence of serious suspected adverse reactions.** The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

(v) **Submission of IND safety reports.** The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a FDA Form 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.
(2) **Unexpected fatal or life-threatening suspected adverse reaction reports.** The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

(3) **Reporting format or frequency.** FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

(4) **Investigations of marketed drugs.** A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the postmarketing safety reporting requirements (e.g., 310.305, 314.80, and 600.80 of this chapter).

(5) **Reporting study endpoints.** Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under paragraph (c) of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under 312.32(c)(1)(i) as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

(d) **Follow-up.** (1) The sponsor must promptly investigate all safety information it receives.

(2) Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."

(3) If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

(e) **Disclaimer.** A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

[75 FR 59961, Sept. 29, 2010]

**Sec. 312.33 Annual reports.**

A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation that includes:

(a) **Individual study information.** A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.
(2) The total number of subjects initially planned for inclusion in the study; the number entered into the 
study to date, tabulated by age group, gender, and race; the number whose participation in the study was 
completed as planned; and the number who dropped out of the study for any reason.

(3) If the study has been completed, or if interim results are known, a brief description of any available 
study results.

(b) **Summary information.** Information obtained during the previous year's clinical and nonclinical 
investigations, including:

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by 
body system.

(2) A summary of all IND safety reports submitted during the past year.

(3) A list of subjects who died during participation in the investigation, with the cause of death for each 
subject.

(4) A list of subjects who dropped out during the course of the investigation in association with any adverse 
experience, whether or not thought to be drug related.

(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's 
actions, including, for example, information about dose response, information from controlled trials, and 
information about bioavailability.

(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year 
and a summary of the major preclinical findings.

(7) A summary of any significant manufacturing or microbiological changes made during the past year.

(c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. 
The general investigational plan shall contain the information required under 312.23(a)(3)(iv).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not 
previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as 
approval of marketing in any country or withdrawal or suspension from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor 
requests or expects a reply, comment, or meeting.

9585, Mar. 4, 2002]

---

**Sec. 312.38 Withdrawal of an IND.**

(a) At any time a sponsor may withdraw an effective IND without prejudice.

(b) If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall 
be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise 
disposed of at the request of the sponsor in accordance with 312.59.

(c) If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all 
participating investigators, and all reviewing Institutional Review Boards, together with the reasons for 
such withdrawal.
Subpart C--Administrative Actions

Sec. 312.40 General requirements for use of an investigational new drug in a clinical investigation.

(a) An investigational new drug may be used in a clinical investigation if the following conditions are met:
   (1) The sponsor of the investigation submits an IND for the drug to FDA; the IND is in effect under paragraph (b) of this section; and the sponsor complies with all applicable requirements in this part and parts 50 and 56 with respect to the conduct of the clinical investigations; and
   (2) Each participating investigator conducts his or her investigation in compliance with the requirements of this part and parts 50 and 56.

(b) An IND goes into effect:
   (1) Thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under 312.42; or
   (2) On earlier notification by FDA that the clinical investigations in the IND may begin. FDA will notify the sponsor in writing of the date it receives the IND.

(c) A sponsor may ship an investigational new drug to investigators named in the IND:
   (1) Thirty days after FDA receives the IND; or
   (2) On earlier FDA authorization to ship the drug.

(d) An investigator may not administer an investigational new drug to human subjects until the IND goes into effect under paragraph (b) of this section.

Sec. 312.41 Comment and advice on an IND.

(a) FDA may at any time during the course of the investigation communicate with the sponsor orally or in writing about deficiencies in the IND or about FDA's need for more data or information.

(b) On the sponsor's request, FDA will provide advice on specific matters relating to an IND. Examples of such advice may include advice on the adequacy of technical data to support an investigational plan, on the design of a clinical trial, and on whether proposed investigations are likely to produce the data and information that is needed to meet requirements for a marketing application.

(c) Unless the communication is accompanied by a clinical hold order under 312.42, FDA communications with a sponsor under this section are solely advisory and do not require any modification in the planned or ongoing clinical investigations or response to the agency.

Sec. 312.42 Clinical holds and requests for modification.

(a) General. A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the
investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

(b) Grounds for imposition of clinical hold --(1) Clinical hold of a Phase 1 study under an IND. FDA may place a proposed or ongoing Phase 1 investigation on clinical hold if it finds that:

(i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;
(ii) The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;
(iii) The investigator brochure is misleading, erroneous, or materially incomplete; or
(iv) The IND does not contain sufficient information required under 312.23 to assess the risks to subjects of the proposed studies.

(v) The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (i.e., affecting reproductive organs) or developmental toxicity (i.e., affecting potential offspring). The phrase "women with reproductive potential" does not include pregnant women. For purposes of this paragraph, "life-threatening illnesses or diseases" are defined as "diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted." The clinical hold would not apply under this paragraph to clinical studies conducted:
(A) Under special circumstances, such as studies pertinent only to one gender (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function);
(B) Only in men or women, as long as a study that does not exclude members of the other gender with reproductive potential is being conducted concurrently, has been conducted, or will take place within a reasonable time agreed upon by the agency; or
(C) Only in subjects who do not suffer from the disease or condition for which the drug is being studied.

(2) Clinical hold of a Phase 2 or 3 study under an IND. FDA may place a proposed or ongoing Phase 2 or 3 investigation on clinical hold if it finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(v) of this section apply; or
(ii) The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

(3) Clinical hold of an expanded access IND or expanded access protocol. FDA may place an expanded access IND or expanded access protocol on clinical hold under the following conditions:

(i) Final use. FDA may place a proposed expanded access IND or treatment use protocol on clinical hold if it is determined that:
(A) The pertinent criteria in subpart I of this part for permitting the expanded access use to begin are not satisfied; or
(B) The expanded access IND or expanded access protocol does not comply with the requirements for expanded access submissions in subpart I of this part.
(ii) **Ongoing use.** FDA may place an ongoing expanded access IND or expanded access protocol on clinical hold if it is determined that the pertinent criteria in subpart I of this part for permitting the expanded access are no longer satisfied.

(4) **Clinical hold of any study that is not designed to be adequate and well-controlled.** FDA may place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if it finds that:

(i) Any of the conditions in paragraph (b)(1) or (b)(2) of this section apply; or

(ii) There is reasonable evidence the investigation that is not designed to be adequate and well-controlled is impeding enrollment in, or otherwise interfering with the conduct or completion of, a study that is designed to be an adequate and well-controlled investigation of the same or another investigational drug; or

(iii) Insufficient quantities of the investigational drug exist to adequately conduct both the investigation that is not designed to be adequate and well-controlled and the investigations that are designed to be adequate and well-controlled; or

(iv) The drug has been studied in one or more adequate and well-controlled investigations that strongly suggest lack of effectiveness; or

(v) Another drug under investigation or approved for the same indication and available to the same patient population has demonstrated a better potential benefit/risk balance; or

(vi) The drug has received marketing approval for the same indication in the same patient population; or

(vii) The sponsor of the study that is designed to be an adequate and well-controlled investigation is not actively pursuing marketing approval of the investigational drug with due diligence; or

(viii) The Commissioner determines that it would not be in the public interest for the study to be conducted or continued. FDA ordinarily intends that clinical holds under paragraphs (b)(4)(ii), (b)(4)(iii) and (b)(4)(v) of this section would only apply to additional enrollment in nonconcurrently controlled trials rather than eliminating continued access to individuals already receiving the investigational drug.

(5) **Clinical hold of any investigation involving an exception from informed consent under 50.24 of this chapter.** FDA may place a proposed or ongoing investigation involving an exception from informed consent under 50.24 of this chapter on clinical hold if it is determined that:

(i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or

(ii) The pertinent criteria in 50.24 of this chapter for such an investigation to begin or continue are not submitted or not satisfied.

(6) Clinical hold of any investigation involving an exception from informed consent under 50.23(d) of this chapter. FDA may place a proposed or ongoing investigation involving an exception from informed consent under 50.23(d) of this chapter on clinical hold if it is determined that:

(i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or

(ii) A determination by the President to waive the prior consent requirement for the administration of an investigational new drug has not been made.

(c) **Discussion of deficiency.** Whenever FDA concludes that a deficiency exists in a clinical investigation that may be grounds for the imposition of clinical hold FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order.
(d) **Imposition of clinical hold.** The clinical hold order may be made by telephone or other means of rapid communication or in writing. The clinical hold order will identify the studies under the IND to which the hold applies, and will briefly explain the basis for the action. The clinical hold order will be made by or on behalf of the Division Director with responsibility for review of the IND. As soon as possible, and no more than 30 days after imposition of the clinical hold, the Division Director will provide the sponsor a written explanation of the basis for the hold.

(e) **Resumption of clinical investigations.** An investigation may only resume after FDA (usually the Division Director, or the Director's designee, with responsibility for review of the IND) has notified the sponsor that the investigation may proceed. Resumption of the affected investigation(s) will be authorized when the sponsor corrects the deficiency(ies) previously cited or otherwise satisfies the agency that the investigation(s) can proceed. FDA may notify a sponsor of its determination regarding the clinical hold by telephone or other means of rapid communication. If a sponsor of an IND that has been placed on clinical hold requests in writing that the clinical hold be removed and submits a complete response to the issue(s) identified in the clinical hold order, FDA shall respond in writing to the sponsor within 30-calendar days of receipt of the request and the complete response. FDA's response will either remove or maintain the clinical hold, and will state the reasons for such determination. Notwithstanding the 30-calendar day response time, a sponsor may not proceed with a clinical trial on which a clinical hold has been imposed until the sponsor has been notified by FDA that the hold has been lifted.

(f) **Appeal.** If the sponsor disagrees with the reasons cited for the clinical hold, the sponsor may request reconsideration of the decision in accordance with 312.48.

(g) **Conversion of IND on clinical hold to inactive status.** If all investigations covered by an IND remain on clinical hold for 1 year or more, the IND may be placed on inactive status by FDA under 312.45.

---


### Sec. 312.44 Termination.

(a) **General.** This section describes the procedures under which FDA may terminate an IND. If an IND is terminated, the sponsor shall end all clinical investigations conducted under the IND and recall or otherwise provide for the disposition of all unused supplies of the drug. A termination action may be based on deficiencies in the IND or in the conduct of an investigation under an IND. Except as provided in paragraph (d) of this section, a termination shall be preceded by a proposal to terminate by FDA and an opportunity for the sponsor to respond. FDA will, in general, only initiate an action under this section after first attempting to resolve differences informally or, when appropriate, through the clinical hold procedures described in 312.42.

(b) **Grounds for termination --(1)Phase 1.** FDA may propose to terminate an IND during Phase 1 if it finds that:

- (i) Human subjects would be exposed to an unreasonable and significant risk of illness or unjury.
- (ii) The IND does not contain sufficient information required under 312.23 to assess the safety to subjects of the clinical investigations.
(iii) The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for subject safety.

(iv) The clinical investigations are being conducted in a manner substantially different than that described in the protocols submitted in the IND.

(v) The drug is being promoted or distributed for commercial purposes not justified by the requirements of the investigation or permitted by 312.7.

(vi) The IND, or any amendment or report to the IND, contains an untrue statement of a material fact or omits material information required by this part.

(vii) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of serious and unexpected adverse experiences in accordance with 312.32 or fails to make any other report required under this part.

(viii) The sponsor fails to submit an accurate annual report of the investigations in accordance with 312.33.

(ix) The sponsor fails to comply with any other applicable requirement of this part, part 50, or part 56.

(x) The IND has remained on inactive status for 5 years or more.

(xi) The sponsor fails to delay a proposed investigation under the IND or to suspend an ongoing investigation that has been placed on clinical hold under 312.42(b)(4).

(2) **Phase 2 or 3.** FDA may propose to terminate an IND during Phase 2 or Phase 3 if FDA finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(xi) of this section apply; or

(ii) The investigational plan or protocol(s) is not reasonable as a bona fide scientific plan to determine whether or not the drug is safe and effective for use; or

(iii) There is convincing evidence that the drug is not effective for the purpose for which it is being investigated.

(3) FDA may propose to terminate a treatment IND if it finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (x) of this section apply; or

(ii) Any of the conditions in 312.42(b)(3) apply.

(c) **Opportunity for sponsor response.** (1) If FDA proposes to terminate an IND, FDA will notify the sponsor in writing, and invite correction or explanation within a period of 30 days.

(2) On such notification, the sponsor may provide a written explanation or correction or may request a conference with FDA to provide the requested explanation or correction. If the sponsor does not respond to the notification within the allocated time, the IND shall be terminated.

(3) If the sponsor responds but FDA does not accept the explanation or correction submitted, FDA shall inform the sponsor in writing of the reason for the nonacceptance and provide the sponsor with an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be terminated. The sponsor's request for a regulatory hearing must be made within 10 days of the sponsor's receipt of FDA's notification of nonacceptance.

(d) **Immediate termination of IND.** Notwithstanding paragraphs (a) through (c) of this section, if at any time FDA concludes that continuation of the investigation presents an immediate and substantial danger to the health of individuals, the agency shall immediately, by written notice to the sponsor from the Director of the Center for Drug Evaluation and Research or the Director of the Center for Biologics Evaluation and Research, terminate the IND. An IND so terminated is subject to reinstatement by the Director on the basis of additional submissions that eliminate such danger. If an IND is terminated under this paragraph, the
agency will afford the sponsor an opportunity for a regulatory hearing under part 16 on the question of
whether the IND should be reinstated.


Sec. 312.45 Inactive status.

(a) If no subjects are entered into clinical studies for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, the IND may be placed by FDA on inactive status. This action may be taken by FDA either on request of the sponsor or on FDA's own initiative. If FDA seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. Upon receipt of such notification, the sponsor shall have 30 days to respond as to why the IND should continue to remain active.

(b) If an IND is placed on inactive status, all investigators shall be so notified and all stocks of the drug shall be returned or otherwise disposed of in accordance with 312.59.

(c) A sponsor is not required to submit annual reports to an IND on inactive status. An inactive IND is, however, still in effect for purposes of the public disclosure of data and information under 312.130.

(d) A sponsor who intends to resume clinical investigation under an IND placed on inactive status shall submit a protocol amendment under 312.30 containing the proposed general investigational plan for the coming year and appropriate protocols. If the protocol amendment relies on information previously submitted, the plan shall reference such information. Additional information supporting the proposed investigation, if any, shall be submitted in an information amendment. Notwithstanding the provisions of 312.30, clinical investigations under an IND on inactive status may only resume (1) 30 days after FDA receives the protocol amendment, unless FDA notifies the sponsor that the investigations described in the amendment are subject to a clinical hold under 312.42, or (2) on earlier notification by FDA that the clinical investigations described in the protocol amendment may begin.

(e) An IND that remains on inactive status for 5 years or more may be terminated under 312.44.


Sec. 312.47 Meetings.

(a) General. Meetings between a sponsor and the agency are frequently useful in resolving questions and issues raised during the course of a clinical investigation. FDA encourages such meetings to the extent that they aid in the evaluation of the drug and in the solution of scientific problems concerning the drug, to the extent that FDA's resources permit. The general principle underlying the conduct of such meetings is that there should be free, full, and open communication about any scientific or medical question that may arise during the clinical investigation. These meetings shall be conducted and documented in accordance with part 10.

(b) "End-of-Phase 2" meetings and meetings held before submission of a marketing application. At specific times during the drug investigation process, meetings between FDA and a sponsor can be especially helpful in minimizing wasteful expenditures of time and money and thus in speeding the drug development and
evaluation process. In particular, FDA has found that meetings at the end of Phase 2 of an investigation (end-of-Phase 2 meetings) are of considerable assistance in planning later studies and that meetings held near completion of Phase 3 and before submission of a marketing application ("pre-NDA" meetings) are helpful in developing methods of presentation and submission of data in the marketing application that facilitate review and allow timely FDA response.

1. **End-of-Phase 2 meetings**
   - **(i) Purpose.** The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.
   - **(ii) Eligibility for meeting.** While the end-of-Phase 2 meeting is designed primarily for IND's involving new molecular entities or major new uses of marketed drugs, a sponsor of any IND may request and obtain an end-of-Phase 2 meeting.
   - **(iii) Timing.** To be most useful to the sponsor, end-of-Phase 2 meetings should be held before major commitments of effort and resources to specific Phase 3 tests are made. The scheduling of an end-of-Phase 2 meeting is not, however, intended to delay the transition of an investigation from Phase 2 to Phase 3.
   - **(iv) Advance information.** At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor's plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, plans for pediatric studies, including a timeline for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies, and, if available, tentative labeling for the drug. The recommended contents of such a submission are described more fully in FDA Staff Manual Guide 4850.7 that is publicly available under FDA's public information regulations in part 20.
   - **(v) Conduct of meeting.** Arrangements for an end-of-Phase 2 meeting are to be made with the division in FDA's Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research which is responsible for review of the IND. The meeting will be scheduled by FDA at a time convenient to both FDA and the sponsor. Both the sponsor and FDA may bring consultants to the meeting. The meeting should be directed primarily at establishing agreement between FDA and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. The adequacy of the technical information to support Phase 3 studies and/or a marketing application may also be discussed. FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and whether their submission will be deferred until after approval. Agreements reached at the meeting on these matters will be recorded in minutes of the conference that will be taken by FDA in accordance with 10.65 and provided to the sponsor. The minutes along with any other written material provided to the sponsor will serve as a permanent record of any agreements reached. Barring a significant scientific development that requires otherwise, studies conducted in accordance with the agreement shall be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug.

2. **"Pre-NDA" and "pre-BLA" meetings.** FDA has found that delays associated with the initial review of a marketing application may be reduced by exchanges of information about a proposed marketing application. The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the
drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. Arrangements for such a meeting are to be initiated by the sponsor with the division responsible for review of the IND. To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:

(i) A brief summary of the clinical studies to be submitted in the application.
(ii) A proposed format for organizing the submission, including methods for presenting the data.
(iii) Information on the status of needed or ongoing pediatric studies.
(iv) Any other information for discussion at the meeting.


Sec. 312.48 Dispute resolution.

(a) General. The Food and Drug Administration is committed to resolving differences between sponsors and FDA reviewing divisions with respect to requirements for IND's as quickly and amicably as possible through the cooperative exchange of information and views.

(b) Administrative and procedural issues. When administrative or procedural disputes arise, the sponsor should first attempt to resolve the matter with the division in FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND, beginning with the consumer safety officer assigned to the application. If the dispute is not resolved, the sponsor may raise the matter with the person designated as ombudsman, whose function shall be to investigate what has happened and to facilitate a timely and equitable resolution. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings and obtaining timely replies to inquiries. Further details on this procedure are contained in FDA Staff Manual Guide 4820.7 that is publicly available under FDA's public information regulations in part 20.

(c) Scientific and medical disputes. (1) When scientific or medical disputes arise during the drug investigation process, sponsors should discuss the matter directly with the responsible reviewing officials. If necessary, sponsors may request a meeting with the appropriate reviewing officials and management representatives in order to seek a resolution. Requests for such meetings shall be directed to the director of the division in FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

(2) The "end-of-Phase 2" and "pre-NDA" meetings described in 312.47(b) will also provide a timely forum for discussing and resolving scientific and medical issues on which the sponsor disagrees with the agency.

(3) In requesting a meeting designed to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other consultants, as designated by the agency.
Applicants may rely on, and may bring to any meeting, their own consultants. For major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of its standing advisory committees for its consideration and recommendations.


Subpart D--Responsibilities of Sponsors and Investigators

Sec. 312.50 General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

Sec. 312.52 Transfer of obligations to a contract research organization.

(a) A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.

(b) A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" in this part apply to a contract research organization to the extent that it assumes one or more obligations of the sponsor.

Sec. 312.53 Selecting investigators and monitors.

(a) Selecting investigators. A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.

(b) Control of drug. A sponsor shall ship investigational new drugs only to investigators participating in the investigation.

(c) Obtaining information from the investigator. Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:

(1) A signed investigator statement (Form FDA-1572) containing:
   (i) The name and address of the investigator;
(ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator;

(iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;

(iv) The name and address of any clinical laboratory facilities to be used in the study;

(v) The name and address of the IRB that is responsible for review and approval of the study(ies);

(vi) A commitment by the investigator that he or she:
   (a) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;
   (b) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;
   (c) Will personally conduct or supervise the described investigation(s);
   (d) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;
   (e) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 312.64;
   (f) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and
   (g) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

(vii) A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

(viii) A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).

(2) Curriculum vitae. A curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.

(3) Clinical protocol. (i) For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

   (ii) For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

(4) Financial disclosure information. Sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under part 54 of this
chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

(d) Selecting monitors. A sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation.


Sec. 312.54 Emergency research under 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under 50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures required by 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor promptly shall submit to the IND file and to Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, copies of the information that was disclosed, identified by the IND number.

(b) The sponsor also shall monitor such investigations to identify when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical investigation, and other IRB's that are asked to review this or a substantially equivalent investigation.


Sec. 312.55 Informing investigators.

(a) Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in 312.23(a)(5).

(b) The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with 312.32.


Sec. 312.56 Review of ongoing investigations.

(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.
(b) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of 312.59 and shall notify FDA.

(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under 312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with 312.33.

(d) A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall discontinue those investigations that present the risk, notify FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by 312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a sponsor on the need to discontinue an investigation.


Sec. 312.57 Recordkeeping and record retention.

(a) A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

(b) A sponsor shall maintain complete and accurate records showing any financial interest in 54.4(a)(3)(i), (a)(3)(ii), (a)(3)(iii), and (a)(3)(iv) of this chapter paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to part 54 of this chapter.

(c) A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

(d) A sponsor shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, 320.38 or 320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in 320.38.

Sec. 312.58 Inspection of sponsor's records and reports.

(a) FDA inspection. A sponsor shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under this part. Upon written request by FDA, the sponsor shall submit the records or reports (or copies of them) to FDA. The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part.

(b) Controlled substances. If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying. In addition, the sponsor shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

Sec. 312.59 Disposition of unused supply of investigational drug.

The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug in accordance with 312.57.


Sec. 312.60 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

### Sec. 312.61 Control of the investigational drug.

An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

### Sec. 312.62 Investigator recordkeeping and record retention.

(a) **Disposition of drug.** An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 312.59.

(b) **Case histories.** An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(c) **Record retention.** An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.


### Sec. 312.64 Investigator reports.

(a) **Progress reports.** The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under 312.33 to submit annual reports to FDA on the progress of the clinical investigations.

(b) **Safety reports.** An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor. The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

(c) **Final report.** An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.
(d) **Financial disclosure reports.** The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.


---

**Sec. 312.66 Assurance of IRB review.**

An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.


---

**Sec. 312.68 Inspection of investigator's records and reports.**

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

---

**Sec. 312.69 Handling of controlled substances.**

If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

---

**Sec. 312.70 Disqualification of a clinical investigator.**

(a) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50 or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research will furnish...
the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered and accepted by the applicable Center, the Center will discontinue the disqualification proceeding. If an explanation is offered but not accepted by the applicable Center, the investigator will be given an opportunity for a regulatory hearing under part 16 of this chapter on the question of whether the investigator is eligible to receive test articles under this part and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50 or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Commissioner will notify the investigator, the sponsor of any investigation in which the investigator has been named as a participant, and the reviewing institutional review boards (IRBs) that the investigator is not eligible to receive test articles under this part. The notification to the investigator, sponsor, and IRBs will provide a statement of the basis for such determination. The notification also will explain that an investigator determined to be ineligible to receive test articles under this part will be ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

(c) Each application or submission to FDA under the provisions of this chapter containing data reported by an investigator who has been determined to be ineligible to receive FDA-regulated test articles is subject to examination to determine whether the investigator has submitted unreliable data that are essential to the continuation of an investigation or essential to the approval of a marketing application, or essential to the continued marketing of an FDA-regulated product.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor, who shall have an opportunity for a regulatory hearing under part 16 of this chapter. If a danger to the public health exists, however, the Commissioner shall terminate the IND immediately and notify the sponsor and the reviewing IRBs of the termination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be reinstated. The determination that an investigation may not be considered in support of a research or marketing application or a notification or petition submission does not, however, relieve the sponsor of any obligation under any other applicable regulation to submit to FDA the results of the investigation.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the product for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval of the product in accordance with the applicable provisions of the relevant statutes.

(f) An investigator who has been determined to be ineligible under paragraph (b) of this section may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ all test articles, and will conduct any clinical investigation that
supports an application for a research or marketing permit for products regulated by FDA, solely in compliance with the applicable provisions of this chapter.

[77 FR 25359, Apr. 30, 2012]

Subpart E--Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

Sec. 312.80 Purpose.

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated 314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedure outlined in this section should be interpreted consistent with that purpose.

Sec. 312.81 Scope.

This section applies to new drug and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

(a) For purposes of this section, the term "life-threatening" means:
   (1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and
   (2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival.

(b) For purposes of this section, the term "severely debilitating" means diseases or conditions that cause major irreversible morbidity.

(c) Sponsors are encouraged to consult with FDA on the applicability of these procedures to specific products.

[53 FR 41523, Oct. 21, 1988, as amended at 64 FR 401, Jan. 5, 1999]

Sec. 312.82 Early consultation.

For products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the
design of necessary preclinical and clinical studies. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members. To the extent FDA resources permit, agency reviewing officials will honor requests for such meetings.

(a) *Pre-investigational new drug (IND) meetings.* Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) *End-of-phase 1 meetings.* When data from phase 1 clinical testing are available, the sponsor may again request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric studies will be required and whether their submission will be deferred until after approval. The procedures outlined in 312.47(b)(1) with respect to end-of-phase 2 conferences, including documentation of agreements reached, would also be used for end-of-phase 1 meetings.


### Sec. 312.83 Treatment protocols.

If the preliminary analysis of phase 2 test results appears promising, FDA may ask the sponsor to submit a treatment protocol to be reviewed under the procedures and criteria listed in 312.305 and 312.320. Such a treatment protocol, if requested and granted, would normally remain in effect while the complete data necessary for a marketing application are being assembled by the sponsor and reviewed by FDA (unless grounds exist for clinical hold of ongoing protocols, as provided in 312.42(b)(3)(ii)).

[53 FR 41523, Oct. 21, 1988, as amended at 76 FR 13880, Mar. 15, 2011]

### Sec. 312.84 Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.

(a) FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in 312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.

(b) In making decisions on whether to grant marketing approval for products that have been the subject of an end-of-phase 1 meeting under 312.82, FDA will usually seek the advice of outside expert scientific
consultants or advisory committees. Upon the filing of such a marketing application under 314.101 or part 601 of this chapter, FDA will notify the members of the relevant standing advisory committee of the application's filing and its availability for review.

(c) If FDA concludes that the data presented are not sufficient for marketing approval, FDA will issue a complete response letter under 314.110 of this chapter or the biological product licensing procedures. Such letter, in describing the deficiencies in the application, will address why the results of the research design agreed to under 312.82, or in subsequent meetings, have not provided sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

(d) Marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in part 314 or part 600 of this chapter, as well as those in this subpart.

[53 FR 41523, Oct. 21, 1988, as amended at 73 FR 39607, July 10, 2008]

Sec. 312.85 Phase 4 studies.

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.

Sec. 312.86 Focused FDA regulatory research.

At the discretion of the agency, FDA may undertake focused regulatory research on critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation. When initiated, FDA will undertake such research efforts as a means for meeting a public health need in facilitating the development of therapies to treat life-threatening or severely debilitating illnesses.

Sec. 312.87 Active monitoring of conduct and evaluation of clinical trials.

For drugs covered under this section, the Commissioner and other agency officials will monitor the progress of the conduct and evaluation of clinical trials and be involved in facilitating their appropriate progress.

Sec. 312.88 Safeguards for patient safety.

All of the safeguards incorporated within parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. This includes the requirements for informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter). These safeguards further include the review of animal studies prior to initial
human testing (312.23), and the monitoring of adverse drug experiences through the requirements of IND safety reports (312.32), safety update reports during agency review of a marketing application (314.50 of this chapter), and postmarketing adverse reaction reporting (314.80 of this chapter).

Subpart F--Miscellaneous

Sec. 312.110 Import and export requirements.

(a) Imports. An investigational new drug offered for import into the United States complies with the requirements of this part if it is subject to an IND that is in effect for it under 312.40 and: (1) The consignee in the United States is the sponsor of the IND; (2) the consignee is a qualified investigator named in the IND; or (3) the consignee is the domestic agent of a foreign sponsor, is responsible for the control and distribution of the investigational drug, and the IND identifies the consignee and describes what, if any, actions the consignee will take with respect to the investigational drug.

(b) Exports. An investigational new drug may be exported from the United States for use in a clinical investigation under any of the following conditions:

(1) An IND is in effect for the drug under 312.40, the drug complies with the laws of the country to which it is being exported, and each person who receives the drug is an investigator in a study submitted to and allowed to proceed under the IND; or

(2) The drug has valid marketing authorization in Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or in any country in the European Union or the European Economic Area, and complies with the laws of the country to which it is being exported, section 802(b)(1)(A), (f), and (g) of the act, and 1.101 of this chapter; or

(3) The drug is being exported to Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or to any country in the European Union or the European Economic Area, and complies with the laws of the country to which it is being exported, the applicable provisions of section 802(c), (f), and (g) of the act, and 1.101 of this chapter. Drugs exported under this paragraph that are not the subject of an IND are exempt from the label requirement in 312.6(a); or

(4) Except as provided in paragraph (b)(5) of this section, the person exporting the drug sends a written certification to the Office of International Programs (HFG-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, at the time the drug is first exported and maintains records documenting compliance with this paragraph. The certification shall describe the drug that is to be exported (i.e., trade name (if any), generic name, and dosage form), identify the country or countries to which the drug is to be exported, and affirm that:

(i) The drug is intended for export;

(ii) The drug is intended for investigational use in a foreign country;

(iii) The drug meets the foreign purchaser's or consignee's specifications;

(iv) The drug is not in conflict with the importing country's laws;

(v) The outer shipping package is labeled to show that the package is intended for export from the United States;

(vi) The drug is not sold or offered for sale in the United States;

(vii) The clinical investigation will be conducted in accordance with 312.120;
(viii) The drug is manufactured, processed, packaged, and held in substantial conformity with current
good manufacturing practices;
(ix) The drug is not adulterated within the meaning of section 501(a)(1), (a)(2)(A), (a)(3), (c), or (d) of
the act;
(x) The drug does not present an imminent hazard to public health, either in the United States, if the
drug were to be reimported, or in the foreign country; and
(xi) The drug is labeled in accordance with the foreign country's laws.
(5) In the event of a national emergency in a foreign country, where the national emergency necessitates
exportation of an investigational new drug, the requirements in paragraph (b)(4) of this section apply as
follows:
(i) Situations where the investigational new drug is to be stockpiled in anticipation of a national
emergency. There may be instances where exportation of an investigational new drug is needed so
that the drug may be stockpiled and made available for use by the importing country if and when a
national emergency arises. In such cases:
(A) A person may export an investigational new drug under paragraph (b)(4) of this section without
making an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv),
(b)(4)(vi), (b)(4)(vii), (b)(4)(viii), and/or (b)(4)(ix) of this section, provided that he or she:
(1) Provides a written statement explaining why compliance with each such paragraph is not
feasible or is contrary to the best interests of the individuals who may receive the
investigational new drug;
(2) Provides a written statement from an authorized official of the importing country's
government. The statement must attest that the official agrees with the exporter's statement
made under paragraph (b)(5)(i)(A)(1) of this section; explain that the drug is to be
stockpiled solely for use of the importing country in a national emergency; and describe the
potential national emergency that warrants exportation of the investigational new drug under
this provision; and
(3) Provides a written statement showing that the Secretary of Health and Human Services (the
Secretary), or his or her designee, agrees with the findings of the authorized official of the
importing country's government. Persons who wish to obtain a written statement from the
Secretary should direct their requests to Secretary's Operations Center, Office of Emergency
Operations and Security Programs, Office of Public Health Emergency Preparedness, Office
of the Secretary, Department of Health and Human Services, 200 Independence Ave. SW.,
Washington, DC 20201. Requests may be also be sent by FAX: 202-619-7870 or by e-mail:
HHS.SOC@hhs.gov.
(B) Exportation may not proceed until FDA has authorized exportation of the investigational new
drug. FDA may deny authorization if the statements provided under paragraphs (b)(5)(i)(A)(1) or
(b)(5)(i)(A)(2) of this section are inadequate or if exportation is contrary to public health.
(ii) Situations where the investigational new drug is to be used for a sudden and immediate national
emergency. There may be instances where exportation of an investigational new drug is needed so
that the drug may be used in a sudden and immediate national emergency that has developed or is
developing. In such cases:
(A) A person may export an investigational new drug under paragraph (b)(4) of this section without making an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(v), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), (b)(4)(ix), and/or (b)(4)(xi), provided that he or she:

(1) Provides a written statement explaining why compliance with each such paragraph is not feasible or is contrary to the best interests of the individuals who are expected to receive the investigational new drug and

(2) Provides sufficient information from an authorized official of the importing country's government to enable the Secretary, or his or her designee, to decide whether a national emergency has developed or is developing in the importing country, whether the investigational new drug will be used solely for that national emergency, and whether prompt exportation of the investigational new drug is necessary. Persons who wish to obtain a determination from the Secretary should direct their requests to Secretary's Operations Center, Office of Emergency Operations and Security Programs, Office of Public Health Emergency Preparedness, Office of the Secretary, Department of Health and Human Services, 200 Independence Ave. SW., Washington, DC 20201. Requests may be also be sent by FAX: 202-619-7870 or by e-mail: HHS.SOC@hhs.gov.

(B) Exportation may proceed without prior FDA authorization.

(c) Limitations. Exportation under paragraph (b) of this section may not occur if:

(1) For drugs exported under paragraph (b)(1) of this section, the IND pertaining to the clinical investigation is no longer in effect;

(2) For drugs exported under paragraph (b)(2) of this section, the requirements in section 802(b)(1), (f), or (g) of the act are no longer met;

(3) For drugs exported under paragraph (b)(3) of this section, the requirements in section 802(c), (f), or (g) of the act are no longer met;

(4) For drugs exported under paragraph (b)(4) of this section, the conditions underlying the certification or the statements submitted under paragraph (b)(5) of this section are no longer met; or

(5) For any investigational new drugs under this section, the drug no longer complies with the laws of the importing country.

(d) Insulin and antibiotics. New insulin and antibiotic drug products may be exported for investigational use in accordance with section 801(e)(1) of the act without complying with this section.

reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected. GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating a study. GCP does not require informed consent in life-threatening situations when the IEC reviewing the study finds, before initiation of the study, that informed consent is not feasible and either that the conditions present are consistent with those described in 50.23 or 50.24(a) of this chapter, or that the measures described in the study protocol or elsewhere will protect the rights, safety, and well-being of subjects; and

(ii) FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.

(2) Although FDA will not accept as support for an IND or application for marketing approval a study that does not meet the conditions of paragraph (a)(1) of this section, FDA will examine data from such a study.

(3) Marketing approval of a new drug based solely on foreign clinical data is governed by 314.106 of this chapter.

(b) Supporting information. A sponsor or applicant who submits data from a foreign clinical study not conducted under an IND as support for an IND or application for marketing approval must submit to FDA, in addition to information required elsewhere in parts 312, 314, or 601 of this chapter, a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP as described in paragraph (a)(1)(i) of this section. The description is not required to duplicate information already submitted in the IND or application for marketing approval. Instead, the description must provide either the following information or a cross-reference to another section of the submission where the information is located:

(1) The investigator's qualifications;
(2) A description of the research facilities;
(3) A detailed summary of the protocol and results of the study and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;
(4) A description of the drug substance and drug product used in the study, including a description of the components, formulation, specifications, and, if available, bioavailability of the specific drug product used in the clinical study;
(5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under 314.126 of this chapter;
(6) The name and address of the IEC that reviewed the study and a statement that the IEC meets the definition in 312.3 of this chapter. The sponsor or applicant must maintain records supporting such statement, including records of the names and qualifications of IEC members, and make these records available for agency review upon request;
(7) A summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion;
(8) A description of how informed consent was obtained;
(9) A description of what incentives, if any, were provided to subjects to participate in the study;
(10) A description of how the sponsor(s) monitored the study and ensured that the study was carried out consistently with the study protocol; and

(11) A description of how investigators were trained to comply with GCP (as described in paragraph (a)(1)(i) of this section) and to conduct the study in accordance with the study protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained. Any signed written commitments by investigators must be maintained by the sponsor or applicant and made available for agency review upon request.

(c) Waivers. (1) A sponsor or applicant may ask FDA to waive any applicable requirements under paragraphs (a)(1) and (b) of this section. A waiver request may be submitted in an IND or in an information amendment to an IND, or in an application or in an amendment or supplement to an application submitted under part 314 or 601 of this chapter. A waiver request is required to contain at least one of the following:

(i) An explanation why the sponsor's or applicant's compliance with the requirement is unnecessary or cannot be achieved;

(ii) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

(iii) Other information justifying a waiver.

(2) FDA may grant a waiver if it finds that doing so would be in the interest of the public health.

(d) Records. A sponsor or applicant must retain the records required by this section for a foreign clinical study not conducted under an IND as follows:

(1) If the study is submitted in support of an application for marketing approval, for 2 years after an agency decision on that application;

(2) If the study is submitted in support of an IND but not an application for marketing approval, for 2 years after the submission of the IND.

[73 FR 22815, Apr. 28, 2008]

Sec. 312.130 Availability for public disclosure of data and information in an IND.

(a) The existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an investigational new drug application for a new drug will be handled in accordance with the provisions established in 314.430 for the confidentiality of data and information in applications submitted in part 314. The availability for public disclosure of all data and information in an investigational new drug application for a biological product will be governed by the provisions of 601.50 and 601.51.

(c) Notwithstanding the provisions of 314.430, FDA shall disclose upon request to an individual to whom an investigational new drug has been given a copy of any IND safety report relating to the use in the individual.

(d) The availability of information required to be publicly disclosed for investigations involving an exception from informed consent under 50.24 of this chapter will be handled as follows: Persons wishing to request the publicly disclosable information in the IND that was required to be filed in Docket Number 95S-0158 in
Sec. 312.140 Address for correspondence.

(a) A sponsor must send an initial IND submission to the Center for Drug Evaluation and Research (CDER) or to the Center for Biologics Evaluation and Research (CBER), depending on the Center responsible for regulating the product as follows:

(1) For drug products regulated by CDER. Send the IND submission to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266; except send an IND submission for an in vivo bioavailability or bioequivalence study in humans to support an abbreviated new drug application to the Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, Metro Park North VII, 7620 Standish Pl., Rockville, MD 20855.

(2) For biological products regulated by CDER. Send the IND submission to the CDER Therapeutic Biological Products Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 12229 Wilkins Ave., Rockville, MD 20852.

(3) For biological products regulated by CBER. Send the IND submission to the Document Control Center (HFM-99), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448.

(b) On receiving the IND, the responsible Center will inform the sponsor which one of the divisions in CDER or CBER is responsible for the IND. Amendments, reports, and other correspondence relating to matters covered by the IND should be sent to the appropriate center at the address indicated in this section and marked to the attention of the responsible division. The outside wrapper of each submission shall state what is contained in the submission, for example, "IND Application", "Protocol Amendment", etc.

(c) All correspondence relating to export of an investigational drug under 312.110(b)(2) shall be submitted to the International Affairs Staff (HFY-50), Office of Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.


Sec. 312.145 Guidance documents.

(a) FDA has made available guidance documents under 10.115 of this chapter to help you to comply with certain requirements of this part.

(b) The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) maintain lists of guidance documents that apply to the centers’ regulations. The lists are maintained on the Internet and are published annually in the Federal Register. A request for a copy of the
CDER list should be directed to the Office of Training and Communications, Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002. A request for a copy of the CBER list should be directed to the Office of Communication, Training, and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.


Subpart G--Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests

Sec. 312.160 Drugs for investigational use in laboratory research animals or in vitro tests.

(a) Authorization to ship. (1)(i) A person may ship a drug intended solely for tests in vitro or in animals used only for laboratory research purposes if it is labeled as follows:

CAUTION: Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans.

(ii) A person may ship a biological product for investigational in vitro diagnostic use that is listed in 312.2(b)(2)(ii) if it is labeled as follows:

CAUTION: Contains a biological product for investigational in vitro diagnostic tests only.

(2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for tests in vitro or in animals used only for laboratory research.

(3) A person who ships a drug under paragraph (a) of this section shall maintain adequate records showing the name and post office address of the expert to whom the drug is shipped and the date, quantity, and batch or code mark of each shipment and delivery. Records of shipments under paragraph (a)(1)(i) of this section are to be maintained for a period of 2 years after the shipment. Records and reports of data and shipments under paragraph (a)(1)(ii) of this section are to be maintained in accordance with 312.57(b). The person who ships the drug shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify records required to be maintained under this section.

(b) Termination of authorization to ship. FDA may terminate authorization to ship a drug under this section if it finds that:

(1) The sponsor of the investigation has failed to comply with any of the conditions for shipment established under this section; or

(2) The continuance of the investigation is unsafe or otherwise contrary to the public interest or the drug is used for purposes other than bona fide scientific investigation. FDA will notify the person shipping the drug of its finding and invite immediate correction. If correction is not immediately made, the person shall have an opportunity for a regulatory hearing before FDA pursuant to part 16.

(c) Disposition of unused drug. The person who ships the drug under paragraph (a) of this section shall assure the return of all unused supplies of the drug from individual investigators whenever the investigation discontinues or the investigation is terminated. The person who ships the drug may authorize in writing alternative disposition of unused supplies of the drug provided this alternative disposition does not expose
humans to risks from the drug, either directly or indirectly (e.g., through food-producing animals). The shipper shall maintain records of any alternative disposition.


Subpart H [Reserved]

Subpart I--Expanded Access to Investigational Drugs for Treatment Use

Sec. 312.300 General.

(a) Scope. This subpart contains the requirements for the use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

(b) Definitions. The following definitions of terms apply to this subpart:

Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Sec. 312.305 Requirements for all expanded access uses.

The criteria, submission requirements, safeguards, and beginning treatment information set out in this section apply to all expanded access uses described in this subpart. Additional criteria, submission requirements, and safeguards that apply to specific types of expanded access are described in 312.310 through 312.320.

(a) Criteria. FDA must determine that:

(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

(b) Submission. (1) An expanded access submission is required for each type of expanded access described in this subpart. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants a right of reference to the IND.

(2) The expanded access submission must include:
   (i) A cover sheet (Form FDA 1571) meeting the requirements of 312.23(a);
   (ii) The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;
   (iii) The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;
   (iv) The method of administration of the drug, dose, and duration of therapy;
   (v) A description of the facility where the drug will be manufactured;
   (vi) Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;
   (vii) Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and
   (viii) A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

(3) The expanded access submission and its mailing cover must be plainly marked "EXPANDED ACCESS SUBMISSION." If the expanded access submission is for a treatment IND or treatment protocol, the applicable box on Form FDA 1571 must be checked.

(c) Safeguards. The responsibilities of sponsors and investigators set forth in subpart D of this part are applicable to expanded access use under this subpart as described in this paragraph.

(1) A licensed physician under whose immediate direction an investigational drug is administered or dispensed for an expanded access use under this subpart is considered an investigator, for purposes of this part, and must comply with the responsibilities for investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(2) An individual or entity that submits an expanded access IND or protocol under this subpart is considered a sponsor, for purposes of this part, and must comply with the responsibilities for sponsors set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(3) A licensed physician under whose immediate direction an investigational drug is administered or dispensed, and who submits an IND for expanded access use under this subpart is considered a sponsor-investigator, for purposes of this part, and must comply with the responsibilities for sponsors and investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(4) Investigators. In all cases of expanded access, investigators are responsible for reporting adverse drug events to the sponsor, ensuring that the informed consent requirements of part 50 of this chapter are met, ensuring that IRB review of the expanded access use is obtained in a manner consistent with the
requirements of part 56 of this chapter, and maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of 312.62. Depending on the type of expanded access, other investigator responsibilities under subpart D may also apply.

(5) **Sponsors.** In all cases of expanded access, sponsors are responsible for submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA as required by 312.32 and 312.33, ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use, providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (the investigator's brochure must be provided if one exists for the drug), maintaining an effective IND for the expanded access use, and maintaining adequate drug disposition records and retaining records in a manner consistent with the requirements of 312.57. Depending on the type of expanded access, other sponsor responsibilities under subpart D may also apply.

(d) **Beginning treatment --(1)INDs.** An expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA that the expanded access use may begin.

(2) **Protocols.** With the following exceptions, expanded access use under a protocol submitted under an existing IND may begin as described in 312.30(a).

(i) Expanded access use under the emergency procedures described in 312.310(d) may begin when the use is authorized by the FDA reviewing official.

(ii) Expanded access use under 312.320 may begin 30 days after FDA receives the protocol or upon earlier notification by FDA that use may begin.

(3) **Clinical holds.** FDA may place any expanded access IND or protocol on clinical hold as described in 312.42.

Sec. 312.310 Individual patients, including for emergency use.

Under this section, FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician.

(a) **Criteria.** The criteria in 312.305(a) must be met; and the following determinations must be made:

(2) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and

(3) FDA must determine that the patient cannot obtain the drug under another IND or protocol.

(b) **Submission.** The expanded access submission must include information adequate to demonstrate that the criteria in 312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of 312.305(b).

(2) If the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician.

(3) A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access.

(4) A licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the expanded access
request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient).

(c) **Safeguards.** (1) Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy.

(2) At the conclusion of treatment, the licensed physician or sponsor must provide FDA with a written summary of the results of the expanded access use, including adverse effects.

(3) FDA may require sponsors to monitor an individual patient expanded access use if the use is for an extended duration.

(4) When a significant number of similar individual patient expanded access requests have been submitted, FDA may ask the sponsor to submit an IND or protocol for the use under 312.315 or 312.320.

(d) **Emergency procedures.** If there is an emergency that requires the patient to be treated before a written submission can be made, FDA may authorize the expanded access use to begin without a written submission. The FDA reviewing official may authorize the emergency use by telephone.

(1) Emergency expanded access use may be requested by telephone, facsimile, or other means of electronic communications. For investigational biological drug products regulated by the Center for Biologics Evaluation and Research, the request should be directed to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, 301-827-1800 or 1-800-835-4709, e-mail: ocod@fda.hhs.gov. For all other investigational drugs, the request for authorization should be directed to the Division of Drug Information, Center for Drug Evaluation and Research, 301-796-3400, e-mail: druginfo@fda.hhs.gov. After normal working hours (8 a.m. to 4:30 p.m.), the request should be directed to the FDA Emergency Call Center, 866-300-4374, e-mail: emergency.operations@fda.hhs.gov.

(2) The licensed physician or sponsor must explain how the expanded access use will meet the requirements of 312.305 and 312.310 and must agree to submit an expanded access submission within 15 working days of FDA's authorization of the use.

[74 FR 40942, Aug. 13, 2009, as amended at 75 FR 32659, June 9, 2010]

**Sec. 312.315 Intermediate-size patient populations.**

Under this section, FDA may permit an investigational drug to be used for the treatment of a patient population smaller than that typical of a treatment IND or treatment protocol. FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use.

(a) **Need for expanded access.** Expanded access under this section may be needed in the following situations:

(1) **Drug not being developed.** The drug is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial.

(2) **Drug being developed.** The drug is being studied in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial. For example, patients may not be able to participate in the trial because they have a different disease or stage of disease than the one being studied or otherwise do not meet the enrollment criteria, because enrollment in the trial is closed, or because the trial site is not geographically accessible.
(3) **Approved or related drug.** (i) The drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application, or
(ii) The drug contains the same active moiety as an approved drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage.

(b) **Criteria.** The criteria in 312.305(a) must be met; and FDA must determine that:
(2) There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and
(3) There is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

(c) **Submission.** The expanded access submission must include information adequate to satisfy FDA that the criteria in 312.305(a) and paragraph (b) of this section have been met. The expanded access submission must meet the requirements of 312.305(b). In addition:
(2) The expanded access submission must state whether the drug is being developed or is not being developed and describe the patient population to be treated.
(3) If the drug is not being actively developed, the sponsor must explain why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed.
(4) If the drug is being studied in a clinical trial, the sponsor must explain why the patients to be treated cannot be enrolled in the clinical trial and under what circumstances the sponsor would conduct a clinical trial in these patients.

(d) **Safeguards.** (1) Upon review of the IND annual report, FDA will determine whether it is appropriate for the expanded access to continue under this section.
(i) If the drug is not being actively developed or if the expanded access use is not being developed (but another use is being developed), FDA will consider whether it is possible to conduct a clinical study of the expanded access use.
(ii) If the drug is being actively developed, FDA will consider whether providing the investigational drug for expanded access use is interfering with the clinical development of the drug.
(iii) As the number of patients enrolled increases, FDA may ask the sponsor to submit an IND or protocol for the use under 312.320.
(2) The sponsor is responsible for monitoring the expanded access protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

---

**Sec. 312.320 Treatment IND or treatment protocol.**

Under this section, FDA may permit an investigational drug to be used for widespread treatment use.

(a) **Criteria.** The criteria in 312.305(a) must be met, and FDA must determine that:
(1) **Trial status.** (i) The drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or
(ii) All clinical trials of the drug have been completed; and
(2) **Marketing status.** The sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence; and

(3) **Evidence.** (i) When the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials; or

(ii) When the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

(b) **Submission.** The expanded access submission must include information adequate to satisfy FDA that the criteria in 312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of 312.305(b).

(c) **Safeguard.** The sponsor is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.


Source: 52 FR 8831, Mar. 19, 1987, unless otherwise noted.
Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

Subpart A_General Provisions
812.1 Scope.
812.2 Applicability.
812.3 Definitions.
812.5 Labeling of investigational devices.
812.7 Prohibition of promotion and other practices.
812.10 Waivers.
812.18 Import and export requirements.
812.19 Address for IDE correspondence.

Subpart B_Application and Administrative Action
812.20 Application.
812.25 Investigational plan.
812.27 Report of prior investigations.
812.30 FDA action on applications.
812.35 Supplemental applications.
812.36 Treatment use of an investigational device.
812.38 Confidentiality of data and information.

Subpart C_Responsibilities of Sponsors
812.40 General responsibilities of sponsors.
812.42 FDA and IRB approval.
812.43 Selecting investigators and monitors.
812.45 Informing investigators.
812.46 Monitoring investigations.
812.47 Emergency research under 50.24 of this chapter.

Subpart D_IRB Review and Approval
812.60 IRB composition, duties, and functions.
812.62 IRB approval.
812.64 IRB's continuing review.
812.65 [Reserved]
812.66 Significant risk device determinations.

Subpart E_Responsibilities of Investigators

812.100 General responsibilities of investigators.
812.110 Specific responsibilities of investigators.
812.119 Disqualification of a clinical investigator.

Subpart F [Reserved]

Subpart G_Records and Reports

812.140 Records.
812.145 Inspections.
812.150 Reports.


Source: 45 FR 3751, Jan. 18, 1980, unless otherwise noted.

Subpart A--General Provisions

Sec. 812.1 Scope.

(a) The purpose of this part is to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose. This part provides procedures for the conduct of clinical investigations of devices. An approved investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device. An IDE approved under 812.30 or considered approved under 812.2(b) exempts a device from the requirements of the following sections of the Federal Food, Drug, and Cosmetic Act (the act) and regulations issued thereunder: Misbranding under section 502 of the act, registration, listing, and premarket notification under section 510, performance standards under section 514, premarket approval under section 515, a banned device regulation under section 516, records and reports under section 519, restricted device requirements under section 520(e), good manufacturing practice requirements under section 820.30, if applicable (unless the
sponsor states an intention to comply with these requirements under 812.20(b)(3) or 812.140(b)(4)(v)) and
color additive requirements under section 721.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21,
unless otherwise noted.


Sec. 812.2 Applicability.

(a) General. This part applies to all clinical investigations of devices to determine safety and effectiveness,
extcept as provided in paragraph (c) of this section.

(b) Abbreviated requirements. The following categories of investigations are considered to have approved
applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is
required:

(1) An investigation of a device other than a significant risk device, if the device is not a banned device
and the sponsor:

(i) Labels the device in accordance with 812.5;

(ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief
explanation of why the device is not a significant risk device, and maintains such approval;

(iii) Ensures that each investigator participating in an investigation of the device obtains from each
subject under the investigator's care, informed consent under part 50 and documents it, unless
documentation is waived by an IRB under 56.109(c).

(iv) Complies with the requirements of 812.46 with respect to monitoring investigations;

(v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required
under 812.150(b) (1) through (3) and (5) through (10);

(vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and
make the reports required under 812.150(a) (1), (2), (5), and (7); and

(vii) Complies with the prohibitions in 812.7 against promotion and other practices.

(2) An investigation of a device other than one subject to paragraph (e) of this section, if the investigation
was begun on or before July 16, 1980, and to be completed, and is completed, on or before January 19,
1981.

(c) Exempted investigations. This part, with the exception of 812.119, does not apply to investigations of the
following categories of devices:

(1) A device, other than a transitional device, in commercial distribution immediately before May 28,
1976, when used or investigated in accordance with the indications in labeling in effect at that time.

(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28,
1976, that FDA has determined to be substantially equivalent to a device in commercial distribution
immediately before May 28, 1976, and that is used or investigated in accordance with the indications in
the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

(3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the
testing:

(i) Is noninvasive,

(ii) Does not require an invasive sampling procedure that presents significant risk,
(iii) Does not by design or intention introduce energy into a subject, and
(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

(5) A device intended solely for veterinary use.

(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).

(7) A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

(d) Limit on certain exemptions. In the case of class II or class III device described in paragraph (c)(1) or (2) of this section, this part applies beginning on the date stipulated in an FDA regulation or order that calls for the submission of premarket approval applications for an unapproved class III device, or establishes a performance standard for a class II device.

(e) Investigations subject to IND's. A sponsor that, on July 16, 1980, has an effective investigational new drug application (IND) for an investigation of a device shall continue to comply with the requirements of part 312 until 90 days after that date. To continue the investigation after that date, a sponsor shall comply with paragraph (b)(1) of this section, if the device is not a significant risk device, or shall have obtained FDA approval under 812.30 of an IDE application for the investigation of the device.


Sec. 812.3 Definitions.

(a) Act means the Federal Food, Drug, and Cosmetic Act (sections 201-901, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301-392)).

(b) Custom device means a device that:
(1) Necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist;
(2) Is not generally available to, or generally used by, other physicians or dentists;
(3) Is not generally available in finished form for purchase or for dispensing upon prescription;
(4) Is not offered for commercial distribution through labeling or advertising; and
(5) Is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice.

(c) FDA means the Food and Drug Administration.

(d) Implant means a device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. FDA may, in order to protect public health, determine that devices placed in subjects for shorter periods are also "implants" for purposes of this part.

(e) Institution means a person, other than an individual, who engages in the conduct of research on subjects or in the delivery of medical services to individuals as a primary activity or as an adjunct to providing
residential or custodial care to humans. The term includes, for example, a hospital, retirement home, confinement facility, academic establishment, and device manufacturer. The term has the same meaning as "facility" in section 520(g) of the act.

(f) Institutional review board (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving subjects and established, operated, and functioning in conformance with part 56. The term has the same meaning as "institutional review committee" in section 520(g) of the act.

(g) Investigational device means a device, including a transitional device, that is the object of an investigation.

(h) Investigation means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

(i) 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.

(j) Monitor, when used as a noun, means an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor or a consultant to the sponsor, or an employee of or consultant to a contract research organization. Monitor, when used as a verb, means to oversee an investigation.

(k) Noninvasive, when applied to a diagnostic device or procedure, means one that does not by design or intention: (1) Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or (2) enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive.

(l) Person includes any individual, partnership, corporation, association, scientific or academic establishment, Government agency or organizational unit of a Government agency, and any other legal entity.

(m) Significant risk device means an investigational device that:

(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

(2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

(n) Sponsor means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

(o) Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered,
dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor.

(p) **Subject** means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

(q) **Termination** means a discontinuance, by sponsor or by withdrawal of IRB or FDA approval, of an investigation before completion.

(r) **Transitional device** means a device subject to section 520(l) of the act, that is, a device that FDA considered to be a new drug or an antibiotic drug before May 28, 1976.

(s) **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.


### Sec. 812.5 Labeling of investigational devices.

(a) **Contents.** An investigational device or its immediate package shall bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with 801.1), the quantity of contents, if appropriate, and the following statement: "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use." The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

(b) **Prohibitions.** The labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.

(c) **Animal research.** An investigational device shipped solely for research on or with laboratory animals shall bear on its label the following statement: "CAUTION--Device for investigational use in laboratory animals or other tests that do not involve human subjects."

(d) The appropriate FDA Center Director, according to the procedures set forth in 801.128 or 809.11 of this chapter, may grant an exception or alternative to the provisions in paragraphs (a) and (c) of this section, to the extent that these provisions are not explicitly required by statute, for specified lots, batches, or other units of a device that are or will be included in the Strategic National Stockpile.


### Sec. 812.7 Prohibition of promotion and other practices.

A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not:
(a) Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.

(b) Commercialize an investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.

(c) Unduly prolong an investigation. If data developed by the investigation indicate in the case of a class III device that premarket approval cannot be justified or in the case of a class II device that it will not comply with an applicable performance standard or an amendment to that standard, the sponsor shall promptly terminate the investigation.

(d) Represent that an investigational device is safe or effective for the purposes for which it is being investigated.

Sec. 812.10 Waivers.

(a) Request. A sponsor may request FDA to waive any requirement of this part. A waiver request, with supporting documentation, may be submitted separately or as part of an application to the address in 812.19.

(b) FDA action. FDA may by letter grant a waiver of any requirement that FDA finds is not required by the act and is unnecessary to protect the rights, safety, or welfare of human subjects.

(c) Effect of request. Any requirement shall continue to apply unless and until FDA waives it.

Sec. 812.18 Import and export requirements.

(a) Imports. In addition to complying with other requirements of this part, a person who imports or offers for importation an investigational device subject to this part shall be the agent of the foreign exporter with respect to investigations of the device and shall act as the sponsor of the clinical investigation, or ensure that another person acts as the agent of the foreign exporter and the sponsor of the investigation.

(b) Exports. A person exporting an investigational device subject to this part shall obtain FDA's prior approval, as required by section 801(e) of the act or comply with section 802 of the act.


Sec. 812.19 Address for IDE correspondence.

(a) If you are sending an application, supplemental application, report, request for waiver, request for import or export approval, or other correspondence relating to matters covered by this part, you must send the submission to the appropriate address as follows:

(1) For devices regulated by the Center for Devices and Radiological Health, send it to Food and Drug Administration, Center for Devices and Radiological Health, Document Mail Center, 10903 New Hampshire Ave., Bldg. 66, rm. G609, Silver Spring, MD 20993-0002.
Subpart B--Application and Administrative Action

Sec. 812.20 Application.

(a) Submission. (1) A sponsor shall submit an application to FDA if the sponsor intends to use a significant risk device in an investigation, intends to conduct an investigation that involves an exception from informed consent under 50.24 of this chapter, or if FDA notifies the sponsor that an application is required for an investigation.

(2) A sponsor shall not begin an investigation for which FDA's approval of an application is required until FDA has approved the application.

(3) A sponsor shall submit three copies of a signed "Application for an Investigational Device Exemption" (IDE application), together with accompanying materials, by registered mail or by hand to the address in 812.19. Subsequent correspondence concerning an application or a supplemental application shall be submitted by registered mail or by hand.

(4)(i) A sponsor shall submit a separate IDE for any clinical investigation involving an exception from informed consent under 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization of FDA. FDA shall provide a written determination 30 days after FDA receives the IDE or earlier.

(ii) If the investigation involves an exception from informed consent under 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in 50.24 of this chapter.

(b) Contents. An IDE application shall include, in the following order:

(1) The name and address of the sponsor.

(2) A complete report of prior investigations of the device and an accurate summary of those sections of the investigational plan described in 812.25(a) through (e) or, in lieu of the summary, the complete plan. The sponsor shall submit to FDA a complete investigational plan and a complete report of prior investigations of the device if no IRB has reviewed them, if FDA has found an IRB's review inadequate, or if FDA requests them.

(3) A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally
familiar with good manufacturing practices can make a knowledgeable judgment about the quality control used in the manufacture of the device.

(4) An example of the agreements to be entered into by all investigators to comply with investigator obligations under this part, and a list of the names and addresses of all investigators who have signed the agreement.

(5) A certification that all investigators who will participate in the investigation have signed the agreement, that the list of investigators includes all the investigators participating in the investigation, and that no investigators will be added to the investigation until they have signed the agreement.

(6) A list of the name, address, and chairperson of each IRB that has been or will be asked to review the investigation and a certification of the action concerning the investigation taken by each such IRB.

(7) The name and address of any institution at which a part of the investigation may be conducted that has not been identified in accordance with paragraph (b)(6) of this section.

(8) If the device is to be sold, the amount to be charged and an explanation of why sale does not constitute commercialization of the device.

(9) A claim for categorical exclusion under 25.30 or 25.34 or an environmental assessment under 25.40.

(10) Copies of all labeling for the device.

(11) Copies of all forms and informational materials to be provided to subjects to obtain informed consent.

(12) Any other relevant information FDA requests for review of the application.

(c) Additional information. FDA may request additional information concerning an investigation or revision in the investigational plan. The sponsor may treat such a request as a disapproval of the application for purposes of requesting a hearing under part 16.

(d) Information previously submitted. Information previously submitted to the Center for Devices and Radiological Health, the Center for Biologics Evaluation and Research, or the Center for Drug Evaluation and Research, as applicable, in accordance with this chapter ordinarily need not be resubmitted, but may be incorporated by reference.


Sec. 812.25 Investigational plan.

The investigational plan shall include, in the following order:

(a) Purpose. The name and intended use of the device and the objectives and duration of the investigation.

(b) Protocol. A written protocol describing the methodology to be used and an analysis of the protocol demonstrating that the investigation is scientifically sound.

(c) Risk analysis. A description and analysis of all increased risks to which subjects will be exposed by the investigation; the manner in which these risks will be minimized; a justification for the investigation; and a description of the patient population, including the number, age, sex, and condition.

(d) Description of device. A description of each important component, ingredient, property, and principle of operation of the device and of each anticipated change in the device during the course of the investigation.
(e) **Monitoring procedures.** The sponsor's written procedures for monitoring the investigation and the name and address of any monitor.

(f) **Labeling.** Copies of all labeling for the device.

(g) **Consent materials.** Copies of all forms and informational materials to be provided to subjects to obtain informed consent.

(h) **IRB information.** A list of the names, locations, and chairpersons of all IRB's that have been or will be asked to review the investigation, and a certification of any action taken by any of those IRB's with respect to the investigation.

(i) **Other institutions.** The name and address of each institution at which a part of the investigation may be conducted that has not been identified in paragraph (h) of this section.

(j) **Additional records and reports.** A description of records and reports that will be maintained on the investigation in addition to those prescribed in subpart G.

### Sec. 812.27 Report of prior investigations.

(a) **General.** The report of prior investigations shall include reports of all prior clinical, animal, and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigation.

(b) **Specific contents.** The report also shall include:

1. A bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety or effectiveness of the device, copies of all published and unpublished adverse information, and, if requested by an IRB or FDA, copies of other significant publications.
2. A summary of all other unpublished information (whether adverse or supportive) in the possession of, or reasonably obtainable by, the sponsor that is relevant to an evaluation of the safety or effectiveness of the device.
3. If information on nonclinical laboratory studies is provided, a statement that all such studies have been conducted in compliance with applicable requirements in the good laboratory practice regulations in part 58, or if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. Failure or inability to comply with this requirement does not justify failure to provide information on a relevant nonclinical test study.


### Sec. 812.30 FDA action on applications.

(a) **Approval or disapproval.** FDA will notify the sponsor in writing of the date it receives an application. FDA may approve an investigation as proposed, approve it with modifications, or disapprove it. An investigation may not begin until:

1. Thirty days after FDA receives the application at the address in 812.19 for the investigation of a device other than a banned device, unless FDA notifies the sponsor that the investigation may not begin; or
2. FDA approves, by order, an IDE for the investigation.
(b) **Grounds for disapproval or withdrawal.** FDA may disapprove or withdraw approval of an application if FDA finds that:

1. There has been a failure to comply with any requirement of this part or the act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA.
2. The application or a report contains an untrue statement of a material fact, or omits material information required by this part.
3. The sponsor fails to respond to a request for additional information within the time prescribed by FDA.
4. There is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, or informed consent is inadequate, or the investigation is scientifically unsound, or there is reason to believe that the device as used is ineffective.
5. It is otherwise unreasonable to begin or to continue the investigation owing to the way in which the device is used or the inadequacy of:
   - The report of prior investigations or the investigational plan;
   - The methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device; or
   - Monitoring and review of the investigation.

(c) **Notice of disapproval or withdrawal.** If FDA disapproves an application or proposes to withdraw approval of an application, FDA will notify the sponsor in writing.

1. A disapproval order will contain a complete statement of the reasons for disapproval and a statement that the sponsor has an opportunity to request a hearing under part 16.
2. A notice of a proposed withdrawal of approval will contain a complete statement of the reasons for withdrawal and a statement that the sponsor has an opportunity to request a hearing under part 16. FDA will provide the opportunity for hearing before withdrawal of approval, unless FDA determines in the notice that continuation of testing under the exemption will result in an unreasonable risk to the public health and orders withdrawal of approval before any hearing.


**Sec. 812.35 Supplemental applications.**

(a) **Changes in investigational plan --(1)Changes requiring prior approval.** Except as described in paragraphs (a)(2) through (a)(4) of this section, a sponsor must obtain approval of a supplemental application under 812.30(a), and IRB approval when appropriate (see 56.110 and 56.111 of this chapter), prior to implementing a change to an investigational plan. If a sponsor intends to conduct an investigation that involves an exception to informed consent under 50.24 of this chapter, the sponsor shall submit a separate investigational device exemption (IDE) application in accordance with 812.20(a).

(2) **Changes effected for emergency use.** The requirements of paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply in the case of a deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviation shall be reported to FDA within 5-working days after the sponsor learns of it (see 812.150(a)(4)).

(3) **Changes effected with notice to FDA within 5 days.** A sponsor may make certain changes without prior approval of a supplemental application under paragraph (a)(1) of this section if the sponsor determines
that these changes meet the criteria described in paragraphs (a)(3)(i) and (a)(3)(ii) of this section, on the basis of credible information defined in paragraph (a)(3)(iii) of this section, and the sponsor provides notice to FDA within 5-working days of making these changes.

(i) Developmental changes. The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of an investigation.

(ii) Changes to clinical protocol. The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to changes to clinical protocols that do not affect:

(A) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol;

(B) The scientific soundness of the investigational plan; or

(C) The rights, safety, or welfare of the human subjects involved in the investigation.

(iii) Definition of credible information. (A) Credible information to support developmental changes in the device (including manufacturing changes) includes data generated under the design control procedures of 820.30, preclinical/animal testing, peer reviewed published literature, or other reliable information such as clinical information gathered during a trial or marketing.

(B) Credible information to support changes to clinical protocols is defined as the sponsor's documentation supporting the conclusion that a change does not have a significant impact on the study design or planned statistical analysis, and that the change does not affect the rights, safety, or welfare of the subjects. Documentation shall include information such as peer reviewed published literature, the recommendation of the clinical investigator(s), and/or the data gathered during the clinical trial or marketing.

(iv) Notice of IDE change. Changes meeting the criteria in paragraphs (a)(3)(i) and (a)(3)(ii) of this section that are supported by credible information as defined in paragraph (a)(3)(iii) of this section may be made without prior FDA approval if the sponsor submits a notice of the change to the IDE not later than 5-working days after making the change. Changes to devices are deemed to occur on the date the device, manufactured incorporating the design or manufacturing change, is distributed to the investigator(s). Changes to a clinical protocol are deemed to occur when a clinical investigator is notified by the sponsor that the change should be implemented in the protocol or, for sponsor-investigator studies, when a sponsor-investigator incorporates the change in the protocol. Such notices shall be identified as a "notice of IDE change."

(A) For a developmental or manufacturing change to the device, the notice shall include a summary of the relevant information gathered during the course of the investigation upon which the change was based; a description of the change to the device or manufacturing process (cross-referenced to the appropriate sections of the original device description or manufacturing process); and, if design controls were used to assess the change, a statement that no new risks were identified by appropriate risk analysis and that the verification and validation testing, as appropriate, demonstrated that the design outputs met the design input requirements. If another method of assessment was used, the notice shall include a summary of the information which served as the credible information supporting the change.
For a protocol change, the notice shall include a description of the change (cross-referenced to the appropriate sections of the original protocol); an assessment supporting the conclusion that the change does not have a significant impact on the study design or planned statistical analysis; and a summary of the information that served as the credible information supporting the sponsor's determination that the change does not affect the rights, safety, or welfare of the subjects.

Changes submitted in annual report. The requirements of paragraph (a)(1) of this section do not apply to minor changes to the purpose of the study, risk analysis, monitoring procedures, labeling, informed consent materials, and IRB information that do not affect:

(i) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol;

(ii) The scientific soundness of the investigational plan; or

(iii) The rights, safety, or welfare of the human subjects involved in the investigation. Such changes shall be reported in the annual progress report for the IDE, under 812.150(b)(5).

IRB approval for new facilities. A sponsor shall submit to FDA a certification of any IRB approval of an investigation or a part of an investigation not included in the IDE application. If the investigation is otherwise unchanged, the supplemental application shall consist of an updating of the information required by 812.20(b) and (c) and a description of any modifications in the investigational plan required by the IRB as a condition of approval. A certification of IRB approval need not be included in the initial submission of the supplemental application, and such certification is not a precondition for agency consideration of the application. Nevertheless, a sponsor may not begin a part of an investigation at a facility until the IRB has approved the investigation, FDA has received the certification of IRB approval, and FDA, under 812.30(a), has approved the supplemental application relating to that part of the investigation (see 56.103(a)).

Sec. 812.36 Treatment use of an investigational device.

(a) General. A device that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of a treatment investigational device exemption (IDE). The purpose of this section is to facilitate the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing begins, and to obtain additional data on the device's safety and effectiveness. In the case of a serious disease, a device ordinarily may be made available for treatment use under this section after all clinical trials have been completed. In the case of an immediately life-threatening disease, a device may be made available for treatment use under this section prior to the completion of all clinical trials. For the purpose of this section, an "immediately life-threatening" disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. For purposes of this section, "treatment use" of a device includes the use of a device for diagnostic purposes.
(b) Criteria. FDA shall consider the use of an investigational device under a treatment IDE if:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
2. There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;
3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and
4. The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

(c) Applications for treatment use. (1) A treatment IDE application shall include, in the following order:

i. The name, address, and telephone number of the sponsor of the treatment IDE;
ii. The intended use of the device, the criteria for patient selection, and a written protocol describing the treatment use;
iii. An explanation of the rationale for use of the device, including, as appropriate, either a list of the available regimens that ordinarily should be tried before using the investigational device or an explanation of why the use of the investigational device is preferable to the use of available marketed treatments;
iv. A description of clinical procedures, laboratory tests, or other measures that will be used to evaluate the effects of the device and to minimize risk;
v. Written procedures for monitoring the treatment use and the name and address of the monitor;
vi. Instructions for use for the device and all other labeling as required under 812.5(a) and (b);
vii. Information that is relevant to the safety and effectiveness of the device for the intended treatment use. Information from other IDE's may be incorporated by reference to support the treatment use;
viii. A statement of the sponsor's commitment to meet all applicable responsibilities under this part and part 56 of this chapter and to ensure compliance of all participating investigators with the informed consent requirements of part 50 of this chapter;
ix. An example of the agreement to be signed by all investigators participating in the treatment IDE and certification that no investigator will be added to the treatment IDE before the agreement is signed; and
x. If the device is to be sold, the price to be charged and a statement indicating that the price is based on manufacturing and handling costs only.

(2) A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is an "investigator" under the IDE and is responsible for meeting all applicable investigator responsibilities under this part and parts 50 and 56 of this chapter.

(d) FDA action on treatment IDE applications. (1) Approval of treatment IDE's. Treatment use may begin 30 days after FDA receives the treatment IDE submission at the address specified in 812.19, unless FDA notifies the sponsor in writing earlier than the 30 days that the treatment use may or may not begin. FDA may approve the treatment use as proposed or approve it with modifications.

(2) Disapproval or withdrawal of approval of treatment IDE's. FDA may disapprove or withdraw approval of a treatment IDE if:

i. The criteria specified in 812.36(b) are not met or the treatment IDE does not contain the information required in 812.36(c);
(ii) FDA determines that any of the grounds for disapproval or withdrawal of approval listed in 812.30(b)(1) through (b)(5) apply;

(iii) The device is intended for a serious disease or condition and there is insufficient evidence of safety and effectiveness to support such use;

(iv) The device is intended for an immediately life-threatening disease or condition and the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the device:

(A) May be effective for its intended use in its intended population; or

(B) Would not expose the patients to whom the device is to be administered to an unreasonable and significant additional risk of illness or injury;

(v) There is reasonable evidence that the treatment use is impeding enrollment in, or otherwise interfering with the conduct or completion of, a controlled investigation of the same or another investigational device;

(vi) The device has received marketing approval/clearance or a comparable device or therapy becomes available to treat or diagnose the same indication in the same patient population for which the investigational device is being used;

(vii) The sponsor of the controlled clinical trial is not pursuing marketing approval/clearance with due diligence;

(viii) Approval of the IDE for the controlled clinical investigation of the device has been withdrawn;

(ix) The clinical investigator(s) named in the treatment IDE are not qualified by reason of their scientific training and/or experience to use the investigational device for the intended treatment use.

(3) Notice of disapproval or withdrawal. If FDA disapproves or proposes to withdraw approval of a treatment IDE, FDA will follow the procedures set forth in 812.30(c).

(e) Safeguards. Treatment use of an investigational device is conditioned upon the sponsor and investigators complying with the safeguards of the IDE process and the regulations governing informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter).

(f) Reporting requirements. The sponsor of a treatment IDE shall submit progress reports on a semi-annual basis to all reviewing IRB's and FDA until the filing of a marketing application. These reports shall be based on the period of time since initial approval of the treatment IDE and shall include the number of patients treated with the device under the treatment IDE, the names of the investigators participating in the treatment IDE, and a brief description of the sponsor's efforts to pursue marketing approval/clearance of the device. Upon filing of a marketing application, progress reports shall be submitted annually in accordance with 812.150(b)(5). The sponsor of a treatment IDE is responsible for submitting all other reports required under 812.150.

device subject to the IDE; or a notice of completion of a product development protocol for the device has become effective.

(b) Availability of summaries or data. (1) FDA will make publicly available, upon request, a detailed summary of information concerning the safety and effectiveness of the device that was the basis for an order approving, disapproving, or withdrawing approval of an application for an IDE for a banned device. The summary shall include information on any adverse effect on health caused by the device.

(2) If a device is a banned device or if the existence of an IDE has been publicly disclosed or acknowledged, data or information contained in the file is not available for public disclosure before approval of an application for premarket approval or the effective date of a notice of completion of a product development protocol except as provided in this section. FDA may, in its discretion, disclose a summary of selected portions of the safety and effectiveness data, that is, clinical, animal, or laboratory studies and tests of the device, for public consideration of a specific pending issue.

(3) If the existence of an IDE file has not been publicly disclosed or acknowledged, no data or information in the file are available for public disclosure except as provided in paragraphs (b)(1) and (c) of this section.

(4) Notwithstanding paragraph (b)(2) of this section, FDA will make available to the public, upon request, the information in the IDE that was required to be filed in Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, for investigations involving an exception from informed consent under 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(c) Reports of adverse effects. Upon request or on its own initiative, FDA shall disclose to an individual on whom an investigational device has been used a copy of a report of adverse device effects relating to that use.

(d) Other rules. Except as otherwise provided in this section, the availability for public disclosure of data and information in an IDE file shall be handled in accordance with 814.9.


Subpart C—Responsibilities of Sponsors

Sec. 812.40 General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. Additional responsibilities of sponsors are described in subparts B and G.
Sec. 812.42 FDA and IRB approval.

A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation.

[46 FR 8957, Jan. 27, 1981]

Sec. 812.43 Selecting investigators and monitors.

(a) Selecting investigators. A sponsor shall select investigators qualified by training and experience to investigate the device.

(b) Control of device. A sponsor shall ship investigational devices only to qualified investigators participating in the investigation.

(c) Obtaining agreements. A sponsor shall obtain from each participating investigator a signed agreement that includes:

1. The investigator's curriculum vitae.
2. Where applicable, a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience.
3. If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination.
4. A statement of the investigator's commitment to:
   (i) Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA;
   (ii) Supervise all testing of the device involving human subjects; and
   (iii) Ensure that the requirements for obtaining informed consent are met.
5. Sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study. This information shall not be submitted in an investigational device exemption application, but shall be submitted in any marketing application involving the device.

(d) Selecting monitors. A sponsor shall select monitors qualified by training and experience to monitor the investigational study in accordance with this part and other applicable FDA regulations.


Sec. 812.45 Informing investigators.

A sponsor shall supply all investigators participating in the investigation with copies of the investigational plan and the report of prior investigations of the device.
Sec. 812.46 Monitoring investigations.

(a) Securing compliance. A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

(b) Unanticipated adverse device effects. (1) A sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect.

(2) A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect.

(c) Resumption of terminated studies. If the device is a significant risk device, a sponsor may not resume a terminated investigation without IRB and FDA approval. If the device is not a significant risk device, a sponsor may not resume a terminated investigation without IRB approval and, if the investigation was terminated under paragraph (b)(2) of this section, FDA approval.

Sec. 812.47 Emergency research under 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under 50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures under 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor shall promptly submit to the IDE file and to Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, copies of the information that was disclosed, identified by the IDE number.

(b) The sponsor also shall monitor such investigations to determine when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical investigation, and other IRB's that are asked to review this or a substantially equivalent investigation.

Subpart D—IRB Review and Approval

Sec. 812.60 IRB composition, duties, and functions.
An IRB reviewing and approving investigations under this part shall comply with the requirements of part 56 in all respects, including its composition, duties, and functions.

[46 FR 8957, Jan. 27, 1981]

Sec. 812.62 IRB approval.
(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all investigations covered by this part.
(b) If no IRB exists or if FDA finds that an IRB's review is inadequate, a sponsor may submit an application to FDA.

[46 FR 8957, Jan. 27, 1981]

Sec. 812.64 IRB's continuing review.
The IRB shall conduct its continuing review of an investigation in accordance with part 56.

[46 FR 8957, Jan. 27, 1981]

Sec. 812.65 [Reserved]

Sec. 812.66 Significant risk device determinations.
If an IRB determines that an investigation, presented for approval under 812.2(b)(1)(ii), involves a significant risk device, it shall so notify the investigator and, where appropriate, the sponsor. A sponsor may not begin the investigation except as provided in 812.30(a).

[46 FR 8957, Jan. 27, 1981]

Subpart E—Responsibilities of Investigators

Sec. 812.100 General responsibilities of investigators.
An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An
investigator also is responsible for ensuring that informed consent is obtained in accordance with part 50 of this chapter. Additional responsibilities of investigators are described in subpart G.


Sec. 812.110 Specific responsibilities of investigators.

(a) **Awaiting approval.** An investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval.

(b) **Compliance.** An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

(c) **Supervising device use.** An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under this part to receive it.

(d) **Financial disclosure.** A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

(e) **Disposing of device.** Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.


Sec. 812.119 Disqualification of a clinical investigator.

(a) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Center for Devices and Radiological Health, the Center for Biologics Evaluation and Research, or the Center for Drug Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered and accepted by the applicable Center, the Center will discontinue the disqualification proceeding. If an explanation is offered but not accepted by the applicable Center, the investigator will be given an opportunity for a regulatory hearing under part 16 of this chapter on the question of whether the investigator is eligible to receive test articles under this part and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.
(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Commissioner will notify the investigator, the sponsor of any investigation in which the investigator has been named as a participant, and the reviewing investigational review boards (IRBs) that the investigator is not eligible to receive test articles under this part. The notification to the investigator, sponsor and IRBs will provide a statement of the basis for such determination. The notification also will explain that an investigator determined to be ineligible to receive test articles under this part will be ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

(c) Each application or submission to FDA under the provisions of this chapter containing data reported by an investigator who has been determined to be ineligible to receive FDA-regulated test articles is subject to examination to determine whether the investigator has submitted unreliable data that are essential to the continuation of an investigation or essential to the clearance or approval of a marketing application, or essential to the continued marketing of an FDA-regulated product.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor, who shall have an opportunity for a regulatory hearing under part 16 of this chapter. If a danger to the public health exists, however, the Commissioner shall terminate the investigational device exemption (IDE) immediately and notify the sponsor and the reviewing IRBs of the termination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 of this chapter on the question of whether the IDE should be reinstated. The determination that an investigation may not be considered in support of a research or marketing application or a notification or petition submission does not, however, relieve the sponsor of any obligation under any other applicable regulation to submit to FDA the results of the investigation.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued clearance or approval of the product for which the data were submitted cannot be justified, the Commissioner will proceed to rescind clearance or withdraw approval of the product in accordance with the applicable provisions of the relevant statutes.

(f) An investigator who has been determined to be ineligible under paragraph (b) of this section may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ all test articles, and will conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, solely in compliance with the applicable provisions of this chapter.

[77 FR 25360, Apr. 30, 2012]
Subpart F [Reserved]

Subpart G--Records and Reports

Sec. 812.140 Records.

(a) Investigator records. A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

(1) All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.

(2) Records of receipt, use or disposition of a device that relate to:

(i) The type and quantity of the device, the dates of its receipt, and the batch number or code mark.

(ii) The names of all persons who received, used, or disposed of each device.

(iii) Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

(3) Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:

(i) Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(ii) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

(iii) A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

(4) The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

(5) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

(b) Sponsor records. A sponsor shall maintain the following accurate, complete, and current records relating to an investigation:

(1) All correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports.

(2) Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

(3) Signed investigator agreements including the financial disclosure information required to be collected under 812.43(c)(5) in accordance with part 54 of this chapter.
(4) For each investigation subject to 812.2(b)(1) of a device other than a significant risk device, the records described in paragraph (b)(5) of this section and the following records, consolidated in one location and available for FDA inspection and copying:
   (i) The name and intended use of the device and the objectives of the investigation;
   (ii) A brief explanation of why the device is not a significant risk device:
   (iii) The name and address of each investigator:
   (iv) The name and address of each IRB that has reviewed the investigation:
   (v) A statement of the extent to which the good manufacturing practice regulation in part 820 will be followed in manufacturing the device; and
   (vi) Any other information required by FDA.

(5) Records concerning adverse device effects (whether anticipated or unanticipated) and complaints and
(6) Any other records that FDA requires to be maintained by regulation or by specific requirement for a
   category of investigation or a particular investigation.

(c) IRB records. An IRB shall maintain records in accordance with part 56 of this chapter.
(d) Retention period. An investigator or sponsor shall maintain the records required by this subpart during the
   investigation and for a period of 2 years after the latter of the following two dates: The date on which the
   investigation is terminated or completed, or the date that the records are no longer required for purposes of
   supporting a premarket approval application or a notice of completion of a product development protocol.
(e) Records custody. An investigator or sponsor may withdraw from the responsibility to maintain records for
   the period required in paragraph (d) of this section and transfer custody of the records to any other person
   who will accept responsibility for them under this part, including the requirements of 812.145. Notice of a
   transfer shall be given to FDA not later than 10 working days after transfer occurs.

57280, Nov. 5, 1996; 63 FR 5253, Feb. 2, 1998]

Sec. 812.145 Inspections.

(a) Entry and inspection. A sponsor or an investigator who has authority to grant access shall permit
authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any
establishment where devices are held (including any establishment where devices are manufactured,
processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
(b) Records inspection. A sponsor, IRB, or investigator, or any other person acting on behalf of such a person
with respect to an investigation, shall permit authorized FDA employees, at reasonable times and in a
reasonable manner, to inspect and copy all records relating to an investigation.
(c) Records identifying subjects. An investigator shall permit authorized FDA employees to inspect and copy
records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent
was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have
not been submitted or are incomplete, inaccurate, false, or misleading.
Sec. 812.150 Reports.

(a) Investigator reports. An investigator shall prepare and submit the following complete, accurate, and timely reports:

1. Unanticipated adverse device effects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

2. Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

3. Progress. An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

4. Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 812.35(a) also is required.

5. Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

6. Final report. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

7. Other. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

(b) Sponsor reports. A sponsor shall prepare and submit the following complete, accurate, and timely reports:

1. Unanticipated adverse device effects. A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

2. Withdrawal of IRB approval. A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

3. Withdrawal of FDA approval. A sponsor shall notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.

4. Current investigator list. A sponsor shall submit to FDA, at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval.

5. Progress reports. At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In the case of a significant risk device, a sponsor shall also submit progress reports to
FDA. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing IRB's and FDA in accordance with 812.36(f) and annual reports in accordance with this section.

(6) **Recall and device disposition.** A sponsor shall notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.

(7) **Final report.** In the case of a significant risk device, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.

(8) **Informed consent.** A sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

(9) **Significant risk device determinations.** If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.

(10) **Other.** A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.


**Source:** 45 FR 3751, Jan. 18, 1980, unless otherwise noted.
Research Projects Involving Planned Emergency Research

To Approve an Exception to Acute Care Informed Consent for Planned Emergency Research, the Institutional Review Board (IRB)\(^1\) must find and document FDA 21 Part 50.24, DHHS 45 CFR Part 46.101(i)\(^2\):

1. Administration involves life threatening situation; Available treatment unproven or unsatisfactory; Collecting of evidence necessary to determine safety and effectiveness

2. Obtaining consent NOT feasible because:
   a. Subject’s medical condition
   b. Intervention must be administered before feasible to consent legally authorized representatives
   c. No reasonable way to identify prospective subjects

3. Research of potential direct benefit to subjects:
   a. Life threatening situation necessitates intervention
   b. Animal and preclinical studies support potential direct benefit of intervention for individuals
   c. Risks reasonable in relationship to
      1. What is known about medical condition
      2. Risks and benefits of standard therapy
      3. Risks and benefits of proposed intervention
4. Investigation could NOT practicably be carried out without waiver

5. Investigator has:
   a. Defined length of potential therapeutic window
   b. Is committed to attempting to contact and obtain consent from legally authorized representative within window
   c. Will summarize efforts to contact authorized representative at the time of continuing review
   d. Is committed to contact within window subject’s family member and ask if he/she objects (if obtaining consent from subject or legally authorized representative is not feasible)
   e. Will summarize efforts to contact family member at the time of IRB continuing review

6. IRB has:
   a. Approved informed consent procedures and documents to be used with subject/legally authorized representative
   b. Approved procedures and information to be used when providing family members opportunity to object

7. Consultation with representatives of communities from which subjects will be drawn and in which research will be conducted

8. Public disclosure in communities prior to initiation including:
   a. Plans for study
   b. Risks and benefits
9. Public disclosure to community at completion of study including:
   a. Demographics of population
   b. Results of study

10. Establishment of an independent data and safety monitoring committee

11. Procedures are in place to inform at earliest opportunity each subject (if competent), legally authorized representative, and/or family member of:
   a. Subject’s inclusion in study
   b. Details of study and other information in informed consent document
   c. Opportunity to discontinue subject’s participation without penalty or loss of benefit to which subject is entitled

12. Additional reporting and recordkeeping, FDA drug and device application requirements must be met [These are outlined in attached document]

Footnotes

专业知识

† IRB review must include concurrence of a licensed physician who is a member or a consultant to IRB and who is not otherwise participating in the clinical investigation.

‡ For Department of Health and Human Services (DHHS) regulated studies, waiver not applicable to research involving prisoners, fetuses, pregnant women, human in vitro, and fertilization.

§ “Family member” is defined as 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.
Additional Planned Emergency Research Informed Consent Exception Reporting Recordkeeping Requirements

FDA 21 CFR Part 50.24; DHHS 45 CFR Part 46.101(i)

1. For Food and Drug Administration (FDA) regulated investigations, a separate Investigational New Drug application (IND) or Investigational Device Exemption (IDE) is required
   a. Separate IND/IDE identifies protocol as including subjects unable to give consent
   b. Submission of separate IND/IDE required even if IND/IDE for same drug/device exists
   c. Applications may not be submitted to FDA as amendments

2. If research is NOT subject to FDA 21 CFR Part 50, but DOES fall in purview of DHHS 45 CFR Part 46, the IRB must report to the Office for Human Research Protections (OHRP) that approved acute care informed consent waiver has occurred. [Note: The conditions for approval of DHHS are identical to those outlined in FDA 50.24]

3. If the IRB does NOT approve request for waiver:
   a. IRB must document findings including reasons for disapproval and promptly provide to:
      1. clinical investigator
      2. sponsor
   b. Sponsor must promptly report disapproval to:
      1. FDA
      2. Other clinical investigators in this or substantially
equivalent clinical investigations

3. Other IRBs reviewing this or substantially equivalent investigations

4. If waiver is approved:
   a. IRB must provide sponsor with copy of information that has been publicly disclosed prior to initiation and at completion of study [Investigator must provide IRB with information]
   b. Sponsors must provide copies to FDA

5. IRB, Investigator, and Sponsor records must be:
   a. retained for three years after completion of clinical investigation
   b. accessible for inspection and copying by FDA

For detailed information on FDA’s policies pertaining to Exceptions to Informed Consent in Planned Emergency Research, see the following document: “Food and Drug Administration (FDA) Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors on Exception from Informed Consent Requirements for Emergency Research”, April 1, 2013
Summary of FDA Regulations on Exemption from IND Requirements
(summary of 21CFR312 and 2013 FDA IND Exemption Guidance)

Introduction

In general, Investigational New Drug (IND) regulations (21CFR312) apply in human research studies that involve use of a drug (as defined in the Food, Drug, and Cosmetic Act (FD&C Act)) in a clinical investigation (as defined in 21CFR312.3) unless otherwise exempt from IND requirements as described below. The following summary includes exemptions based on the IND Regulations, determinations from the 2013 FDA IND Exemption Guidance and examples from the 2004 FDA Guidance on IND exemptions for cancer treatment studies.

Where questions still exist, sponsor-investigators are encouraged to contact the appropriate FDA review division for guidance.

- For drug studies, an inquiry concerning the application of the IND regulations should be directed to the Chief, Project Management Staff, in the appropriate CDER review division. Organizational charts listing the CDER review divisions and their phone numbers are available on the Internet at http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135674.htm.

- For biologics, the inquiry should be directed to the applications division of the appropriate review Office. Organizational charts listing the CBER review divisions and their phone numbers are available on the Internet at http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135943.htm.

Note: The determination of need for an IND does not depend on whether the intent of the clinical investigation is commercial or non-commercial. Also, the number of subjects to be enrolled or the clinical condition of the subjects has no bearing on whether the study is subject to the IND regulations. Unless a study meets one of the exemptions below, it is subject to IND regulations.

Exemption for Clinical Investigations involving a Lawfully Marketed Drug(s)
21CFR312.2(b)(1)

The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of an IND, if all of the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly
increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for review by an IRB (21CFR56) and the requirements for informed consent (21CFR 50); and

(v) The investigation is conducted in compliance with the requirements of 21CFR312.7 (Promotion and sale of investigational drugs).

How do you determine whether a planned study will be used to support a new indication or other significant labeling or advertising claim?

Whether a planned clinical investigation will be used to support a new indication, other significant labeling change, or advertising claim may not always be known or apparent at the outset of the investigation. Generally, it seems reasonable to infer that the intent of any well-controlled trial of a marketed drug sponsored by the manufacturer of the drug would be to influence labeling or promotion in some way. On the other hand, the sponsor-investigator of an investigator-initiated study in an academic setting (a study designed and initiated by the investigator independent of the manufacturer) probably does not intend that his or her study of a marketed drug influence labeling or promotion, even if the sponsor-investigator is receiving some limited support from the drug’s manufacturer. However, certain investigator-initiated research has the potential to influence labeling or promotion, notwithstanding the investigator’s intent (e.g., a controlled trial with an endpoint representing improvement of a serious disease). Similarly, certain studies of effectiveness conducted by government agencies (e.g., National Institutes of Health, Veterans Administration) have the potential to influence labeling. FDA strongly encourages IND submissions for these types of studies so that the Agency can have an opportunity to provide advice on study design.

How do you determine whether changes to a lawfully marketed dosage form increase risk?

FDA does not require that the exact same dosage, population, form described in approved labeling in order to meet the exemption category, but permits changes that do not increase the risks above that presented by the use of the product according to approved labeling.

Investigators are advised to carefully consider risk implications of any conditions of use that deviate from those described in approved labeling, particularly in regard to route of administration, dose, and patient population.

- **Route of Administration:** A change in the route of administration can introduce a significant new risk. For example, there could be a significant increase in risk if a marketed drug for oral administration is converted to a dosage form that is to be administered by injection or intravenous, intrathecal, or inhalation route. These other routes of administration introduce concerns with sterility, pyrogenicity, hypersensitivity (e.g., airway
reactivity), variations in metabolism, and other issues not present with oral administration.

- **Dose**: Increases in dose, frequency, or duration of administration, compared to labeled dosing regimens, can significantly increase the risk in a study using a marketed drug. It is possible that a decrease in dose could also significantly increase risk. For example, administering a low dose of a pure polysaccharide vaccine to study subjects can induce hypo-immunologic or non-immunologic responses in the subjects and can also induce tolerance to the vaccine, thus making subjects at risk for the infectious disease the vaccine is intended to prevent. The significance of changes in dose (in particular increases in dose) can vary across therapeutic areas. For example, the cancer treatment guidance provides some latitude for conducting studies of high-dose cancer treatments without an IND because of oncologists’ familiarity with the implications of high dose regimens, generally.

- **Population**: The acceptability of known and unknown risks can vary considerably across different treatment populations (see § 312.2(b)(1)(iii)). For example, a drug with significant toxicity can be approved for use in a population with life-threatening or severely debilitating disease because the risk of toxicity is acceptable in that population. Use of that drug in a clinical investigation in a population that is not so ill (e.g., to evaluate the drug for prevention of disease or symptomatic relief), however, would present a different risk-benefit situation in which the risks would likely not be acceptable. When the acceptability of the risk is significantly decreased, the study would have to be conducted under an IND as required under 21CFR312.

**Exemption of Clinical Investigations involving In-Vitro Diagnostics**

*21CFR312.2(b)(2)*

A clinical investigation of an *in vitro* diagnostic biological product is exempt from requirements of an IND, **if all** of the following apply:

(i) The *in vitro* diagnostic biological product involving one or more of the following:
   - Blood grouping serum.
   - Reagent red blood cells.
   - Anti-human globulin.

(ii) The diagnostic product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure

(iii) The diagnostic product is shipped in compliance with 21CFR312.160.
Exemption for a Clinical Investigation involving a Placebo
21CFR312.2(b)(5)

A clinical investigation involving use of a placebo is IND exempt if the investigation does not otherwise require submission of an IND. Note: additional requirements apply for research in children/minors based on FDA Subpart D final rule.

Additional IND Exemption Determinations for Specific Types of Clinical Investigations Summarized From the 2013 FDA IND Exemption Guidance

Exemption for Bioavailability or Bioequivalence Studies (BA/BE) 21CFR320.31

BA/BE studies using unapproved versions of approved drugs be conducted without an IND (21CFR320.31), if all of the following conditions are met:

(i) The drug product does not contain a new chemical entity (21CFR314.108), is not radioactively labeled, and is not cytotoxic.

(ii) The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product.

(iii) The investigation is conducted in compliance with the requirements for review by an IRB (21CFR56) and the requirements for informed consent (21CFR50).

(iv) The sponsor meets the requirements for retention of test article samples (21CFR 320.31(d)(1)).

Potential Exemption for Radioactive Drugs 21CFR361.1

FDA regulations (21CFR361.1) describe conditions under which radioactive drugs can be used for certain research without an IND when recognized as safe and effective for use in the research. See the 2010 FDA Guidance on Radioactive Drug Research for clarification regarding what research studies may be conducted under the Radioactive Drug Research Committee (RDRC) vs. IND process.

Exemption for Studies Using Cold Isotopes of Approved or Unapproved Drugs

In exercising its enforcement discretion, FDA does not intend to object to clinical investigations using cold isotopes of unapproved drugs being conducted without an IND, if the following conditions are met:

(i) The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry.
(ii) The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject.

(iii) The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies.

(iv) The quality of the cold isotope meets relevant quality standards.

(v) The research is reviewed and approved by an IRB (21CFR56) and informed consent is obtained from the research subjects (21CFR50).

**Potential Requirement for an IND for Other Items Meeting Drug Definition**

- **Endogenous Compounds**

  An IND is required for Endogenous Compounds, (i.e. histamine), when used in provocation or challenge studies to illicit a physiologic response, characterize a disease, or establish a mechanism of action. The IND is required even though the compound is not being used for a therapeutic purpose.

- **Live Organisms**

  An IND is required for challenge studies in which a live organism, (e.g. bacteria, virus) is administered to subjects to study the pathogenesis of disease or the host response to the organism. The IND is required even though the organism is not intended to have a therapeutic purpose.

- **Dietary Supplements***

  The IND determination for items meeting the definition of dietary supplement under the *Dietary Supplement Health and Education Act (DSHEA)* is based on the intent of the clinical investigation.

  Dietary Supplements, (e.g. vitamins, minerals, amino acids, botanicals, etc.), when used only to evaluate effect on structure or function of the body do not require an IND (e.g., fiber supplement affect on gastric motility). However, if the clinical investigation is intended to evaluate the dietary supplements ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required (e.g., soluble fiber affect on hypercholesterolemia prevention or treatment). This criteria also applies to products containing substances generally recognized as safe (GRAS) for use in food.

- **Conventional Food***

  Several criteria must be considered for determining when an IND is required for conventional foods.
Therapeutic Use: An IND is required for uses of conventional foods to evaluate their ability to diagnose, cure, mitigate, treat, or prevent a disease. Structure or function: Whether or not studies evaluating structure or function in a human require an IND depends. An IND may not be required if the affect is based on a “food characteristic” such as taste, aroma, or nutritive value. An IND may be required if the affect is based on any other characteristic (e.g., block absorption of carbohydrate in the gut). Intent to support a health claim: An IND may not be required if the substance-disease relationship being studied is already the subject of an FDA Authorized Health Claim. However, for a study of a new or expended health claim, an IND may be required.

- **Cosmetics***

According to the 2013 Exemption guidance, an IND is required for cosmetic studies evaluating therapeutic use and structure/function affects. This includes studies intended to support a cosmetic claim about the ingredient or product’s ability to cleanse, beautify, promote attractiveness, or alter the appearance (e.g., research on skin repair affects of a product with a biological material ingredient, to support a claim of younger looking skin.

**2-6-14 FEDERAL REGISTER NOTICE**: The FDA reopened the final 2013 guidance for comment related only to the applicability of IND regulations to clinical studies involving cosmetics, foods, and dietary supplements. IND exemption criteria for these three categories may be subject to change based on FDA assessment of submitted comments.

- **Other Products**

See [2013 FDA IND Exemption Guidance](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM229175.pdf) for additional FAQs regarding need for an IND including radiolabeled peptides, positron emission tomography (PET) drugs, attenuated microorganisms, radioisotopes, and others.


Cancer Treatment Determinations

Below is additional guidance for when studies of lawfully marketed drugs or biological product, for the treatment of cancer, are exempt from the requirement of an IND application and examples of when they are not.

When does an IND application need to be submitted for studies of marketed drugs for treating cancer?
(a summary of 2004 FDA Guidance)

When determining if an IND needs to be submitted to study marketed drugs for treating cancer, investigators must apply the exemption criteria listed in § 312.2(b)(1)(i-v) in light of the discussion in this guidance. Planned studies may be considered exempt from the requirements of an IND if the studies involve a new use, dosage, schedule, route of administration, or new combination of marketed cancer products in a patient population with cancer and the following conditions apply:

- The studies are not intended to support FDA approval of a new indication or a significant change in the product labeling.
- The studies are not intended to support a significant change in the advertising for the product.
- Investigators and their IRBs determine that based on the scientific literature and generally known clinical experience, there is no significant increase in the risk associated with the use of the drug product.
- The studies are to be conducted in compliance with IRB and informed consent regulations, pursuant to parts 50 and 56.
- The studies will not be used to promote unapproved indications, in compliance with §312.7.

EXAMPLES OF STUDIES
The following examples of studies are being provided to illustrate FDA’s current thinking on the types of studies that the FDA considers to be exempt from IND regulation based on a risk assessment.

A. Studies That Generally Are Exempt

As noted above, of the five criteria in § 312.2(b)(1), four are not protocol related and one is protocol related. The following are examples of general categories of studies of marketed cancer drugs that would likely be exempt from IND regulation based on protocol-related issues.

1. Single-arm, phase 2 trials using marketed drugs to treat a cancer different from that indicated in the approved labeling and using doses and schedules similar to those in the marketed drug labeling are usually exempt. An exception may exist when standard therapy in the population to be studied is very effective (e.g., is associated with a
survival benefit); in that case, use of another regimen may expose patients to the risk of receiving an ineffective therapy and an IND would be necessary.

2. Phase 1 oncology trials of marketed drugs may be considered exempt if such therapy is appropriate for the patient population (i.e., if patients have residual cancer) and if there is no effective therapy (i.e., therapy producing cure or a documented increase in survival) that the patients have not yet received. It remains the investigator’s responsibility to use starting doses that appear safe based on approved labeling or detailed literature reports, use incremental changes in dose or schedule, and carefully evaluate toxicity prior to dose escalation.

3. The study of new combinations of drugs would not ordinarily constitute a significant risk if these combinations have been described in the professional medical literature. Even when the regimen described in the literature does not use exactly the doses planned for study, incremental differences in doses from those described in the literature would not normally pose a significant risk and would not require an IND. Because of the danger of synergistic toxicity (i.e., enhanced effects from the combination) occurring with a new drug combination, if there are no data from the literature on its safety, the initial study of a new drug combination should ordinarily be performed under an IND. 

Synergistic toxicity may be anticipated when one agent interferes with the metabolism or elimination of the other agent; when both agents target the same metabolic pathway or cellular function; or when one agent targets signaling pathways that are reasonably expected to modulate sensitivity to the other agent. If it is determined that synergistic toxicity is likely, animal studies should be considered for determining a safe starting dose for the drug combination in humans.

4. Studies of new routes or schedules of administration not described in the approved labeling are generally exempt if there is sufficient clinical experience described in the literature documenting safety to determine that treatment is safe. On the other hand, initial experience with a new route of administration should be based on studies in animals, and an IND should be submitted.

5. Studies of high-dose therapy in cancer patients are likely to be considered exempt if the studies use adequately evaluated regimens that appear to have an acceptable therapeutic ratio for the population being studied. Similarly, phase 1 studies involving incremental changes from such well-described regimens are generally exempt.

B. Studies That Generally Are Not Exempt

As noted above, of the five criteria in § 312.2(b)(1), four are not protocol related and one is protocol related. The following are examples of general categories of studies of marketed cancer drugs that would likely not be exempt from IND regulation because of protocol-related issues.

1. Studies of cytotoxic drugs are normally not exempt in patients for whom cytotoxic therapy would not be considered standard therapy and would require special justification. Any use of cytotoxic agents in nonmalignant disease (e.g., rheumatoid arthritis, multiple sclerosis) would, most likely, be considered to alter the acceptability of the risk of the agent.
2. Studies of adjuvant chemotherapy (chemotherapy given after surgery to remove cancer) are likely not exempt for the following reasons:

- If the population studied has a low risk of cancer recurring after surgery, treatment with any toxic therapy may indicate a significantly increased risk.

- If standard adjuvant therapy is available and produces a survival benefit, substitution of new therapy for standard therapy poses a significant risk that the new therapy will not produce the same survival benefit.

- If adjuvant trials are properly designed, they usually will be able to demonstrate whether the new therapy is safe and effective, and such results may lead to a marketing application. As discussed earlier, under regulations at § 312.2(b)(1), all investigations intended to support marketing of a new product indication, significant change in product labeling, or a significant change in the advertising for a product require an IND. During FDA review of INDs intended to support marketing applications, the Agency will provide feedback about the acceptability of trial design for this purpose.

3. Studies involving substitution of a new agent of unproven activity are generally not exempt in settings where standard therapy provides a cure or increase in survival. For instance, in the first-line treatment of testicular cancer, ovarian cancer, breast cancer, leukemia, and lymphoma, studies of new agents without proven efficacy would likely not be exempt. In this case, the critical judgment is whether it is ethical to withhold standard therapy while testing a new agent.

4. Studies are generally not exempt in settings where animal studies should be conducted to determine a safe starting dose or schedule. For example:

- Initial studies of a marketed drug given by a new route of administration are likely not exempt.

- Unless adequately described in the literature, initial studies of new drug combinations should usually be performed under an IND because of the possible occurrence of synergistic toxicity. As noted earlier, synergistic toxicity may be anticipated when one agent interferes with the metabolism or elimination of the other agent; when both agents target the same metabolic pathway or cellular function; or when one agent targets signaling pathways that are reasonably expected to modulate sensitivity to the other agent.

- Initial studies in humans of changes in the schedule of drug administration should generally be submitted in an IND. Some drugs have demonstrated significantly greater toxicity when given by an alternative schedule (e.g., methotrexate demonstrates much more hematologic toxicity when given by prolonged administration compared to intermittent administration).

- Initial studies of drugs intended to be chemosensitizers, radiosensitizers, or resistance modulators should generally be submitted in an IND. Animal studies should be used to estimate the effect of the modulator on toxicity and to allow estimation of a safe starting dose in humans.
5. Studies intended to support approval of a new indication, a significant change in the product labeling, or a significant change in advertising are not exempt (§ 312.2(b)(1)(i), (ii)).

Please note: A clinical investigation is defined as “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects... except of a marketed drug in the course of medical practice.” (21CFR312.3). If you conduct a study in which you administer a drug not approved for marketing to human subjects, and accordingly, conduct a clinical investigation. You must submit an IND for the conduct of a clinical investigation with an investigational new drug as required by 21CFR 312.20(a).

Summary of FDA Regulations on Investigational Device Exemptions and Exemption from IDE Requirements
(21 CFR 812)

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification 510(k) submission to FDA.

Investigations covered under the IDE regulation are subject to differing levels of regulatory control depending on the level of risk. The IDE regulation distinguishes between significant risk (SR) and nonsignificant risk (NSR) device studies. Submit the device information and investigational plan to the IRB for concurrence with the sponsor’s SR/NSR determination.

The Investigational Device Exemptions (IDE) regulations describe the following types of device studies:

- Studies exempt from IDE requirements
- Studies subject to IDE requirements-
  - SR device research with formal IDE submission to FDA
  - NSR device research which with IRB approval is “considered” to have an approved IDE (sometimes referred to as an Abbreviated IDE). In this case the IRB acts as a surrogate for FDA.
Is an IDE Needed?

<table>
<thead>
<tr>
<th>Not typically needed</th>
<th>Yes, would be indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practice of Medicine</td>
<td>Studies that support research or marketing applications</td>
</tr>
<tr>
<td>Basic physiological research - Device is used to:</td>
<td>Studies of new indications for an approved device</td>
</tr>
<tr>
<td>Device is used to:</td>
<td>• Different age population</td>
</tr>
<tr>
<td>• test a physiological principle</td>
<td>• New condition or disease</td>
</tr>
<tr>
<td>• as a tool to address a research question</td>
<td>• Different area of the body</td>
</tr>
<tr>
<td>No intent to:</td>
<td>• Change in indication (treatment, diagnosis, prevention)</td>
</tr>
<tr>
<td>• collect safety and effectiveness data on the device</td>
<td>• Significant design changes</td>
</tr>
<tr>
<td>• develop the device for marketing</td>
<td></td>
</tr>
<tr>
<td>IDE exempt studies (see below)</td>
<td>Study results will be submitted to FDA</td>
</tr>
</tbody>
</table>

Studies Exempt from IDE

No IDE is required if the study meets one of the exemption categories in 21 CFR 812.2(c) that apply to human research. All criteria under each category must be true in order to meet the exemption category. IRB review and informed consent are still required.

**Category 1-2**

A clinical investigation with approved devices used in accordance with labeling. The device may have been approved for commercial distribution before May 28, 1976 or deemed substantially equivalent to a device commercially approved before May 28, 1976.

**Category 3**

A clinical investigation with *in vitro* diagnostic devices, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:
(i) is noninvasive;
(ii) does not require an invasive sampling procedure that presents significant risk;
(iii) does not by design or intention introduce energy into a subject; and
(iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. 21 CFR 812.2(c)(3).

**Category 4**

A clinical investigation with a marketed device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, unless testing is for determining safety and efficacy and/or puts subjects at risk.
## Category 7*

A clinical investigation of a custom device as defined in 21CFR812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

*Category 5 & 6 do not apply to human research.

### Submission and Regulatory Requirements for SR and NSR Device Studies

Clinical studies with SR devices must be approved by FDA and by an Institutional Review Board (IRB) before the study can begin. Studies with NSR devices must be approved only by the IRB before the study can begin. Ongoing regulatory requirements apply to both.

### Significant Risk Device Studies (standard IDE)

| Definition | A significant risk device means an investigational device that:
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;</td>
<td></td>
</tr>
<tr>
<td>• Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;</td>
<td></td>
</tr>
<tr>
<td>• Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or</td>
<td></td>
</tr>
<tr>
<td>• Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. <em>(21 CFR 812.3(m))</em></td>
<td></td>
</tr>
</tbody>
</table>

| FDA Submission Requirements | Sponsors are responsible for making the initial risk determination and ensuring the investigator presents it to the IRB. Unless FDA has already made a risk determination for the study, the IRB must review the sponsor's SR or NSR determination and modify the determination if the IRB disagrees with the sponsor. If FDA has already made the risk determination, the IRB does not need to duplicate this effort. Sponsors of investigational SR device studies must have an IDE application approved by FDA and IRB approval of the study before they may proceed. |

<table>
<thead>
<tr>
<th>Ongoing Regulatory Requirements</th>
<th>SR device studies must follow <strong>all regulatory requirements</strong> in the IDE regulations in 21 CFR 812.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Responsibilities of Sponsors for Significant Risk Device Studies</td>
<td></td>
</tr>
<tr>
<td>• Responsibilities of Investigators for Significant Risk Device Studies</td>
<td></td>
</tr>
<tr>
<td>• ORI Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Devices (pg. 1-2)</td>
<td></td>
</tr>
</tbody>
</table>

### Nonsignificant Risk Device Studies (abbreviated IDE)

| Definition | An NSR device study is one that does not meet the definition for an SR device study. |
Sponsors are responsible for making the initial risk determination and ensuring the investigator presents it to the IRB. Unless FDA has already made a risk determination for the study, the IRB must review the sponsor's SR or NSR determination and modify the determination if the IRB disagrees with the sponsor. If FDA has already made the risk determination, the IRB does not need to duplicate this effort.

However, if FDA has not made the risk determination or the IRB disagrees with the NSR determination made by a sponsor, then the IRB must notify the investigator and, where appropriate, the sponsor, that the study involves a significant risk device. If the IRB agrees with the NSR determination and approves the study, the study is "considered" to have an approved application for IDE. No formal submission to FDA is required. The IRB serves as an FDA surrogate for NSR studies.

NSR device studies must follow abbreviated regulatory requirements in 21 CFR 812.2(b).

- Responsibilities of Sponsors of Nonsignificant Risk Device Studies
- Responsibilities of Investigators for Nonsignificant Risk Device Studies
- ORI Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Devices (pg. 2-3)

Where questions still exist, sponsor-investigators should contact the appropriate FDA review division for guidance.

Contacts for Center for Devices and Radiological Health
- 800-638-2041 or 301-796-7100
- IDE Inquiries: 301-796-5640
dsmica@cdrh.fda.gov

The FDA website outlines the FDA's Procedure for responding to inquiries regarding need for an IDE -
www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm126598.htm

Sources:
Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors, Significant Risk and Nonsignificant Risk Medical Device Studies, January 2006

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors Frequently Asked Questions About Medical Devices, January 2006

Code of Federal Regulations, Title 21 CFR 812, Investigational Device Exemptions

PRIM&R webinar, Investigational Device Exemption Overview, Marian Serge, RN, Division of Bioresearch Monitoring, Office of Compliance CDRH, FDA, 2009.

J:\Master Outreach Documents\Survival Handbook\D - Guidance-Policy-Educational\97-Summary_of_FDA_Regulations_on_Exemption_from_IDE_Requirements.doc 10-22-09, updated 1/31/11
Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Devices

This document provides an overview of the Food and Drug Administration (FDA) requirements for sponsors of device research trials. The IRB sponsor-investigator mandatory training provides additional information for new sponsor-investigators.

This overview is divided into two sections:
1) responsibilities of sponsors for significant risk device studies; and
2) responsibilities of sponsors for nonsignificant risk device studies.

For detailed descriptions consult the referenced FDA regulation or the FDA’s IDE Responsibilities Website.

FDA expectations regarding appropriate delegation, supervision, and training for personnel involved in clinical investigations is described in the FDA Guidance for Industry: Investigator Responsibilities-Protecting the Rights, Safety, and Welfare of Study Subjects.

Major Responsibilities of Sponsors with Significant Risk Device Studies

1. Submit a complete IDE application to FDA. (21 CFR 812.20)
2. Submit the investigational plan and report of prior investigations (21 CFR 812.25 and 21 CFR 812.27) to the IRB at each institution where the investigation is to be conducted.
3. Obtain FDA & IRB approval for IDE. (21 CFR 812.42)
4. Select investigator(s) with appropriate training and experience. (21 CFR 812.43)
5. Obtain a signed agreement from the investigator with the required FDA documents. (21 CFR 812.43)
6. Select a monitor in accordance with FDA regulations. (21 CFR 812.43)
7. Ship investigational devices only to qualified investigators. (21 CFR 812.43)
8. Supply the investigator(s) with copies of the investigational plan and copies of prior device investigations. (21 CFR 812.45)
9. Label the device in accordance with FDA labeling provisions of the IDE regulation and with the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use." (21 CFR 812.5)
10. Ensure that investigator(s) are complying with FDA, IRB and sponsor requirements. (21 CFR 812.46)
11. Conduct an evaluation of unanticipated adverse events and terminate the study if necessary. (21 CFR 812.46)
12. Resume terminated studies only after receiving approval from the FDA and IRB. (21 CFR 812.46)
Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Devices

13. Ensure that each investigator obtains consent for each subject before being enrolled in the study. (21 CFR 50)
14. Maintain accurate and complete records in accordance with FDA regulations. (21 CFR 812.140)
15. Permit and facilitate monitoring and auditing by the IRB or inspection by federal or state regulatory agencies as appropriate. (21 CFR 812.145)
16. Provide required reports to IRB, investigator(s) and FDA in a timely manner. (21 CFR 812.150)
17. Limit promotion of the device. Commercialization, promotion, and misrepresentation of an investigational device and prolongation of the study are prohibited. (21 CFR 812.7)
18. Comply with federal regulations regarding emergency use. (21 CFR 812.47)
19. Register the study at ClinicalTrials.gov per the Food and Drug Administration Amendments Act (FDAAA) of 2007 (Public Law 110-85). For requirements and instructions on registering trials see the information page at http://clinicaltrials.gov/ct2/manage-recs/fdaaa. To obtain access to the University of Kentucky organizational account on ClinicalTrials.gov see guidance at http://www.ccts.uky.edu/BRIC/ClinicalTrialsgov.aspx.

Major Responsibilities of Sponsors with Nonsignificant Risk Device Studies –

Nonsignificant risk device sponsors must comply with the abbreviated IDE requirements under 21 CFR 812.2 (b):

1. Select investigator(s) with appropriate training and experience. (21 CFR 812.43)
2. Select a monitor in accordance with FDA regulations. (21 CFR 812.43)
3. Ship investigational devices only to qualified investigators. (21 CFR 812.43)
4. Supply the investigator(s) with copies of the investigational plan and copies of prior device investigations. (21 CFR 812.45)
5. Label the device in accordance with FDA labeling provisions of the IDE regulation and with the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use". (21 CFR 812.5)
6. Obtain IRB approval of the investigation as a nonsignificant risk device study and maintain IRB approval during the investigation. (21 CFR 812.2)
7. Ensure that investigator(s) are complying with FDA, IRB and sponsor requirements. (21 CFR 812.46)
Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Devices

8. Conduct an evaluation of unanticipated adverse events and terminate the study if necessary. (21 CFR 812.46)

9. Resume terminated studies only after receiving approval from the IRB and if terminated due to an unanticipated adverse device effect, also obtain FDA approval to resume the study. (21 CFR 812.46)

10. Ensure that each investigator obtains consent for each subject unless the IRB grants a waiver under 21CFR56.109(c).

11. Ensure that each investigator maintains accurate and complete records in accordance with FDA regulations and reports the results to the appropriate parties. (21 CFR 812.140 & 21 CFR 812.150)

12. Permit and facilitate monitoring and auditing by the IRB or inspection by federal or state regulatory agencies as appropriate. (21 CFR 812.145)

13. Limit promotion of the device. Commercialization, promotion, and misrepresentation of an investigational device and prolongation of the study are prohibited. (21 CFR 812.7)

14. Register the study at ClinicalTrials.gov per the Food and Drug Administration Amendments Act (FDAAA) of 2007 (Public Law 110-85). For requirements and instructions on registering trials see the information page at http://clinicaltrials.gov/ct2/manage-recs/fdaaa. To obtain access to the University of Kentucky organizational account on ClinicalTrials.gov see guidance at http://www.ccts.uky.edu/BRIC/ClinicalTrialsgov.aspx.


Revised 11/29/12

J:\Master Outreach Documents\Survival Handbook\D - Guidance-Policy-Educational\45-Revised_IDE_Document.doc

Return to TOC
Summary of FDA Requirements For Investigators Who Are Also Considered Sponsors of New Drugs

This document provides an overview of the Food and Drug Administration (FDA) requirements for Sponsors with Investigational New Drugs (INDs). The IRB sponsor-investigator mandatory training provides additional information for new sponsor-investigators.

For detailed descriptions, consult the referenced FDA regulation.


Major Responsibilities of Sponsors with IND Studies

Enter the Code of Federal Register (CFR) citation in the FDA Title 21 Data Base for details.

1. Submit IND application, form 1571 and other required documents to FDA. (21 CFR 312.23)
2. Label the investigational drug in accordance with FDA regulations. (21 CFR 312.6)
3. Limit promotion. If any promotion is done, it must be done in accordance with IRB and FDA requirements. (21 CFR 312.7)
4. Select qualified investigators based on training and experience. (21 CFR 312.53)
5. Ship investigational drugs only to investigator(s) participating in the investigation. (21 CFR 312.53)
6. Obtain FDA Form 1572 from the investigator(s). (21 CFR 312.53)
7. Obtain a written statement that the investigator(s) will conduct the study as outlined in the protocol. (21 CFR 312.53)
8. Obtain relevant financial information from the investigator(s). (21 CFR 312.53)
9. Select a monitor to oversee the progress of the investigation. (21 CFR 312.53)
10. Comply with FDA regulations regarding emergency use. (21 CFR 312.54)
11. Keep investigator(s) informed on the safety and effectiveness of the drug. (21 CFR 312.55)
12. Monitor the progress of all IND investigations. (21 CFR 312.56)
13. Terminate investigator(s) participation when investigator(s) fails to follow protocol. (21 CFR 312.56)
14. Review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from each investigator(s). (21 CFR 312.56)
15. Send safety reports to FDA according to the 2010 final rule, Investigational New Drug Safety Reporting Requirements for human drug and biologics (21 CFR 312.32) and for Bioavailability and Bioequivalence Studies (21 CFR 320).
16. Discontinue the study if the investigational drug presents an unreasonable and significant risk to subjects. (21 CFR 312.56)
17. Notify the FDA, IRB and the investigator(s) if the study is discontinued. (21 CFR 312.56)
18. Maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. (21 CFR 312.57)
19. Maintain complete and accurate records of payments made to clinical investigator(s). (21 CFR 312.57)
20. Permit and facilitate monitoring and auditing by the IRB or inspection by federal or state regulatory agencies (e.g. FDA or Drug Enforcement Administration for investigations of controlled substances) as appropriate. (21 CFR 312.58)
21. Assure that investigator(s) return all unused investigational drugs. (21 CFR 312.59)
22. Require investigator(s) to maintain adequate drug records (21 CFR 312.62)
23. Require investigator(s) to keep case histories on each individual administered the investigational drug or employed as a control in the investigation. (21 CFR 312.62)
24. Collect reports (financial, progress, safety, and final report) from investigator(s). (21 CFR 312.64)
25. Require investigator(s) to meet local IRB requirements. (21 CFR 312.66)
26. Require investigator(s) to store the investigational drug in a secure area. (21 CFR 312.69)
27. Register the study at ClinicalTrials.gov per the Food and Drug Administration Amendments Act (FDAAA) of 2007 (Public Law 110-85). For requirements and instructions on registering trials see the information page at http://clinicaltrials.gov/ct2/manage-recs/fdaaa. To obtain access to the University of Kentucky organizational account on ClinicalTrials.gov see guidance at http://www.ccts.uky.edu/BRIC/ClinicalTrialsgov.aspx.

Revised 11/29/12

J:\Master Outreach Documents\Survival Handbook\D - Guidance-Policy-Educational\44- Revised_IND_Document.doc
FDA's Bioresearch Monitoring (BIMO) program is a comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research. The BIMO Program was established to assure the quality and integrity of data submitted to the agency in support of new product approvals, as well as, to provide for protection of the rights and welfare of the thousands of human subjects involved in FDA regulated research. It has become a cornerstone of the FDA preapproval process for new medicines, medical devices, food and color additives and veterinary products introduced to the U.S. consumer.

The program is implemented domestically and internationally through seven multi-center compliance programs\(^1\) resulting in over 1000 inspections annually. These compliance programs address inspections of nonclinical testing laboratories in accordance with Good Laboratory Practice (GLP), clinical investigators in accordance with Good Clinical Practice (GCP), sponsors/Contract Research Organizations (CROs)/clinical trial monitors, in vivo bioequivalence facilities, and institutional review boards (IRBs).

The BIMO program is unique in the scope of its compliance programs and regulations which are shared by all six of FDA's Centers (CBER, CDER, CDRH, CFSAN, CTP, CVM).

The program also has international and interagency components. The Bioresearch Monitoring Program Coordinator, located organizationally within FDA's Office of Global Regulatory Operations and Policy (OGROP), Office of Regulatory Affairs (ORA), Office of Policy and Risk Management (OPRM), Medical Products and Tobacco Policy Staff (MPTPS), is responsible the coordination of policy related to the BIMO Program.

**Program Coordinator**

**Contact**

Robert Hummel  
Medical Products and Tobacco Policy Staff, Office of Policy and Risk Management, Office of Regulatory Affairs, Office of Global Regulatory Operations and Policy, US Food and Drug Administration  
Voice: (301) 796-4510  
Email: robert.hummel@fda.hhs.gov  
Mail: Robert Hummel, US Food and Drug Administration, Office of Global Regulatory Operations and Policy, Office of Regulatory Affairs, Office of Policy and Risk Management, Medical Products and Tobacco Policy Staff, Element Building, 12420 Parklawn Drive, Room 4152, Rockville, MD 20857

Page Last Updated: 04/24/14
Summary of Requirements for Department of Defense (DoD) 
Supported Human Research

In addition the Common Rule, human Research supported by the DoD is subject to requirements and ethical standards outlined in the Department of Defense Directive (DoDD) 3216.02. The University of Kentucky DoD/IRB/ORI Coordination SOP describes policies and procedures for review, conduct and oversight of human research supported by the DoD.

Support of a study generally means the provision of funding, personnel (both military and civilian DoD employees), facilities, and any other resource. Office of Research Integrity (ORI) Staff may:

☑ Discuss with Principal Investigator (PI) to Confirm the proposed research is DoD supported.

☑ Request PI contact DoD Component (i.e., Army, Navy) supporting the research to confirm additional human subject research requirements. The Human Research Protection Official (HRPO) for specific Components provides administrative review and approval to confirm protocol is compliant with federal and DoD requirements.

General DoD Requirements

☑ Use the IRB DoD Checklist for DoD supported research to facilitate IRB review.

1. Scientific Merit

The IRB must consider the review by the investigator’s department relative to scientific merit of the research.

☑ Ensure scientific review discussions are documented in IRB review materials or minutes.

2. Research Monitor

An independent Research Monitor (RM) is required for greater than minimal risk research. While not mandated, the IRB may at its discretion, require an RM be assigned to a study or portion of research that is not greater than minimal risk. The investigator may recommend individuals for this role; however the RM operates under the direction of and reports to the IRB. The RM has the authority to stop a research study, remove individuals from a study, observe group recruitment, and take any other steps to protect the safety and well-being of subjects until the IRB can assess the research monitor’s report.

☑ Ensure IRB has curriculum vita and any other material to assess proposed RM’s expertise and credentials.

☑ Ensure IRB determines and documents RM’s:
  • educational and professional experience
  • independence from the research personnel
  • designated authorities and responsibilities

☑ Ensure investigator provides the IRB with a letter from the RM accepting the assignment and responsibilities.
Summary of Requirements for Department of Defense (DoD) Supported Human Research

3. **Classified Research**

Research involving classified information must be reviewed by the full convened IRB; requires descriptions and clarifications be included in the informed consent process (waiver is prohibited); and must be approved by the Secretary of Defense, prior to initiation.

4. **Survey Research**

If DoD supported study involves survey research or surveys in DoD personnel, additional level of DoD review is typically required.

5. **Compensation**

Dual compensation rules limit subject payment. Options vary depending on participation on or off active duty and source of funds for payment.

- Ensure that investigator is aware of compensation policies as applied to proposed research if subject payment is involved.

For DoD supported research involving more than minimal risk, subjects are provided with 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.

Additional requirements may apply to collaborative research where the DoD component is engaged in the conduct of the research. Additional injury payment rules apply to research conducted by DoD; not research supported by DoD.

6. **International citizen populations**

Research involving international citizen populations should adhere to any local applicable laws, regulations, customs, and required local ethics review. Consult the current edition of the *International Compilation of Human Research Standards* for reference.

- Ensure researcher has permission to conduct research in the country by certification or local ethics review.
- Ensure knowledge of local context is met by standing or ad hoc IRB member or cultural consultant.

7. **Armed Services personnel, Military or Civilian DoD Employees**

If study is a clinical investigation including Armed Services personnel, women and minorities must be included as subjects.

Research with DoD personnel (military or civilian DoD employees) must include a recruitment plan that incorporates safeguards to minimize undue influence from superiors in the chain of command (i.e.
Summary of Requirements for Department of Defense (DoD)  
Supported Human Research

Superiors may not be present at time of recruitment and must be provided a separate opportunity to consider participation themselves.

If research includes military personnel, the HRPO may require PIs to obtain permission from local command to allow subject’s participation during or off duty particularly if research could impact the Service members ability to perform his/her military duties.

If recruitment for a greater than minimal risks study occurs in a group setting (e.g. involved a percentage of a unit), the research monitor must observe the recruitment and informed consent process to ensure voluntariness. This is required for military, (not civilian), DoD personnel, but the IRB may require use of this safeguard for civilian DoD employees when appropriate.

8. Humans as Experimental Subjects

The following additional requirements apply only to the sub-category of human research entitled, 
*Research involving Humans as Experimental Subjects*. This is a category of research conducted for the purpose of obtaining data regarding the effect of an intervention or interaction.

- For Research involving Humans as Experimental Subjects, ensure that:
  - informed consent is obtained;
  - waiver of informed consent is never granted (unless prohibition waived by Secretary of Defense based on specific criteria); and
  - the research intends and has potential to benefit the subjects in studies where consent could be obtained from a subject’s legally authorized representative.

9. Planned emergency research

As planned emergency research meets the above definition of research involving humans as experimental subjects, a waiver of informed consent is prohibited unless DoD has issued a waiver.

10. Vulnerable Subject Subparts

The DoD has adopted 45 CFR 46 Subpart B (pregnant women, fetuses, and neonates), C (prisoners), and D (children) with limitations and modifications.

- Subpart B:
  - For the purposes of applying Subpart B risk-benefit analysis, DoD replaces the phrase “biomedical knowledge” with “generalizable knowledge”.
  - The DoD limits the applicability of Subpart B to research involving:
    - pregnant women as participants in research that is more than minimal risk and includes interventions or invasive procedures to the woman or the fetus; or
Summary of Requirements for Department of Defense (DoD) Supported Human Research

- fetuses or neonates as participants.
  - Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.

- Subpart C:
  - For research intended to enroll prisoners, the DoD does not allow review by expedited mechanism. When the IRB reviews research involving prisoners, at least one prisoner representative is present.
  - Epidemiological research is also allowable when: the research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease; the research presents no more than minimal risk; and the research presents no more than an inconvenience to the participant.
  - If a PI attests that it is in the best interest of a subject who becomes a prisoner to continue participation in the research, the DoD allows the IRB chair to make a preliminary determination until the convened IRB (and DoD Component if applicable) can review the request. Otherwise, the IRB may require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB with consultation from the prisoner representative, can review this request to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy.
    - If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant’s confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-participant to continue.

- Subpart D:
  - The DoD does not apply subpart D to active duty personnel under the age of 18 as it considers all active duty military to be adults with legal capacity to participate in DoD supported research.

Should the DoD protocol include or have potential to enroll any vulnerable population protected under the Common Rule subparts, refer to the DoDD 3216.02 and/or the supporting Component for specific determinations required on the part of the IRB.

Determinations authorizing or requiring any action by an official of HHS about any requirements of subparts B-D would be submitted to and authorized by the Assistant Secretary of Defense for Research and Engineering ASD(R&E).
Summary of Requirements for Department of Defense (DoD) 
Supported Human Research

11. Detainees

☑ Research with detainees is prohibited (or prisoners of war). Prohibition of detainee participation may not apply to specific research involving investigational drugs and devices when the same products would be offered to US military personnel in the same location for the same condition.

12. Multi-site or Collaborative Research

Standard requirements apply to multi-site or collaborative research supported by the DoD.

- Ensure investigators conducting DoD-sponsored multi-site research have provided the IRB with information on the federal assurance(s) held by collaborating institutions, including the existence of any DoD Addendum or other direct DoD assurance.

DoD Components (Army, Navy, Air Force, etc.)

1. DoD Components may have additional requirements beyond those outlined in the OHRP FWA. The Component will communicate the unique requirements by providing the investigator with an early communication applicable to the proposed research, (common Army practice) or by requiring an FWA Addendum which conveys the unique requirements (common Navy and Air Force practice). Once a DoD Addendum is in place it covers all DoD research sponsored or initiated by that Component.

☑ Ensure investigator has provided the IRB with any specific unique requirements outlined in DoD Component communication or FWA addendum.

Potential additional Component requirements may include:

- Requirement for an FWA Addendum
- Specific educational or certification requirements
- Documentation submission (e.g. meeting minutes for all meetings in which research is reviewed; continuation review approval or materials)
- Reporting or record retention requirements
- Additional levels of review

2. The investigator submits documentation of IRB review and approval to the DoD Component. The HRPO provides an administrative review to confirm the protocol is compliant with Federal and DoD requirements and to concur with UK IRB’s determinations (i.e., activity not HSP research; research is exempt; level of risk; protocol approval).

☑ Investigator should not initiate the study until approved by HRPO or relevant Component designee.
3. Standard reporting and recordkeeping procedures apply unless additional requirements are made by the supporting DoD Component. Any determinations of serious or continuing non-compliance of DoD supported research must be promptly (no longer than within 30 days) reported to the DoD HRPO.
Summary: The No Child Left Behind Act of 2001 (Public Law 107-110) amended the Protection of Pupil Rights Amendment (PPRA), which concerns surveys of students, in two ways: First, it added an eighth category to the categories of protected information in surveys of minors that were already covered by PPRA. Second, it gave parents new rights with regard to the surveying of minor students, the collection, disclosure, or use of information from students for marketing purposes, and certain non-emergency medical examinations.

PPRA, as amended, has two sets of requirements for surveys:

1. Requirements that apply to “protected information” surveys that are funded in whole or in part by the U.S. Department of Education.
2. Requirements that apply to “protected information” surveys that are funded by sources other than the U.S. Department of Education and that are administered or distributed by education institutions that receive funds from any Department of Education program (i.e. public elementary and secondary schools and some private schools).

PPRA lists eight categories of protected information for survey responses:

1. political affiliations of student or student's parent;
2. mental or psychological problems of student or student's family;
3. sex behavior or attitudes;
4. illegal, anti-social, self-incriminating or demeaning behavior;
5. critical appraisals of others with whom students have close family relationships;
6. legally recognized privileged or analogous relationships;
7. religious practices, affiliations or beliefs of student or student's parent;
8. income.

PPRA has implications for IRBs in applying the Common Rule criteria for waiving informed consent (in section 116(d) of the Common Rule). Specifically the second IRB criterion: "research does not adversely affect the rights and welfare of subjects" is impacted because of the "rights" that PPRA gives parents.

Practical Implications in Applying the Common Rule Waiver Requirement pertaining to rights and welfare:

First Set of Requirements: US Department of Education Funded Protected Information Surveys

- Does the research involve "protected information" surveys?
- Are the surveys U.S. Department of Education-funded in whole or part?
- Are the surveys "required"?

If the answer is yes to the three questions, PPRA affords parents the right to provide active consent. Under the circumstances, it would be difficult for an IRB to determine that the "rights and welfare" criterion for waiving informed consent entirely could be met; therefore, prior written parental consent would be required, even if the IRB determined that some of the basic elements of informed consent specified in section 116(a) could be waived as inappropriate to the activity.

[The U.S. Department of Education has not yet written regulations providing guidance about some of the key terms in the current law. For example, the Department has not taken a position about whether the word "required" should be interpreted to mean that surveys that are clearly voluntary are exempt from PPRA requirements. Also, the law does not directly address the question of whether anonymous
surveys are exempt from PPRA because anonymous surveys do not provide individually identifiable information about students or their families. Until the Department issues revised regulations implementing PPRA, IRBs need to use their judgments in complying with the first set of requirements.

**Second Set of Requirements for Protected Information Surveys that are NOT Funded by the U.S. Department of Education and that are administered or distributed by education institutions that receive funds from any U.S. Department of Education administered program (i.e., public schools and some private schools)**

- Do the surveys include protected information?
- Are the surveys being administered or distributed by schools that receive any U.S. Department Education funds?

[Note that in this set of requirements there is no language about students being "required" to respond to the survey, so here the issue of voluntariness appears to be moot].

If the answer is yes to both questions, PPRA affords parents the right to inspect the surveys before they are administered or distributed and to opt the student out of the surveys.

For IRBs, these requirements suggest that local schools have the discretion to set up their own individual policies for non-US Department of Education protected information surveys. For example, local schools can choose whether to have an active written consent policy or some other policy such as passive consent.

IRBs will have to decide how they will handle these requirements in those protocols where the investigators are requesting passive consent. For example, an IRB might require that if an investigator asks for passive consent procedures, that he/she must also document that the procedures are consistent with the policy of the local school(s) to be included in the research sample. The IRB then can use that information in determining if the "rights and welfare" criterion for waiving informed consent has been met.

### PROVISIONS OF THE PPRA

A list of the general PPRA provisions is included below and the specific amendments are detailed at [www2.ed.gov/policy/gen/guid/fpco/hottopics/ht04-10-02.html](http://www2.ed.gov/policy/gen/guid/fpco/hottopics/ht04-10-02.html).

**U.S. Department of Education Surveys**

Subsection (a) of the legislation was not changed. Subsection (b) added an additional category Number 7 and made minor changes to the existing seven categories. This provision applies to surveys funded in whole or part by any program administered by the U. S. Department of Education (DoED).

**PPRA provides:**

- that schools and contractors make instructional materials available for inspection by parents if those materials will be used in connection with a DoED-funded survey, analysis, or evaluation in which their children participate; and

- that schools and contractors obtain prior **written parental consent** before minor students are required to participate in any DoED-funded survey, analysis, or evaluation that reveals information concerning:
  1. political affiliations or beliefs of the student or the student’s parent;
  2. mental and psychological problems of the student or the student’s family, sex, behavior or attitudes;
  3. illegal, anti-social, self-incriminating, or demeaning behavior;
  4. critical appraisals of other individuals with whom respondents have close family relationships;
5. legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers;
6. religious practices, affiliations, or beliefs of the student or student’s parent; or,
7. income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program).

*Prior consent means:
- Prior consent of the student, if the student is an adult or emancipated minor; or
- Prior written consent (permission) of the parent or guardian, if the student is an unemancipated minor.

Subsections (a) and (b) of PPRA generally apply when a survey is funded, at least in part, by any program administered by the Secretary of Education.

**Surveys Funded by Sources Other than U.S. Department of Education**

The new provisions (contained in subsection c) apply (as does FERPA) to educational agencies or institutions that receive funds from any program of the Department of Education. Thus, public elementary and secondary schools are subject to the new provisions of PPRA. The amendment requirements include:

- Schools are required to develop and adopt policies, in conjunction with parents, regarding the following:
  1. The right of parents to inspect, upon request, a survey created by a third party before the survey is administered or distributed by a school to students;
  2. Arrangements to protect student privacy in the event of the administration of a survey to students, including the right of parents to inspect, upon request, the survey, if the survey contains one or more of the same eight items of information noted above;
  3. The right of parents to inspect, upon request, any instructional material used as part of the educational curriculum for students;
  4. The administration of physical examinations or screenings that the school may administer to students;
  5. The collection, disclosure, or use of personal information collected from students for the purpose of marketing or selling, or otherwise providing the information to others for that purpose; and
  6. The right of parents to inspect, upon request, any instrument used in the collection of information, as described in number 5.

- Local educational agencies (LEAs) must “directly” notify parents of these policies and, at a minimum, provide the notice at least annually.

- In the notification, the LEA shall offer an opportunity for parents to opt out of (remove their child) from participation in the administration of any third party (non-Department of Education funded) survey containing one or more of the above described eight items of information.

**US Department of Education Contact:** The Family Policy Compliance Office is the office charged with administration of PPRA [http://www.ed.gov/offices/OM/fpco/ppra/parents.html](http://www.ed.gov/offices/OM/fpco/ppra/parents.html)
Family Policy Compliance Office
U.S. Department of Education
400 Maryland Avenue, SW
Washington, D.C. 20202-5920
Phone: 1-800-USA-LEARN (1-800-872-5327)
Guidance regarding the Family Education Rights and Privacy Act (FERPA) may be found at [http://www.research.uky.edu/ori/ORIForms/31-FERPA-Summary.pdf](http://www.research.uky.edu/ori/ORIForms/31-FERPA-Summary.pdf)

Prepared: Ada Sue Selwitz, MA, University of Kentucky, March 2003, Updated 2006, 12/ 2012, 7/18/13
J:\Master Outreach Documents\Survival Handbook\D - Guidance-Policy-Educational\60-Protection-Pupil-Rights-Amendment.doc
Summary of Requirements and University of Kentucky (UK) Resources for United States Department of Education (DoED) Supported or Regulated Human Research

Human research supported or regulated by the US DoED is subject to additional requirements and ethical standards set forth in 34 CFR 97 including Subpart A (general) and Subpart D (protections for children); 34 CFR 99 (Family Educational Rights and Privacy Act); 34 CFR 350, 356 (Disability and Rehabilitation Research) and 34 CFR 98 (Protection of Pupil Rights Amendment). Related guidance and university policies are referenced below.

General DoED Requirements

1. **National Institute on Disability and Rehabilitation Research** [34 CFR 350, 356]  
   - For research supported by the National Institute on Disability and Rehabilitation Research, the IRB membership includes at least one person primarily concerned with the welfare of children with disabilities or individuals with mental disabilities when the study purposefully requires their inclusion as research participants.

2. **Conditions for allowing exceptions to parental or student consent to release student records for research under FERPA [34 CFR 99]**:  
   - FERPA is a federal law that protects the privacy of personally identifiable information contained within a student’s educational record at K-12 and postsecondary institutions.

   - [The University of Kentucky Office of the Registrar FERPA website](#) outlines what information is designated as “directory” information at UK and what information may be released in general without a student’s consent. Each institution designates what information is considered directory information.

   - [UK IRB FERPA guidance](#) outlines conditions under which student records can be disclosed without consent for research purposes as well as guidance for researchers on accessing educational records.

   - ORI forwards any protocols that include requests to access information without consent to UK’s legal counsel. Legal counsel will make the final determination if the study meets the FERPA criteria to release personally identifiable educational information without a signed consent form. Legal counsel develops appropriate agreements as required by *[34 CFR 99.31]*.

*Elements of Written Agreement:* (1) Specifies the purpose, scope, and duration of the study or studies and the information to be disclosed; (2) Requires the organization to use personally identifiable information from education records only to meet the purpose or purposes of the study as stated in the written agreement; (3) Requires the organization to conduct the study in a manner that does not permit personal identification of parents and students, as defined in this part, by anyone other than representatives of the organization with legitimate interests; and (4) Requires the organization to destroy all personally identifiable information when the information is no longer needed for the purposes for which the study was conducted and specifies the time period in which the information must be destroyed.

3. **Protection of Pupil Rights Amendment (PPRA)**  
   - US Department of Education, PPRA [34 CFR 98] is a federal law that affords certain rights to parents of minor students with regard to surveys that ask questions of a personal nature. It outlines requirements that apply to “protected information” surveys that are funded in whole or in part by the DoED and to surveys that are funded by sources other than the DoED that are administered by or in institutions that receive DoED support.
Summary of Requirements and University of Kentucky (UK) Resources for United States Department of Education (DoED) Supported or Regulated Human Research

- Access to instructional material used in a research or experimentation program: All instructional material—including teachers' manuals, films, tapes, or other supplementary instructional material—which will be used in connection with any research or experimentation program or project must be available for inspection by the parents or guardians of the children engaged in such research. *Research or experimentation program or project* means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques. *Children* are persons enrolled in research not above the elementary or secondary education level, who have not reached the age of majority as determined under state law.

- See the [Department of Education PPRA guidance](#) for a list of protected information for survey responses and practical implications in applying IRB informed consent waiver requirements pertaining to the rights and welfare of minor students.

As described in the DOE HSP Resource Book, DOE supported research protocols encompass a broad range of medical and scientific technologies from nuclear fission to human biology. Studies may include device testing, tissue testing, medical or exposure records, and categories of subjects such as worker subgroups.

The Principal Investigator (PI) and IRB may refer to the DOE Directive O 443/1B for interpretation of what meets the definition of human subject research relative to DOE sponsored research. In 2013, the DoE issued a memorandum defining when activities that intentionally modify or manipulate human occupied environments require IRB review. This memo applies to the following studies:

- Generalizable* studies in human environments (e.g., occupied homes and offices, classrooms, and transit centers like subway systems and airports) that use tracer chemicals, particles, and/or other materials, such as perfluorocarbons, to characterize airflow.

- Generalizable* studies in occupied homes and/or offices that:
  - manipulate the environment to achieve research aims, e.g., increasing humidity and/or reducing influx of outside air through new energy-saving ventilation systems.
  - test new materials (e.g., sequentially changing the filter materials in the HVAC system while monitoring the effects on air quality and energy use).
  - involve collecting information on occupants’ views of appliances, materials, or devices installed in their homes or their energy saving behaviors through surveys and focus groups. Some surveys may be online surveys administered through providers such as Amazon Mechanical Turk and Survey Monkey.

*Generalizable should be viewed in terms of contribution to knowledge within the field of study.

The PI is responsible for working with designated officials at the DOE such as a Human Subject Protection (HSP) Program manager.

In conducting its review, the IRB assesses risks associated with the research and whether the individuals to be included in the research will be properly informed and protected. The IRB determines the level of review and sends a letter to the investigator indicating that the research has been approved in accordance with DOE expectations and will be monitored by the IRB. For additional information see the DOE process flowchart.

---

1. **Confidentiality and Data Security**

   - For DOE supported research utilizing or collecting personally identifiable information (PII) or protected health information (PHI), the investigator completes the [Investigator Checklist for Verification of Compliance with the Department of Energy (DOE) Requirements for the Protection of](http://humansubjects.energy.gov/other-resources/pii.htm)
PII/PHI. The investigator signs the checklist to indicate understanding and intent to comply with the technical requirements. In general, the IRB uses the information to verify that the investigator has a clear and detailed plan for:

- protecting PII/PHI including reasonable safeguards to prevent unauthorized use or disclosure;
- immediate notification of any incident involving potential compromise or loss of PII data;
- making no further use or disclosure except when approved by the IRB and DOE; and
- encryption of any data to be transferred.

PII/PHI transferred from one organization to another as part of a human research project (when/as authorized by the approving IRBs, the responsible DOE Program Office, and the research/screening participant) must first be encrypted consistent with PII protection requirements stated in DOE M 205.1-7 using a program such as Entrust.

For assistance in complying with technical requirements, the PI may consult departmental Information Technology (IT) personnel or University of Kentucky IT Security personnel [http://www.uky.edu/ukit/shared/security].

2. Reporting

The DoE reporting requirements are more stringent than the University of Kentucky (UK) requirements relative to reporting timelines. In addition to reporting to the UK IRB (using UK reporting forms), the investigator notifies the DoE as follows.

- The notification period for reporting unanticipated problems for loss or compromising of data differs, depending on whether PII/PHI is involved.
  
  The investigator notifies the DoE HSP Program Manager immediately, (upon discovery), of a suspected or confirmed data breach involving PII or PHI in printed or electronic form and reported to the DOE-Cyber Incident Response Capability in accordance with the requirements of DOE O 206.1.

  The investigator informs the DoE HSP Program Manager regarding any corrective actions planned or taken.

- DoE requires prompt reporting, (within 48 hours), and coordination with, and approval from the HSR Program Manager in determining plans to correct any noncompliance or to deal with unanticipated problems.

  The investigator notifies the DoE HSP Program Manager in writing within 48 hours, with a description of corrective actions taken, and shall concur on the plan for any remaining corrective actions, following:

  a) significant adverse events, unanticipated problems, and complaints about the research, suspension or termination of IRB approval of research;

  b) known or potential incidents of noncompliance with requirements of this Order, 10 CFR Part 745, 45 CFR Part 46.

- The PI is also responsible for implementing any IRB or DOE required corrective action.
Summary of Department of Justice (DOJ), National Institute of Justice (NIJ), and Bureau of Prisons Human Research Requirements

Human research which is supported by the National Institute of Justice (NIJ) is governed by the Department of Justice (DOJ) regulations for the protection of human subjects (28 CFR 46) and the DOJ Confidentiality of Identifiable Research and Statistical Information regulations (28 CFR 22). Of the many DOJ agencies, the NIJ has a primary mission to advance scientific research.

In addition, research conducted within the federal Bureau of Prisons (BoP) is subject to additional requirements set forth in 28 CFR 512.

In addition to this summary guidance, an IRB Checklist is available for use by the IRB in conducting review of DOJ regulated research.

Investigator requirements for research funded by NIJ:

Confidentiality Statements:

- All researchers and research staff are required to sign employee confidentiality statements as a condition of grant or proposal approval by the NIJ. Certificates are maintained by the responsible Research Investigator.

Privacy Certificates:

- All NIJ funded projects are required to have a Privacy Certificate approved by the NIJ human subjects protection officer. The Privacy Certificate is the grant applicant’s assurance that he/she understands his/her responsibilities to protect the confidentiality of research and statistical information. In cases where no personally identifiable information will be collected, the Privacy Certificate contains a statement to this effect and a brief project description. Investigators should refer to the NIJ Privacy Certificate Guidance and Model Privacy Certificate at http://www.nij.gov/nij/funding/humansubjects/privacy-certificate-guidance.htm for information that must be included, sample format, and instructions to avoid common problems. Note: The NIJ only accepts the Privacy Certificate. It does not issue or accept Certificate of Confidentiality issued by the National Institutes of Health (NIH).

- Under a Privacy Certificate, researchers and research staff do not have to report current or past abuse. Since this is in conflict with Kentucky child and elder abuse reporting laws, the investigator is obligated to such reporting, and therefore must make available a second consent (addendum) to allow such reporting, should a subject self-disclose or give staff strong reasons to believe the subject may be in a dangerous situation. A sample separate consent form (addendum) for reporting is available at http://www.nij.gov/nij/funding/humansubjects/sample-form-consent-for-reporting.doc.doc

- If data collection methodology and/or information provided in the privacy certificate changes as a result of Institutional Review Board (IRB) requirements, a revised privacy certificate must be provided prior to the commencement of research.

Consent requirements (http://www.nij.gov/nij/funding/humansubjects/informed-consent.htm):

- The consent must include a statement describing the extent to which confidentiality of records identifying the subject will be maintained.
For studies sponsored by NIJ the subject should be informed that private, identifiable information will be kept confidential and will only be used for research and statistical purposes. However disclosure of future criminal intent is not covered or protected by DOJ regulations.

If, due to sample size or some unique feature, the identity of the individual cannot be maintained, the subjects need to be explicitly notified. If the investigator intends to disclose any information, the subject needs to be explicitly informed what information would be disclosed, under what circumstances, and to whom. The subject must be informed of any potential risks which may result from this disclosure and must explicitly provide prior written consent.

Subjects must be informed that study is funded by NIJ.

28 CFR 46.117 allows for waiver of documentation of informed consent where criteria met.

**Archiving:**

At the end of the award period, recipients of NIJ funding follow guidelines to submit data resulting from their projects to NIJ for archiving with the National Archive of Criminal Justice Data (NACJD), including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.

For additional guidance, refer to the frequently asked questions available at the NIJ FAQ website at [http://www.nij.gov/funding/humansubjects/faqs.htm](http://www.nij.gov/funding/humansubjects/faqs.htm).

**Requirements for research conducted within the Bureau of Prisons (BOP) [28 CFR 512]:**

Regional BOP facilities are identified on the Federal BOP website- [www.bop.gov/locations/maps/MXR.jsp](http://www.bop.gov/locations/maps/MXR.jsp)

**Federal Bureau of Prisons Research Proposals:**

- Investigators submit preliminary research proposal for review by the BOP Office of Research and Evaluation. If the study is to be conducted at only one institution, the applicant submits a formal proposal to the warden of that institution. If the study is to be conducted at more than one institution or at any other Bureau location, the applicant submits the research proposal to the Chief, Office of Research and Evaluation,

- When submitting a research proposal to the BOP Office of Research and Evaluation the researcher applicant provides the following information:
  - A summary statement, which includes:
    - Names and current affiliations of the researchers.
    - Title of the study.
    - Purpose of the study.
    - Location of the study.
    - Methods to be employed.
    - Anticipated results.
    - Duration of the study.
    - Number of participants (staff or inmates) required and amount of time required from each.
    - Indication of risk or discomfort involved as a result of participation.
A comprehensive statement, which includes:

- Review of related literature.
- Detailed description of the research method.
- Significance of anticipated results and their contribution to the advancement of knowledge. Specific resources required from the Bureau of Prisons.
- Description of all possible risks, discomorts, and benefits to individual participants or a class of participants, and a discussion of the likelihood that the risks and discomorts will actually occur.
- Description of steps taken to minimize any risks.
- Description of physical or administrative procedures to be followed to:
  - Ensure the security of any individually identifiable data that are being collected for the study, and
  - Destroy research records or remove individual identifiers from those records when the research has been completed.
- Description of any anticipated effects of the research study on organizational programs and operations.
- Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.
- A statement regarding assurances and certification required by federal regulations, if applicable.

Bureau Research Review Board:

- All research proposals must be reviewed by the Bureau Research Review Board (BRRB). The BRRB monitors research projects at least yearly, for compliance with Bureau policies. It is the investigator’s responsibility to communicate and submit proposals to the BRRB.
- Implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered by the Bureau to be research.
- A non-employee of the Bureau is limited in access to information available under the Freedom of Information Act. He/she may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as a statistical research or reporting record is provided to the agency.

Informed Consent:

- For research conducted within the Bureau of Prisons, additional required elements of informed consent include:
  - Identification of the researchers.
  - Anticipated uses of the results of the research.
  - A statement that participation is completely voluntary and that the participant may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
  - A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, a researcher may not guarantee confidentiality when the participant indicates intent to commit future criminal conduct or harm himself or herself or
someone else, or, if the participant is an inmate, indicates intent to leave the facility without authorization.
- A statement that participation in the research project will have no effect on the inmate participant’s release date or parole eligibility.

Additional requirements for researchers based on 28 CFR 512:

- The project must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
- The research design must be compatible with both the operation of prison facilities and protection of human participants. The researcher must observe the rules of the institution or office in which the research is conducted.
- Any researcher who is a non-employee of the Bureau must sign a statement in which the researcher agrees to adhere to the requirements of 28 CFR 512.
- The project must have an adequate research design and contribute to the advancement of knowledge about corrections.
  - The selection of participants within any one organization must be equitable.
  - Incentives may not be offered to help persuade inmate participants to participate. However, soft drinks and snacks to be consumed at the test setting may be offered.
  - Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research participants who are both:
    - No longer in Bureau of Prisons custody; and
    - Participating in authorized research being conducted by Bureau employees or contractors.
- Except as noted in the informed consent document presented to the participant, the researcher must not provide research information that identifies a participant to any person without that participant’s prior written consent to release the information. For example, research information identifiable to a particular individual cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without the written consent of the individual to whom the data pertain.
- Except for computerized data records maintained at an official Department of Justice site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system.
- If the researcher is conducting a study of special interest to the Office of Research and Evaluation (ORE) but the study is not a joint project involving ORE, the researcher may be asked to provide ORE with the computerized research data, not identifiable to individual participants, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.
- The researcher must have academic preparation or experience in the area of study of the proposed research.
- The researcher must assume responsibility for actions of any person engaged to participate in the research project as an associate, assistant, or subcontractor to the researcher.
- At least once a year, the researcher shall provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.
- At least 12 working days before any report of findings is to be released, the researcher shall distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance. The researcher shall include an abstract in the report of findings.
- In any publication of results, the researcher shall acknowledge the Bureau's participation in the research project.
- The researcher shall expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
- Prior to submitting for publication the results of a research project conducted under this subpart, the researcher shall provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.
Department of Veteran Affairs

Basic VA Regulations on Protection of Human Subjects in Research

- 38 Code of Federal Regulations Part 16 and Select Sections of Part 17
  [This regulation was based on the Federal Policy/Common Rule]

- Veteran Health Administration Handbook 1200.05 (Basic IRB) and 1058.01 (Reporting)

- For additional information:
  Go to www.research.va.gov
**Summary of Requirements for Environmental Protection Agency (EPA) Supported Human Research**

Human research supported by the EPA is subject to requirements and ethical standards outlined in 40 CFR 26 including Subparts B-D.

The EPA regulations for protecting human research participants apply to research supported by the EPA and research in which the intent is submission of data to the EPA.

In addition to this summary guidance, an IRB Checklist is available for use by the IRB in conducting review of EPA regulated research.

**EPA Study Types:**

EPA regulations implement protections applicable to two basic study types:

- **Intentional exposure** of a human subject is defined as a study where the exposure experienced by the subject would not have occurred but for the human subject's participation in the study. This includes any research in which the subject's exposure is artificially manipulated or controlled.

- **Observational research** means any research that does not involve intentional exposure. Studies that involve naturally occurring environmental exposures may meet the regulatory definition of observational.

Risk level is irrelevant to the determination of whether the research involves intentional exposure or is observational.

1. **The following describes limitations and protections defined in the EPA regulation subparts for vulnerable subject populations involved in intentional exposure and observational research.**

   **Note:** The EPA subparts are different from Department of Health and Human Services (DHHS) subparts.

**INTENTIONAL EXPOSURE:**

EPA has a categorical ban on research involving intentional exposure of pregnant women, nursing women, or children to any substance.

**Subpart B Prohibition of Research Conducted or Supported by EPA Involving Intentional Exposure of Human Subjects who are Children or Pregnant or Nursing Women**

This subpart prohibits intentional exposure research, under all circumstances, in children and women who are pregnant or nursing. All circumstances include studies involving controlled exposures to neutral substances (such as clean, filtered air), foods, or therapeutic drugs. This prohibition is absolute and does not incorporate reference to either risk level or potential benefit.

EPA extends the provisions of 40 CFR 26 to human research involving intentional exposure of non-pregnant, non-nursing adults to substances. A **substance** includes any chemical, biological organism, or physical property tracked or regulated by the EPA or identified in an environmental statute. The
Substance Registry Services (SRS) is the EPA’s central system for information about substances that are tracked or regulated by EPA.

**OBSERVATIONAL RESEARCH:**

Observational research supported by or submitted to the EPA may be permitted if conditions outlined in the following regulations are met.

**Subpart C Observational Research: Additional Protections for Pregnant Women and Fetuses Involved as Subjects in Observational Research Conducted or Supported by EPA**

Subpart C establishes rules for studies that involve pregnant women (and thus their fetuses) participating in observational research.

Research of this nature can be conducted when there is direct benefit to the woman or the fetus. However, in the absence of direct benefit, **if the risk is no greater than minimal to the fetus** and the research is important for biomedical knowledge which cannot be obtained in any other manner, the research is permissible by EPA.

**Subpart D Observational Research: Additional Protections for Children Involved as Subjects in Observational Research Conducted or Supported by EPA**

Subpart D establishes rules for studies that involve children participating in observational research.

Research of this nature, involving no more than minimal risk of this nature can be conducted on children.

Research involving greater than minimal risk can only be conducted when there is direct benefit to the subject. The IRB reviews and approves observational research involving children that does involve greater than minimal risk but presenting the prospect of direct benefit to the individual participants if the IRB finds and documents that:

- The intervention or procedure holds out the prospect of direct benefit to the individual participant or is likely to contribute to the participant's well-being.
- The risk is justified by the anticipated benefit to the participants.
- The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.
- Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 40 CFR 26.406.

The IRB reviews and approves observational research involving children that does not involve greater than minimal risk 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 40 CFR 26.406. Permission by parents or guardians shall be documented in accordance with and to the extent required by 40 CFR 26.117. When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.
There is no provision in the EPA rule for the conduct of research when there is greater than minimal risk and no direct benefit to the child. Also, EPA regulations do not recognize a category of research on children involving “a minor increase over minimal risk”.

Subpart K - Basic Ethical Requirements for Third-Party Human Research for Pesticides Involving Intentional Exposure of Non-pregnant, Non-nursing Adults

EPA 2013 Final Rule – Enhanced protections for all other adult subjects in human research involving pesticides.

Defines pesticide as a substance or mixture of substances intended for pesticidal effect.

Informed Consent Requirements:

If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function. In consideration of risks currently unforeseen, investigator should include any potential risk to embryo or fetus, should subject become pregnant.

Subpart K does not include provision for consent by a subject’s legally authorized representative (LAR). No investigator may involve a human being as a subject in pesticide research unless the investigator has obtained the legally effective informed consent of the subject.

Subpart L—Prohibition of Third-Party Research involving Intentional Exposure to a Pesticide of Human Subjects who are Children or Pregnant or Nursing Women

Submission of IRB Documentation to EPA for Project Review

The PI must submit the following documentation to the EPA Human Subjects Research Review Official (HSRRO) for final review and approval before the research can begin:

- UK’s Federalwide Assurance (FWA) number
- Copies of:
  - the IRB approval (or exemption) letter;
  - the study protocol(s) as submitted to the IRB (the pre-award document is not sufficient);
  - the IRB approved consent forms and subject recruitment materials if applicable; and
  - all supplementary IRB correspondence between the IRB and the investigator (i.e., submission, requested revisions, etc.).

2. Additional Resources:

- The online course, Human Subjects Research at the Environmental Protection Agency: Ethical Standards and Regulatory Requirements, provides training for investigators involved in human subject research supported by EPA.
• The online manual Scientific and Ethical Approaches for Observational Exposure Studies serves as a resource tool and source of information for researchers involved in the development and conduct of observational human exposure studies.

Sources:

40 CFR 26

Conducting Human Subjects Research (HSR) at EPA

Oversight of Human Research Regulated by EPA: Special Considerations for HRPPs, AAHRPP Presentation, 2010

Human Subjects Research at the Environmental Protection Agency: Ethical Standards and Regulatory Requirements

12/20/12, revised 3/22/13, revised 1/17/14
J:\Master Outreach Documents\Survival Handbook\D - Guidance-Policy-Educational\D114-Summary-of-EPA-Requirements.doc
Family Educational Rights and Privacy Act (FERPA) Guidance

This document provides a brief summary of the Family Educational Rights and Privacy Act (FERPA; 20 U.S.C. § 1232g; 34 CFR Part 99) regulations and gives guidance for researchers and IRB members on accessing educational records.

Summary of the FERPA Regulations

FERPA is a federal law that protects the privacy of personally identifiable information contained within a student’s educational record. FERPA applies to all schools (K-12 including postsecondary institutions) that receive funds under various programs from the U.S. Department of Education.

FERPA defines educational records as records containing information (in any medium – paper, electronic, microfilm, etc) that directly relate to a student and are maintained by an educational institution or by a party acting for the institution.

The information listed below is not considered part of an educational record and thus not regulated by FERPA; however, the information may be regulated or protected by other federal and state laws.

Items not considered part of an educational record include:

- Records kept in sole possession of the maker that are not accessible or revealed to any other person except as a temporary substitute;
- Certain law enforcement records;
- Employment records that relate exclusively to the individual as an employee;
- Records that only contain information about an individual after he or she is no longer a student.

Conditions for Which Student Records Can Be Disclosed Without Consent

Generally, schools must have written permission from the student (or parent if the student is a minor) in order to release any information from a student's education record. However, FERPA allows schools to disclose educational records without consent under special circumstances.

The U.S. Department of Education’s summary of the FERPA regulations lists the following conditions for which student records can be disclosed without consent:

- Develop, validated, or administer predictive tests;
- *School officials with legitimate educational interest (e.g., improve instruction);
- Other schools to which a student is transferring;
- Specified officials for audit or evaluation purposes;
- Appropriate parties in connection with financial aid to a student;
- Organizations conducting certain studies for or on behalf of the school;
- Accrediting organizations;
- To comply with a judicial order or lawfully issued subpoena;
- Appropriate officials in cases of health and safety emergencies; State and local authorities, within a juvenile justice system, pursuant to specific state law; and

* Included in the University of Kentucky’s designation of school official are persons employed in administrative, supervisory, academic or research positions.
Family Educational Rights and Privacy Act (FERPA) Guidance

- Directory information. FERPA defines directory information as information contained in a student’s education record that would not generally be considered harmful or an invasion of privacy if disclosed. FERPA also provides guidance on what may be considered directory information; however, each institution is free to designate less information as directory information. FERPA permits the following to be designated as directory information: the student’s name, address, telephone listing, electronic mail address, photograph, date and place of birth, major field of study, dates of attendance, grade level, enrollment status (e.g., undergraduate or graduate; full-time or part-time), participation in officially recognized activities and sports, weight and height of members of athletic teams, degrees, honors and awards received, and the most recent educational institution attended. The University of Kentucky (UK) definition of directory information includes the maximum amount of information protected under FERPA, and available at the following website: http://www.uky.edu/StudentAffairs/Code/part5.htm.

Researchers should note that the following are never designated as directory information: a student’s social security number, and most instances student identification number, citizenship, gender, religious preference, grades, and Grade Point Average (GPA). Subjects must sign a consent form to release any of these items unless request for access falls under any of the exempt conditions outlined in FERPA.

Under FERPA, students are also given the opportunity to file a request to prevent disclosure of directory information, commonly known as “opting out”. An institution will not release any information on a student, even directory information, if a student has “opted out”. UK’s process for “opting out” involves setting a privacy flag on the student’s directory information. Instructions are available at http://www.uky.edu/registrar/obligation-privacy.

FERPA allows the release of educational records without consent if all personally identifiable information (PII) has been removed. Under FERPA the term personally identifiable information (PII) includes but is not limited to:

- student’s name and other direct personal identifiers, such as the student’s social security number or student identification number;
- indirect identifiers, such as the name of the student’s parent or other family members; the student’s or family’s address, and personal characteristics or other information that would make the student’s identity easily traceable;
- date and place of birth and mother’s maiden name;
- biometric records, including one or more measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting; and
- other information that, alone or in combination, is linked or linkable to a specific student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify the student with reasonable certainty.

Guidance for Researchers & IRB Members

It is important that researchers apply FERPA and human subject protection regulations when accessing educational records. Generally FERPA and IRB requirements are met if a student signs a consent form to participate in a study and authorizes release of his/her educational records for research purposes.
Family Educational Rights and Privacy Act (FERPA) Guidance

The written consent must:

(1) Specify the records that may be disclosed;
(2) State the purpose of the disclosure; and
(3) Identify the party or class of parties to whom the disclosure may be made.

A “Signed and dated written consent” may include a record and signature in electronic form that:
- Identifies and authenticates a particular person as the source of the electronic consent; and
- Indicates such person’s approval of the information contained in the electronic consent.

In instances where a researcher requests to waive the informed consent process, the following conditions must be met:

1. Generally, FERPA allows a researcher to access and release information in an educational record for any of the items listed in the section above entitled: “Conditions for Which Student Records Can Be Disclosed without Consent”. Please note that the Office of Research Integrity may forward any requests to access PII without a consent form to UK’s legal counsel. Legal counsel makes the final determination if the study meets the exception criteria to release educational information without a signed consent form and develops appropriate agreements as required by 34 CFR 99.31.

2. Researchers must have permission from UK’s Registrar to access educational records at the University of Kentucky. University requirements are available at the Office of the Registrar’s web page: [http://www.uky.edu/Registrar/ferpa.htm](http://www.uky.edu/Registrar/ferpa.htm). Please note that UK Registrar does not maintain educational records for the College of Medicine or the College of Dentistry. Researchers should contact the respective colleges and abide by their FERPA requirements.

3. In developing the IRB application, researchers should address:
   - purpose, scope, and duration of study;
   - use and disclosure of PII;
   - plans to protect PII and not release to any other party (other than representatives of the University of Kentucky with legitimate interests) without prior consent of parent or eligible student; and
   - plan to destroy information when no longer needed.

4. If researchers propose to access student records at institutions other than UK, researchers should contact each institution and follow that institution’s FERPA policy when accessing directory information. Each educational institution designates what information is considered directory information.

5. In accordance with FERPA, an educational institution has the authority to determine what information may be accessed from an educational record. If an institution denies an investigator access to information in an educational record, the IRB cannot overrule the decision.
Family Educational Rights and Privacy Act (FERPA) Guidance

6. According to the IRB federal regulations, for non-exempt studies, an IRB cannot waive informed consent or documentation of informed consent unless specific conditions are met. Consequently, researchers should include rationale for waiver requests in the IRB application even in circumstances where FERPA allows access without prior consent.

7. FERPA and the Health Insurance Portability and Accountability Act (HIPAA) regulations provide conflicting requirements for medical records. In some situations FERPA is more restrictive than HIPAA for researchers. Researchers should contact each educational institution and follow that institution’s applicable policies, whether FERPA and/or HIPAA policy when accessing student medical records. Please note that the University of Kentucky has elected to follow both FERPA and HIPAA regulations for University Health Services (UHS) medical records. Please contact ORI or UHS at the numbers listed below if your research proposal involves accessing student medical records.

Contacts for Additional Information:

If you have research questions, contact: Joe Brown, Research Privacy Specialist, at (859) 257-9084 or jrbrow3@email.uky.edu.

For questions regarding UK FERPA requirements, contact: the Student Records Office, at (859) 859 257-7157.

Information regarding University Health Services medical records may be found at http://ukhealthcare.uky.edu/uhs/records/.

For other healthcare privacy questions, contact the UK Healthcare Privacy Officer, at 323-8002.


Last revised: 4/10/14
J:\Master Outreach Documents\Survival Handbook\D - Guidance-Policy-Educational\31-FERPA.doc
IRB Review Mechanisms

Exempt

Expedited
Making a determination that a study is eligible for exemption is not always an easy task. Below are examples of issues that the IRB reviewers should consider when conducting the Exemption Review.

**Additional Regulatory Protection for Children and Prisoners**

Certain research activities can **not** be exempt because additional protection has been granted by federal regulations for vulnerable populations. The categories of research that can **not** be exempt are as follows:

1. Research involving survey or interview of children;
2. Research involving the observation of public behavior of children unless the investigators do not participate in the activities being observed;
3. Research involving prisoners.

**All Research Activities Must Fit Within Six Federal Categories**

For a study to be eligible for exemption all of the research activities must fit in one or more of the six categories listed below. In some cases, all but one of the activities will fit in the categories. For example, sending a mail questionnaire on a non-sensitive topic which requests that the survey be returned without identifiers would appear to be a methodology that meets category 2 below. However, if the researcher obtained the list of subjects and their addresses from private records (e.g., student transcripts or medical records), then the research might not be eligible because it does not meet the conditions of category 4 listed below.

**Risk Assessment Considerations**

Research eligible for exemption usually involves little or no risk to subjects. Some reviews apply the “minimal risk” standard when conducting exempt review. When determining “minimal risk” the IRB reviewer must first identify all the risks associated with the study. Department of Health & Human Services defines “minimal risk” to mean “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” [45 CFR 46.102(2)(i)].

**Exemption Applications that Do Not Meet the Definition of Human Research**

The exemption process is further complicated because occasionally an activity that is sent to the IRB using an Exemption Application Form does not meet the federal definitions of “research” or “human subject”. These definitions are included in the UK “When do activities involving human subjects need Institutional Review Board (IRB) review and approval?” guidance document on [http://www.research.uky.edu/ori/human/guidance.htm](http://www.research.uky.edu/ori/human/guidance.htm).

In analyzing whether activities involve human subjects, it is important to focus on what is being obtained by the investigators. If the investigators are not obtaining either data about living individuals through intervention or interaction, or identifiable private information, then the research activity does not involve human subjects. Reviewers should contact ORI staff if they think that might be the case in a specific application.
Guidance for Applying the Six Exemption Categories

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

The IRB reviewer has to consider whether the proposed activities constitute "normal educational practice" and if the setting is a "commonly accepted educational setting". For example, a study to develop an innovative method for teaching math in the second grade would be eligible under this exemption provided the curriculum development methods reflected normal educational practices. Typically the educational setting would be a classroom. However, teaching students to drive in a driver's education class or teaching children or adults to cook in a formal cooking class could be considered a "normal educational setting". The IRB reviewer can contact one of the IRB College of Education representatives for guidance regarding whether the research is occurring in an "accepted education setting" or whether it involves "normal educational practices."

This category does not apply to Food and Drug Administration (FDA) regulated research.

(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.

Several research activities are addressed in this category. These activities are:

- use of educational tests;
- survey procedures;
- interview procedures; and
- observation of public behavior.

The category defines two conditions, that when both exist, exclude the activities from consideration for exemption. The study can be exempt if the activities only meet one of the conditions below:

- the information gathered during these activities can be linked to the subject, either directly or by some coding system if the researchers can access the codes

- should a third party gain access to that information, the subject would be placed at risk. The risk can be for criminal or civil liability or can be the risk of damaging a subject's financial standing, reputation, employability, or insurability.

An example would be a survey randomly sent to individuals selected from an employment roster. The survey asks the subjects their opinions on the managerial skills of their supervisors, without naming the supervisors. The investigator wants a 95% response rate so although she does not ask the subject's name or social security number, she codes the questionnaires so she can tell who responds. After a certain period of time, she sends a
second questionnaire to those randomly selected individuals who did not respond to the first request. Also, she plans to keep the code so that she has the option to follow up with subjects if she needs clarification regarding their responses.

Since there is a code that links data with names, breach of confidentiality is possible even though it might be unlikely to occur. That could potentially place the employee’s job security and financial standing at risk. Consequently, this study would not be eligible for exemption.

If, however, there is no risk associated with a subject’s responses, having identifiers will not disqualify a study from exemption. There are many studies that ask for information that, if disclosed, would not put a subject at any type of risk. A study could have identifying information on the survey or questionnaire and still be eligible for exempt review provided disclosure of subject responses would not put subjects at risk.

This exemption is narrowed in scope by 45 CFR 46 Subpart D’s additional protections for research involving children. Where children will be involved as research subjects, the use of survey or interview procedures is eliminated from this exemption, and so is any research involving the investigators participating in the activity being observed. OHRP has also stated that observing a classroom does not constitute public behavior and is not permitted for this exempt category.

**Audio taping in exempt research**

The Department of Health & Human Services Office of Human Research Protection (OHRP) has stated that “… even when audio taping is done, a research project involving non-prisoner adult human subjects may meet the criteria for exempt #2 if the information is not sensitive in nature and could not reasonably place the subject at risk of criminal or civil liability or be damaging to the subjects’ financial standing employability or reputation …”.

This category does not apply to FDA regulated research.

**(3) Research involving the use of education tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under category (b) 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.**

This category can be confusing and actually applies to two very different criteria.

Item (i) of this category includes the research procedures previously identified in category 2 (i.e., use of educational tests, survey procedures, interview procedures, and observation of public behavior). However, this category differs from the previous one in the situations to which it applies. If the population targeted for the research activities are elected or appointed officials or candidates running for public office, the research qualifies for exempt review.

OHRP has provided guidance on what constitutes public officials. Public officials could include mayors, governors, school superintendent, school board members, police chief and others appointed by a state official. Public officials would not include public employees such as teachers or police officers.
An example of research that fits this category would be a survey administered to town mayors within a county that contains questions that might expose information which the public might not support. The PI can plan to report that data, identifying the mayors that participated in the study and even identify how certain mayors answered specific questions, and still qualify for exempt review. Public officials or candidates running for public office give up their right to confidentiality in lieu of the public’s “right to know.”

The second part of this category (ii) addresses the use of educational tests, surveys, interviews, or observation of public behavior to collect data for specific federal programs conducted or supported by the Department of Justice or data collected for the Institute of Education Sciences which includes the National Center for Education Statistics of the United States Department of Education. These agencies have specific programs that create databases which are then protected by law from ever being accessed by anyone other than those federal agencies. No officer or employee of the Federal Government, and no recipient of assistance under the provisions of this category is allowed to use or reveal any research or statistical information furnished under this category by any person and identifiable to any specific private person for any purpose other than the purpose for which it was obtained. Data collected for these programs will be immune from legal process and cannot, without the consent of the individual concerned, be admitted as evidence or used for any purpose in any action, suit or other judicial or administration proceeding.

The only circumstance in which an exemption application would be submitted to the University of Kentucky’s IRB for consideration utilizing part (ii) of the category would be if a PI from the University of Kentucky was issued a grant to conduct research involving specific programs by the Department of Justice or the National Center for Education Statistics.

This category does not apply to FDA regulated research.

(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.

Clarification on Existing Data

According to the Office for Human Research Protections (OHRP), to qualify for this exemption criterion the data, documents, records, or specimens must be in existence at the time of IRB review. OHRP interprets the term “existing” to mean that all of the data, documents, records, or specimens to be used in the research are in existence prior to IRB review and were collected for purposes other than the proposed research. The IRB reviewer must assure that the investigator has shown that all of the data to be collected under this category are currently in existence at the time of IRB review.

Based on the federal definition of “existing data,” research conducted on biological or pathological specimens obtained prospectively and taken strictly for research purposes does not qualify for exempt review.

Based on the federal definition of “existing data,” research conducted on biological or pathological specimens obtained prospectively from future discarded clinical samples does not qualify for exempt review. A prospective study does not meet the definition of “existing”. Also, if there is any “prospective” component of the research procedures, the
research will not qualify for exempt review (for example information taken from existing records which will be compared to information to be collected at some future date).

**Publicly Available or Subject Identifiers**

IRB Reviewer must determine if:

1. the data, documents, records, or specimens are collected from publicly available sources or
2. of the information is recorded so that subjects can be identified directly or through identifiers linked to a subject.

If the collection of data, records, or specimens meet either of these two conditions, the research cannot be exempt.

What is meant by “publicly available resources”? This language in the regulation was intended to apply to public sources of data, such as local telephone directory information. For example, student records which are covered by the Family Educational Rights and Privacy Act (FERPA) are not public records. The meaning of this language with respect to human tissue specimens is widely debated. Although there are organizations that make human cells and tissues broadly accessible to the research community, these materials are not usually available to the public at large and are not generally considered to be publicly available.

What is meant by “identifiers linked to the subjects”? Identifiers can include names, social security numbers, medical record numbers, or other codes that permit specimens or data to be linked to living individuals and perhaps also to associated medical information.

For example, biological or pathological samples obtained by means of retrospective collection from existing sources may not be eligible if the subject’s identity is readily ascertainable to the researchers through direct or coded identifiers or the information is obtained from nonpublic sources such as medical records. If the samples are given to the investigator with any hospital numbers, codes or links that tie the data back to a list of subjects, then there is a mechanism in which the subject can be identified, directly or indirectly and the research does not qualify for exempt review in this category.

**Recording identifiers**

It is important for the person making the exempt determination to understand the investigators plans for recording the data. Temporarily recording a name or other identifiers that allow individual subjects to be identified will exclude this type of research activity from meeting the exempt 4 criteria.

**Definition of Human Subject and Coded Private Information/Data or Coded Specimens**

Exemption Category 4 is difficult to apply because in some cases the activities do not technically meet the category but still do not require expedited or full review because they do not meet the federal definition of “human subject” (i.e. identity of the subject is not readily ascertainable by the PI).
For example, if the research involves only coded private information/data or coded specimens, OHRP does not consider the research to involve human subjects as defined under the HHS Protection of Human Subjects Regulations (45 CFR Part 46.102(f)) if the following conditions are both met:

- the private information/data or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

- the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
  
  (a) the key to decipher the code is destroyed before the research begins;
  (b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased;
  (c) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased
  (d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

To demonstrate how the determination of whether a research study is human subjects research differs from the determination of whether a human subjects research study is exempt under 45 CFR 46.101(b)(4), consider the following examples, in which an investigator obtains health information of living patients who were treated for arthritis with either Drug A or Drug B. The investigator obtains this information in order to evaluate and compare the treatment outcomes associated with these two drugs:

(1) An investigator receives only coded information on the treatment outcomes of patients treated for arthritis with Drug A versus Drug B from the patients’ treating physician. The only involvement of the treating physician is to provide coded information to the investigator. The investigator and the treating physician enter into an agreement prohibiting the release of the key to decipher the code to the investigator under any circumstances, until the individuals are deceased. In this example, the investigator is not conducting human subjects research because the investigator cannot readily ascertain the patients’ identity.

(2) An investigator obtains individually identifiable information on the treatment outcomes of patients treated for arthritis with either Drug A or Drug B by viewing patients’ existing individually identifiable medical records at the clinics where the patients were treated. The investigator records the patients’ treatment outcomes in a coded manner that could permit the identification of the patients. In this example, the investigator is conducting human subjects research because the investigator is obtaining identifiable private information from patients’ (and now subjects’) medical records. The study would not be exempt under 45 CFR 46.101(b)(4) since the investigator is recording the information in a coded manner, thus allowing the subjects to be identified indirectly through identifiers linked to the subjects.

(3) An investigator obtains individually identifiable information on the treatment outcomes of patients treated for arthritis with either Drug A or Drug B by viewing patients’ existing individually identifiable medical records at the clinics where the
patients were treated. The investigator records only patient age, sex, diagnosis, treatment, and health status at the end of 6 months of treatment so that the investigator cannot link the recorded information back to the patients. In this example, the investigator is conducting human subjects research because the investigator is obtaining identifiable private information from patients' (and now subjects') medical records. However, the study would be exempt under 45 CFR 46.101(b)(4) since the investigator records the information in such a manner that subjects cannot be identified either directly or indirectly through identifiers linked to the subjects.

Category four does not apply to FDA regulated research.

(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 payments for benefits or services under those programs.

This category applies to:
(i) the projects conducted pursuant to specific federal statutory authority such as programs under the Social Security Act, or other federal statutory public benefit or services 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.
(v) projects for which there is no statutory requirement for IRB review;
(vi) projects that do not involve significant physical invasions or intrusions upon the privacy interests of participants;
(vii) authorization or concurrence by funding agencies that exemption from IRB review is acceptable.

This category of research is narrowly defined and only applies to Social Security Act programs and other public benefit programs that are specifically designated by the Department of Health and Human Services or the Secretary of one of the 19 other Federal Departments which have adopted the Common Rule. This criterion is so specific that the University of Kentucky IRB rarely receives applications that fit in this category.

Research and demonstration projects in general (e.g. state funded public service programs) do not fit in this category. Only projects which are conducted under federal statutory authority or the Social Security Act fit under this exemption criterion. OHRP recommends that institutions consult with the investigator's Department of Health & Human Services (HHS) funding agency before determining that a research project meets research category 5.

This category does not apply to FDA regulated research.

(6) Taste and food quality evaluation and consumer studies, (i) if wholesome food 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
This category addresses two different types of research activity.

1. First, if the taste test involves wholesome food without any additives it is then eligible for exemption. The IRB reviewer must make sure that the food product to be researched is “wholesome” (no additives).

An example of such a research project would be a taste-test conducted on different types of grapefruit to determine consumer preference. The grapefruits are those normally grown in different sections of the country, using normal agricultural practices, and do not involve the addition of food additives or chemicals. The subjects merely indicate which of the grapefruit tasted they prefer.

2. The second item (ii) is more difficult to understand. Research conducted on human subjects who consume plants or animals raised for food products may qualify for exempt review.

The Food and Drug Administration has determined levels of safety for various agricultural chemicals, referred to as GRAS (FDA generally recognized as safe) and GRAE (generally recognized as effective) additives which are fed to animals raised for food production. If these agricultural additives are given to animals at or below the levels found to be safe by FDA, the research can receive exempt review.

An example of such research would be taste-testing pork products where the swine have been fed corn and a chemical additive at a level designated below FDA guidelines that make the animal gain weight more quickly. The objective of the study is to determine whether the addition of the chemical changes the flavor of the pork.

There are also approved levels for environmental contaminants set forth by the Food and Drug Administration, the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the U.S. Department of Agriculture (USDA) that may affect the grass or grain consumed by grazing food animals such as chemicals sprayed on a field to combat chickweed. If the research involves taste-testing of food products that come from animals exposed to environmental contaminants and the investigator can show that the use of these contaminants was at or below those approved levels, the research can receive exempt review.

In all of these situations, the investigator should provide some documentation that the alterations, either chemical, environmental or agricultural, have been found to be safe by FDA, USDA, and/or EPA.

However, if there have been food and color additives incorporated into the food product and these additives are used in research with the intent to apply to FDA for marketing that additive, the research would not qualify for exemption. Even if the procedures are preliminary in nature, if the research would eventually lead to FDA approval for marketing the food or color additive, it would not qualify for exempt review. The additives are viewed as investigational by FDA and, therefore, do meet the exemption criteria.
2008 Guidance from OHRP regarding exemptions and the HIPAA Privacy Rule

The Privacy Rule and the IRB regulations differ with respect on what is considered individually identifiable.

The Privacy Rule is a Federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 (see 45 CFR part 160 and subparts A and E of part 164). The Privacy Rule permits covered entities under the Rule to determine that health information is de-identified even if the health information has been assigned, and retains, a code or other means of record identification, provided that:

(1) the code is not derived from or related to the information about the individual;

(2) the code could not be translated to identify the individual; and

(3) the covered entity under the Privacy Rule does not use or disclose the code for other purposes or disclose the mechanism for re-identification (see HHS guidance entitled, Institutional Review Boards and the HIPAA Privacy Rule, page 6, Q and A #3, at http://privacyruleandresearch.nih.gov/pdf/IRB_Factsheet.pdf).

Regarding condition (1) above, in contrast to the Privacy Rule, information that is linked with a code derived from identifying information or related to information about the individual is not considered to be individually identifiable under the HHS regulations for the protection of human subjects at 45 CFR 46.102(f), if the investigators cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimen pertains. Therefore, some coded information, in which the code has been derived from identifying information linked to or related to the individual, would be individually identifiable under the Privacy Rule, but might not be individually identifiable under 45 CFR part 46.

Prepared by: Ada Sue Selwitz, University of Kentucky
Office of Research Integrity
Lexington, KY 40506-0057, (859) 257-2978
Copyright August 1997 University of Kentucky
Revised 10/24/03 by Ada Sue Selwitz
Revised 2/06 by Ada Sue Selwitz
Updated by Joe Brown 08/09; Jennifer Harris 04/04/11

References:


September 24, 2004 OHRP Human Subject Regulations Decisions Charts (charts 1 - 7) at http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html

Office of Human Research Protections, Department of Health and Human Services Frequently Asked Question Section: http://answers.hhs.gov/ohrp/categories
Issues to Address when Conducting Expedited Reviews

Definition
The Institutional Review Board (IRB) uses an expedited review process to review studies that meet the expedited categories adopted by the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA), and that involve no greater than "minimal risk." Expedited review procedures can also be utilized for the review of minor revisions submitted for previously approved research during the period for which approval is authorized. (See Guidance on Expedited Review of Minor Changes in Previously Approved Research.)

The expedited review process can be carried out by the Chair of the IRB or one or more experienced reviewers designated by the Chair from among voting members of the IRB. Federal regulations also dictate that when an IRB uses expedited review procedures, there must be a mechanism in place for advising all of the members of the IRB of the research procedures approved under this review process.

Authority of an Expedited Reviewer
The expedited reviewer is responsible for ensuring that all of the information requested in the Expedited Review application is provided. The expedited reviewer makes the final determination as to whether research activities meet the expedited review criteria as outlined in the section of this document titled, Definition of Minimal Risk and Guidance to PI and Reviewers.

The expedited reviewer also determines whether the research meets the federal criteria for approval as outlined in 45 CFR 46.111, 21 CFR 56.111, and 38 CFR 16.111. (See Criteria for IRB approval: Reviewer Checklist.)

The expedited reviewer has the authority to approve a study or request additional information. The expedited reviewer does not have the authority to disapprove a study. (See Expedited Initial Review SOP and Continuation Review SOP)

Informed Consent
Expedited reviewers ensure that the investigator conducts the informed consent process and obtains documentation of informed consent, as specified in 45 CFR 46.116 and 117, 21 CFR 50.25, and 38 CFR 16.116 and 117, unless the IRB waives the requirements in accord with federal regulations. (See Informed Consent SOP and Forms E and F in the IRB application which is on the Office of Research Integrity website)

When children are involved as research subjects, the expedited reviewer is also charged with ensuring that there are adequate provisions for obtaining assent from these children. (See UK IRB Policy on Children in Research.)

Vulnerable Subject Populations
Federal regulations do not specify whether any certain populations should be globally excluded from a study for it to be eligible for expedited review. The expedited reviewer gives special consideration to protecting the welfare of vulnerable subjects such as children, prisoners, fetuses/neonates, pregnant women, and decisionally challenged/impaired persons. The expedited reviewer also recognizes that additional populations such as students may qualify as vulnerable populations and need safeguards in place for their protection during study participation. (See Protection of Vulnerable Subjects SOP)

Definition of Minimal Risk and Guidance to PI and Reviewers
Expedited procedures can only be used to review a study if the only involvement of human subjects fits one or more of the categories specified in the federal regulations and if all of the procedures present no greater than "minimal risk."

The IRB reviewer confirms that all of the research activities fit in one or more of the expedited categories. If the research includes activities that do not fit in the categories, the study is not eligible for expedited review even if the research involves "minimal risk."
Issues to Address when Conducting Expedited Reviews

The Department of Health and Human Services defines *minimal risk* to mean “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” [45 CFR 46.102(2)(i)].

Investigators are asked to provide a risk assessment, but it is the IRB reviewer’s responsibility to determine whether the research meets the federal definition.

The IRB reviewer must consider two questions:

- Is the probability of the harm or discomfort anticipated in the proposed research greater than that encountered ordinarily in daily life or during the performance of routine physical or psychological examinations or tests?

- Is the magnitude of the harm or discomfort greater than that encountered ordinarily in the daily life or during the performance of routine physical or psychological examinations or tests?

If the answer is “yes” to either of these questions, then the research does not meet the definition of minimal risk.

The IRB policy on risk assessment is included in the UK Assessing the Research Risk document, which is on the ORI website and in the IRB Survival Handbook.

Federal Expedited Review Applicability and Categories

(A) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. 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.

(B) The categories in this list apply regardless of the age of subjects, except as noted.

(C) 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.

(D) The expedited review procedure may not be used for classified research involving human subjects.

(E) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the IRB.

(F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

1) Clinical studies of drugs and medical devices only when 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.)
Issues to Address when Conducting Expedited Reviews

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
   (a) From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
   (b) From other adults and children considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

   NOTE: Intravenous (IV), Port, Central, or any other lines are NOT eligible under this category even if the research involves “minimal risk”.

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) uncanulated 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- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (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, electromyelography, 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 nonresearch purposes (such as medical treatment or diagnosis). (Note: 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.)
Issues to Address when Conducting Expedited Reviews

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.
Educational Materials
and Useful References

Educational Materials

OHRP Listserv

Electronic/Web Sites

OHRP Contacts

FDA Contacts

VA Contacts
Educational Materials


The entire training should take you about 90 minutes to complete; however, you can complete each module independently of the others. Module 1 is 22 minutes. Module 2 is 28 minutes and Module 3 is 36 minutes.

- **Module 1**: Evolving Concern: Protection for Human Subjects
- **Module 2**: The Belmont Report: Basic Ethical Principles and Their Application
- **Module 3**: Balancing Society's Mandates: Criteria for Protocol Review
- **Institutional Review Board Guidebook** provides additional information on protecting the rights and welfare of human subjects as defined in the HHS regulations (45 CFR 46), Protection of Human Subjects, revised June 18, 1991

**What You Will Learn**

- Historical background for behavioral and biomedical research
- Ethical principles for human subject research
- Case studies
- Information on the role of an Institutional Review Board

**Why HRSA Protects Human Participants in Research Studies**

HRSA is required to protect human subjects under its FederalWide Assurance with the HHS Office for Human Research Protections and the Protection of Human Subjects Participating in Research Programs Conducted or Supported by HRSA policy. The protections apply to studies conducted internally by Federal staff and to external studies conducted by grantees and contractors.

_____________________________________________________


OHRP Educational Videos were developed by the Division of Education and Development and are intended to provide information regarding the requirements of the Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 CFR part 46. The videos represent OHRP's current thinking on these topics and should be viewed as recommendations unless specific regulatory requirements are cited. The use of the word must in OHRP guidance means that something is required under HHS regulations at 45 CFR part 46. The use of the word should in OHRP guidance means that something is recommended or suggested, but not required. An institution may use an alternative approach if the approach satisfies the requirements of the HHS regulations at 45 CFR part 46. OHRP is available to discuss alternative approaches at 240-453-6900 or 866-447-4777.

OHRP anticipates the release of additional training videos in the future.
OHRP On-line Tutorials ([http://www.hhs.gov/ohrp/education/training/introduction.html](http://www.hhs.gov/ohrp/education/training/introduction.html))

OHRP offers an on-line tutorial that includes three modules related to roles, requirements, and procedures in conducting research involving human subjects. This tutorial consists of three modules:

1. HHS Regulations & Institutional Responsibilities
2. Investigator Responsibilities & Informed Consent
3. Human Research Protections Program

These modules are not designed to satisfy the investigator education requirements of the National Institutes of Health (NIH) grant recipients. For NIH investigator training, please see the following URL: [http://phrp.nihtraining.com/users/login.php](http://phrp.nihtraining.com/users/login.php).

OHRP/PRIM&R “INVESTIGATOR 101” CD ROM ([http://www.hhs.gov/ohrp/education/training/101cdrom.html](http://www.hhs.gov/ohrp/education/training/101cdrom.html))

OHRP is pleased to provide a copy of the PRIM&R “Investigator 101” CD ROM to each institution with an OHRP-approved FWA. Each institution will receive a Site License that allows them to make copies for each investigator.

**Description:**

- **Three hours of high quality full motion video**
  - Based on PRIM&R’s highly acclaimed “IRB 101 - On the Road” training program.
  - Two presentations:
    - Part 1: The History and Ethics of Human Subject Research with Dr. Jeffrey Cooper
    - Part 2: The Top 10 Responsibilities of Investigators with Ms. Ada Sue Selwitz
  - Both talks are divided into short modules

- **Synchronized animated slide presentations**
  - Printable slide handouts are included for convenience.

- **Synchronized transcripts of the audio track**
  - Play the video and the highlighted transcript moves with the video. Scroll the transcript and the video moves to the corresponding point. The transcripts may be printed for convenience.

- **Comprehensive set of hyper-linked references and reading materials**
  - Includes key regulatory and compliance documents.
• Search function
  - Search on any keyword and jump directly to the point in the video where the keyword is discussed.

• Notes function
  - Investigators may record notes through the CD-ROM software.

The CD-ROM operates on both Macintosh and Microsoft Windows platforms.

Instructions:
1. Download the CD ROM Order Form and the Recipient License Agreement.
2. Fill out the Order Form and sign the License Agreement
3. No fax copies will be accepted. Send the order form and the signed Recipient License Agreement to:

   Lannette Myers
   Office for Human Research Protections
   1101 Wootton Parkway, Suite 200
   Rockville MD 20852

Note: Assured VA institutions should not follow this procedure, but can obtain the CD ROM from the Office of Research Compliance and Assurance at their website; http://www.va.gov/oro/

___________________________________________________


PRIM&R is widely acknowledged as the premier educator in the research ethics and oversight field. At in-person meetings and through online learning, PRIM&R’s consistent, high-quality programming features respected and experienced teachers who provide participants with the most relevant and reliable information available. PRIM&R events are opportunities to share information and strategies with experts and colleagues from around the globe. Everyone is both a teacher and a learner at PRIM&R because the organization fosters collaborative relationships between and among those it serves. You can:

• See the Events Calendar for a complete list if upcoming programs (http://www.primr.org/eventcalendar.aspx).
• Learn more about PRIM&R conferences (http://www.primr.org/subpage.aspx?id=4286).
• Attend a Regional Meeting (http://www.primr.org/Subpage.aspx?id=1538).
• Subscribe to PRIM&R's Ethical Research Oversight Course (E-ROC) (http://www.primr.org/Subpage.aspx?id=1910).
• Bring PRIM&R to your institution with the At Your Doorstep program (http://www.primr.org/AYD/).
• View and order publications from PRIM&R (http://www.primr.org/edmaterials/).
• Attend a PRIM&R webinar (http://www.primr.org/webinars/).
• Obtain a Certificate of Attendance for past conferences or educational programs (http://www.primr.org/Subpage.aspx?id=4285).

• IRB Forum (http://www.irbforum.org/)

The IRB Forum (previously known as "MCWIRB") promotes the discussion of ethical, regulatory and policy concerns with human subjects research. The IRB Forum strives to create an atmosphere for open and respectful conversation about issues of mutual interest to the members. Although the privacy of e-mail cannot be guaranteed, the members of The IRB Forum should respect the confidentiality and opinions of others on the list. Please review the features, policy and procedures of The IRB Forum before requesting membership. Individuals who fail to abide by the terms of membership are subject to removal from The IRB Forum.

The IRB Forum is open to past and current members of Institutional Review Boards (IRB) or Research Ethics Committees (REC), IRB/REC administrators, individuals involved in IRB/REC oversight, and others with professional involvement in IRB/REC and/or research activities. Others will be admitted if their involvement in human subjects research will contribute to the discussion of issues pertinent to The IRB Forum. International participants are welcome. There is no membership fee.

Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) Educational Resources (http://www.aahrpp.org/)

AAHRPP takes a peer-review, educational approach to accreditation and provides a variety of print, online, and training resources to help organizations interpret the accreditation standards and navigate the accreditation process.

Metrics on HRPP Performance uses objective data to show how accredited human research protection programs actually perform. The figures and tables provide sponsors, researchers, and IRBs themselves with objective data to answer such questions as how long it takes the average accredited institutional review board or ethics committee to move a protocol from submission to approval. In fact, because so many have asked such questions about the research enterprise—without uncovering many evidenced-based answers—AAHRPP updates these charts regularly and adds new data annually. http://aahrpp.org/apply/resources/metrics-on-hrpp-performance

Introductory Webinars The major focus of the Getting Started and Getting On Board webinar is your self-assessment. This webinar is for individuals responsible for preparing an organization's self-assessment, or who are leading a team, and need assistance in initiating the process.

The webinar covers the process of accreditation, successful conduct and leadership of the self-assessment process, effective use of the Evaluation Instrument for Accreditation, and approaches for responding to accreditation standards organizations commonly find difficult. The format is interactive; participants are asked to offer local concerns for discussion, idea-sharing, and problem-solving.

You can schedule a one-hour Getting Started or Getting On Board Webinar, tailored to your organization's needs, by calling AAHRPP or sending an email to accredit@aahrpp.org. You might want to check the webinar system requirements before you register to make sure your organization can participate.
AAHRPP’s quarterly newsletter, **AAHRPPADVANCE**, provides focused, practical, and topical information on accreditation and the organizations that earn it. Feel free to e-mail AAHRPP at [accredit@aahrpp.org](mailto:accredit@aahrpp.org) to subscribe, letting them know whether you prefer receiving it by e-mail or the Postal Service, and with any other questions about accreditation.

The **Annual Conference** benefits professionals from both accredited and non-accredited organizations, including those working on accreditation or those new to the accreditation process. Government, industry, voluntary health agencies, and community groups that promote human research protection and quality research, as well as institutional officials, IRB professionals and chairs, compliance professionals, researchers, sponsors, and patient group leaders all learn together at these yearly meetings.

The **Document Library** contains all the documents you need in order to apply for and maintain accreditation.

---


**National Heart, Lung, and Blood Institute: Children and Clinical Studies**

**Center for Information Technology: NIH VideoCasting and Podcasting Archives**

CIT can broadcast your seminar, conference or meeting live to a world-wide audience over the Internet as a real-time streaming video. The event can be recorded and made available for viewers to watch at their convenience as an on-demand video or a downloadable podcast. CIT can also broadcast NIH-only or HHS-only content.

---

**Food and Drug Administration (FDA)** ([http://www.fda.gov/](http://www.fda.gov/))

**FDA Center for Drug Evaluation and Research (CDER) Learn Course List**
[http://www.fda.gov/Training/ForHealthProfessionals/default.htm](http://www.fda.gov/Training/ForHealthProfessionals/default.htm)

CDERLearn is the web page for educational tutorials offered by the Center for Drug Evaluation and Research (CDER). CDER's primary mission is to make certain that safe and effective drugs are available to the American people. There is, however, a strategic initiative to inform and educate people about the safe use of medicine, the drug regulatory process, the vital role health care professionals play to assist FDA in fulfilling its duties, and many other important issues. Online training is one way to share FDA expertise with many more people than face-to-face classroom sessions would allow, and we will offer additional CDERLearn courses in the future.

- **CDER World**
  A series of educational modules based on The CDER Forum for International Regulatory Authorities
Lectures. The modules present an overview of the work of the Center for Drug Evaluation and Research.

- **The FDA Bad Ad Program and Prescription Drug Promotion**
  This self-paced Web education course is designed to raise awareness among health care professionals (HCPs) about prescription drug promotion that may be misleading and educates HCPs about how to easily report these problems to FDA's Office of Prescription Drug Promotion.

- **CDER Small Business and Industry Education Series**
  CDER's Small Business and Industry Assistance Program has developed a series of Web-based courses to educate regulated small pharmaceutical industry.

- **Bringing an Over-the-Counter (OTC) Drug to Market**

- **Electronic Common Technical Document (eCTD)**

- **The Past, Present, and Future of FDA Human Drug Regulation**
  This 2010 version of “Drug Review and Related Activities in the United States” gives health care professionals, industry, consumers, and other interested participants an overview of the human drug regulatory process. Course time: approximately 90 minutes.

- **Medicines in My Home - An Interactive Home**
  This educational program is designed to help consumers from adolescence to adulthood understand and use the *Drug Facts* label to choose over-the-counter medicines and use them safely.
  - Student Guide
  - Instructor Guide

- **Risk Assessment and Communication**
  This CME program offered through Discover Health explains ways that physicians can communicate risk to their patients to help them make informed health care decisions. *Available for credit through June 27, 2011*

- **FDA Medwatch and Patient Safety**
  An online tutorial covering the MedWatch program goals of broadcasting safety information and encouraging adverse event reporting


- **The FDA Process for Approving Generic Drugs**
  Credit is no longer available for this course.

- **An Introduction to the Improved FDA Prescription Drug Labeling**
  Credit is no longer available for this course. The primary audience for this course content is physicians, physician assistants, pharmacists, nurses, nurse practitioners, and dentists. Secondary audiences include other health practitioners who are interested in the revised prescription drug labeling
FDA Center for Devices and Radiological Health (CDRH) Learn Course List
http://www.fda.gov/training/cdrhlearn/default.htm

CDRH Learn, FDA’s Center for Devices and Radiological Health (CDRH) is a web page for multimedia industry education. CDRH Learn is our innovative educational tool, which consists of learning modules describing many aspects of medical device and radiation emitting product regulations, covering both premarket and postmarket topics. This tool is intended to provide industry with information that is comprehensive, interactive, and easily accessible. Modules are provided in various formats, including videos, audio recordings, and slide presentations. CDRH will determine the most appropriate format for the particular topic being presented, and will post the learning module on this site to meet your educational needs!

- The Basics
- How to Market Your Device
- Postmarket Activities
- Unique Device Identification (UDI) System
- Specialty Technical Topics
- Radiation-Emitting Products
- In Vitro Diagnostics (IVD)
OHRP Listserv

Join OHRP's News distribution list by sending an e-mail to:

[LISTSERV@LIST.NIH.GOV](http://archive.hhs.gov/ohrp/news/distributionlist.html), with the following text message body:

SUBSCRIBE OHRP-L Firstname Lastname, replacing Firstname and Lastname with your name.

Your e-mail address will automatically be captured from the "From" address of your message.

At any time, if you wish to remove your name from the list, send an e-mail to:

[LISTSERV@LIST.NIH.GOV](http://archive.hhs.gov/ohrp/news/distributionlist.html) with UNSUBSCRIBE OHRP-L in the message body.
<table>
<thead>
<tr>
<th>Category</th>
<th>Homepage</th>
<th>Subcategory Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advisory Committee on Human Radiation Experiments</td>
<td><a href="http://www.gwu.edu/~nsarchiv/radiation/">http://www.gwu.edu/~nsarchiv/radiation/</a></td>
<td></td>
</tr>
<tr>
<td>American Society for Bioethics and Humanities</td>
<td><a href="http://www.asbh.org">http://www.asbh.org</a></td>
<td></td>
</tr>
<tr>
<td>Association of American Universities (AAU)</td>
<td><a href="http://www.aau.edu/">http://www.aau.edu/</a></td>
<td></td>
</tr>
<tr>
<td>Belmont Report (Ethical Principles and Guidelines)</td>
<td><a href="http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html">http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html</a></td>
<td></td>
</tr>
<tr>
<td>Bioresearch Monitoring (FDA Program)</td>
<td><a href="http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm160670.htm">http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm160670.htm</a></td>
<td></td>
</tr>
<tr>
<td>CBER (Center for Biologics Evaluation and Research, FDA)</td>
<td><a href="http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm106001.htm">http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm106001.htm</a></td>
<td></td>
</tr>
<tr>
<td>CDC (Center for Disease Control and Prevention, DHHS)</td>
<td><a href="http://www.cdc.gov/">http://www.cdc.gov/</a></td>
<td></td>
</tr>
<tr>
<td>CDRH (Center for Devices and Radiological Health, FDA)</td>
<td><a href="http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/default.htm">http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/default.htm</a></td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Homepage</td>
<td>Subcategory Sites</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Council for International Organizations of Medical Sciences (CIOMS)</td>
<td><a href="http://www.cioms.ch/">http://www.cioms.ch/</a></td>
<td></td>
</tr>
<tr>
<td>Department of Education (Protection of Human Subjects)</td>
<td><a href="http://www2.ed.gov/about/offices/list/ocfo/humansub.html">http://www2.ed.gov/about/offices/list/ocfo/humansub.html</a></td>
<td>Human Subjects Homepage = <a href="http://humansubjects.energy.gov/research/default.htm">http://humansubjects.energy.gov/research/default.htm</a></td>
</tr>
<tr>
<td>DHHS (Dept. of Health and Human Services)</td>
<td><a href="http://www.hhs.gov/">http://www.hhs.gov/</a></td>
<td></td>
</tr>
<tr>
<td>FDA (Food and Drug Administration)</td>
<td><a href="http://www.fda.gov">http://www.fda.gov</a></td>
<td>FDA Bioresearch Monitoring Information = <a href="http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/default.htm">http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/default.htm</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Title 21 CFR 50 = <a href="http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50">http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50</a></td>
</tr>
<tr>
<td>Category</td>
<td>Homepage</td>
<td>Subcategory Sites</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ICH (International Conference on Harmonization)</td>
<td><a href="http://www.ich.org/home.html">http://www.ich.org/home.html</a></td>
<td></td>
</tr>
<tr>
<td>IRB Forum (formerly MCWIRB now maintained by PRIM&amp;R)</td>
<td><a href="http://www.irbforum.org/">http://www.irbforum.org/</a></td>
<td></td>
</tr>
<tr>
<td>NCTR (National Center for Toxicological Research)</td>
<td><a href="http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/ucm2006206.htm">http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/ucm2006206.htm</a></td>
<td></td>
</tr>
<tr>
<td>NHGRI (National Human Genome Research Institute)</td>
<td><a href="http://www.genome.gov/">http://www.genome.gov/</a></td>
<td></td>
</tr>
<tr>
<td>NHRPAC Archive (National Human Research Protections Advisory Committee)</td>
<td><a href="http://www.hhs.gov/ohrp/archive/nhrpac/nhrpac.htm">http://www.hhs.gov/ohrp/archive/nhrpac/nhrpac.htm</a></td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Subcategory Sites</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Division of Extramural Research: Ethical, Legal, and Social Implications Research Program = <a href="http://www.genome.gov/10001618">http://www.genome.gov/10001618</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human Genome Project = <a href="http://www.genome.gov/10001772">http://www.genome.gov/10001772</a></td>
<td></td>
</tr>
<tr>
<td>NSF (National Science Foundation)</td>
<td>Nuremberg Code (Directives for Human Experimentation) = <a href="http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018191.htm">http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018191.htm</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Office of Good Clinical Practice (formerly Office of Human Research Trial) FDA = <a href="http://www.fda.gov/ForHealthProfessionals/default.htm">http://www.fda.gov/ForHealthProfessionals/default.htm</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OHRP IRB Guidebook = <a href="http://www.hhs.gov/ohrp/archive/irb/irb_guidebook.htm">http://www.hhs.gov/ohrp/archive/irb/irb_guidebook.htm</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORA (Office of Regulatory Affairs) FDA = <a href="http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ora/default.htm">http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ora/default.htm</a></td>
<td></td>
</tr>
<tr>
<td>OBA (Office of Biotechnology Activities)</td>
<td>OHA (Office of Health Affairs) OHA has been reorganized as “Information for Health Professionals”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORA (Office of Regulatory Affairs) FDA</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Homepage</td>
<td>Subcategory Sites</td>
</tr>
<tr>
<td>----------</td>
<td>----------</td>
<td>-------------------</td>
</tr>
<tr>
<td>ORI (Office of Research Integrity) Department of Health and Human Resources</td>
<td><a href="http://ori.dhhs.gov">http://ori.dhhs.gov</a></td>
<td>ORI (Office of Research Integrity) Department of Health and Human Resources</td>
</tr>
<tr>
<td>ORO (Office of Research Oversight)</td>
<td><a href="http://www.va.gov/oro/">http://www.va.gov/oro/</a></td>
<td></td>
</tr>
<tr>
<td>PRIM&amp;R (Public Responsibility in Medicine and Research)</td>
<td><a href="http://www.primr.org/">http://www.primr.org/</a></td>
<td></td>
</tr>
<tr>
<td>R&amp;D (VA Research &amp; Development)</td>
<td><a href="http://www.research.va.gov/default.cfm">http://www.research.va.gov/default.cfm</a></td>
<td></td>
</tr>
<tr>
<td>UK Homepage (University of Kentucky)</td>
<td><a href="http://www.uky.edu/">http://www.uky.edu/</a></td>
<td></td>
</tr>
</tbody>
</table>
# Office for Human Research Protections (OHRP)

OHRP Staff Telephone Numbers and E-Mail Addresses - Organizationally

OHRP Main Telephone Number: Toll-Free (866) 447-4777 or (240) 453-6900  
OHRP Fax Number: (240) 453-6909  
E-mail: OHRP@hhs.gov

<table>
<thead>
<tr>
<th>Staff Member</th>
<th>Telephone</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Office of the Director</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menikoff, Jerry</td>
<td>(240) 453-6900</td>
<td><a href="mailto:jerry.menikoff@hhs.gov">jerry.menikoff@hhs.gov</a></td>
</tr>
<tr>
<td>Director</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pritchard, Ivor</td>
<td>(240) 453-8230</td>
<td><a href="mailto:ivor.pritchard@hhs.gov">ivor.pritchard@hhs.gov</a></td>
</tr>
<tr>
<td>Acting Deputy Director</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Administrative Services**      |             |                               |
| Goodwin, Toni                    | (240) 453-8145 | toni.goodwin@hhs.gov         |
| Administrative Support           |             |                               |
| Fan, Yi-Chiu (Debbie)            | (240) 453-8124 | yi-chiu.fan@hhs.gov         |
| Administrative Support           |             |                               |
| James, Carla                     | (240) 453-8234 | carla.brown@hhs.gov         |
| Administrative Support           |             |                               |

<p>| <strong>Division of Compliance Oversight</strong> |             |                               |
| Borror, Kristina                  | (240) 453-8132 | <a href="mailto:kristina.borror@hhs.gov">kristina.borror@hhs.gov</a>      |
| Division Director                 |             |                               |
| Banks-Shields, Marinna            | (240) 453-8297 | <a href="mailto:marinna.banks-shields@hhs.gov">marinna.banks-shields@hhs.gov</a>|
| Compliance Oversight              |             |                               |</p>
<table>
<thead>
<tr>
<th>Staff Member</th>
<th>Telephone</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchanan, Lisa</td>
<td>(240) 453-8298</td>
<td><a href="mailto:lisa.buchanan@hhs.gov">lisa.buchanan@hhs.gov</a></td>
</tr>
<tr>
<td>Compliance Oversight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheaves, Sarita</td>
<td>(240) 453-8211</td>
<td><a href="mailto:sarita.cheaves@hhs.gov">sarita.cheaves@hhs.gov</a></td>
</tr>
<tr>
<td>Compliance Oversight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramnath, Kemnique</td>
<td>(240) 453-8120</td>
<td><a href="mailto:kemnique.ramnath@hhs.gov">kemnique.ramnath@hhs.gov</a></td>
</tr>
<tr>
<td>ORISE Fellow</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Division of Education and Development

<table>
<thead>
<tr>
<th>Staff Member</th>
<th>Telephone</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feige, Michelle</td>
<td>(240) 453-8207</td>
<td><a href="mailto:michelle.feige@hhs.gov">michelle.feige@hhs.gov</a></td>
</tr>
<tr>
<td>Acting Division Director</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myers, Lannette</td>
<td>(240) 453-8142</td>
<td><a href="mailto:lannette.myers@hhs.gov">lannette.myers@hhs.gov</a></td>
</tr>
<tr>
<td>Division Support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ross, Darlene</td>
<td>(240) 453-8127</td>
<td><a href="mailto:darlene.ross@hhs.gov">darlene.ross@hhs.gov</a></td>
</tr>
<tr>
<td>Education/Quality Improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoder, Freda</td>
<td>(240) 453-8239</td>
<td><a href="mailto:freda.yoder@hhs.gov">freda.yoder@hhs.gov</a></td>
</tr>
<tr>
<td>Education/Quality Improvement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Division of Policy and Assurances

<table>
<thead>
<tr>
<th>Staff Member</th>
<th>Telephone</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stith-Coleman, Irene</td>
<td>(240) 453-8138</td>
<td><a href="mailto:irene.stith-coleman@hhs.gov">irene.stith-coleman@hhs.gov</a></td>
</tr>
<tr>
<td>Division Director</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blatt, Harold</td>
<td>(240) 453-8232</td>
<td><a href="mailto:hal.blatt@hhs.gov">hal.blatt@hhs.gov</a></td>
</tr>
<tr>
<td>Assurances/IRB Registrations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brooks, Sanjur</td>
<td>(240) 453-8227</td>
<td><a href="mailto:sanjur.brooks@hhs.gov">sanjur.brooks@hhs.gov</a></td>
</tr>
<tr>
<td>ORISE Fellow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gorey, Julia</td>
<td>(240) 453-8141</td>
<td><a href="mailto:julia.gorey@hhs.gov">julia.gorey@hhs.gov</a></td>
</tr>
<tr>
<td>Policy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holloway, Gail</td>
<td>(240) 453-8221</td>
<td><a href="mailto:gail.holloway@hhs.gov">gail.holloway@hhs.gov</a></td>
</tr>
<tr>
<td>Division Support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaneshiro, Julie</td>
<td>(240) 453-8293</td>
<td><a href="mailto:julie.kaneshiro@hhs.gov">julie.kaneshiro@hhs.gov</a></td>
</tr>
<tr>
<td>Team Leader, Policy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Makle, Jean</td>
<td>(240) 453-8292</td>
<td><a href="mailto:jeanmarie.makle@hhs.gov">jeanmarie.makle@hhs.gov</a></td>
</tr>
<tr>
<td>Assurances/IRB Registrations</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Staff Member</strong></td>
<td><strong>Telephone</strong></td>
<td><strong>E-mail</strong></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td><strong>International Activities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bartlett, Edward</td>
<td>(240) 453-8249</td>
<td><a href="mailto:edward.bartlett@hhs.gov">edward.bartlett@hhs.gov</a></td>
</tr>
<tr>
<td>International</td>
<td></td>
<td></td>
</tr>
<tr>
<td>James, Carla</td>
<td>(240) 453-8234</td>
<td><a href="mailto:carla.brown@hhs.gov">carla.brown@hhs.gov</a></td>
</tr>
<tr>
<td>Administrative Support</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secretary's Advisory Committee</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gorey, Julia</td>
<td>(240) 453-8141</td>
<td><a href="mailto:julia.gorey@hhs.gov">julia.gorey@hhs.gov</a></td>
</tr>
<tr>
<td>Executive Director, SACHRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chirinos, Cecilia</td>
<td>(240) 453-8248</td>
<td><a href="mailto:cecilia.chirinos@hhs.gov">cecilia.chirinos@hhs.gov</a></td>
</tr>
<tr>
<td>SACHRP Support</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Content last reviewed on March 6, 2014
Good Clinical Practice Contacts

Good Clinical Practice Program (GCPP)

Members of our staff:

- Joanne Less, Ph.D., Director, Office of Good Clinical Practice
- Janet Donnelly, CIP, RAC, Policy Analyst
- Bridget Foltz, MS, MT(ASCP), Policy Analyst
- Doreen Kezer, M.S.N., Senior Health Policy Analyst
- Patrick McNeilly, Ph.D., R.Ph., C.I.P., Senior Health Policy Analyst
- Kathleen (Swisher) Pfaender, R.N., J.D., Senior Health Policy Analyst
- Kevin A. Prohaska, D.O., M.P.H., Senior Medical Policy Analyst
- Jean Toth-Allen, Ph.D., Biophysicist

Contact the Office of Good Clinical Practice if you have:

- general questions about FDA good clinical practice regulations and policy
- general questions about the FDA clinical Bioresearch Monitoring Program, and specifically clinical investigator, Institutional Review Board (IRB), sponsor, monitor, and contract research organization programs
- questions about or suggestions related to FDA’s Information Sheets for IRB’s and Clinical Investigators
- questions about reports made pursuant to 21 CFR 56.108(b) and 56.113 involving an FDA-regulated product if you do not know which FDA Center has jurisdiction (e.g., drug, medical device, biological product), including:
  - unanticipated problems involving risks to subjects [21 CFR 56.108(b)(1)]
  - serious or continuing noncompliance by an investigator with FDA regulations or with the IRB’s determinations [21 CFR 56.108(b)(2)]
  - suspension or termination of IRB approval of a protocol [21 CFR 56.108(b)(3)]

Questions about Good Clinical Practice

Submit questions via email, in writing, or direct them to our general telephone number. We try to respond to each question as soon as possible.

(Please note: FDA cannot comment about products that are in the review process. We cannot comment about clinical trials for specific products, diseases, or conditions. We cannot answer questions about when a new product subject to pre-market approval will be approved or not approved.)
E-mail: gcp.questions@fda.hhs.gov  
Telephone: 301-796-8340  
Facsimile: 301-847-8640  
Write: Food and Drug Administration  
Office of Good Clinical Practice  
Office of Special Medical Programs  
10903 New Hampshire Ave., WO32-5103  
Silver Spring, MD 20993

Biological Products

Bioresearch Monitoring Branch  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research (CBER)  
Telephone: 301-827-6221  
Facsimile: 301-827-6748

Contact the Bioresearch Monitoring Branch for questions about:

- The legal status of a test article  
- Human subject production regulations relating to biologics  
- CBER assigned IRB inspections  
- CBER assigned Clinical Investigator inspections  
- Reports made pursuant to 21 CFR 56.108(b) and 56.113 involving a biologic product including:
  - unanticipated problems involving risks to subjects  
  - serious or continuing noncompliance by an investigator with FDA regulations or with the IRB’s determinations  
  - suspension or termination of IRB approval of a protocol

Drug Products

Office of Scientific Investigations (OSI)  
Office of Compliance  
Center for Drug Evaluation and Research (CDER)  
Telephone: 301-796-3150  
Facsimile: 301-847-8748  
Email: CDER-OSI@fda.hhs.gov

Contact the Office of Scientific Investigations for questions about:

- Human subject protection regulations pertaining to drugs (21 CFR Parts 50, 56, 312, 361)  
- CDER-assigned IRB inspections (e.g., FDA-483’s)  
- Reports made pursuant to 21 CFR 56.108(b) and 56.113 involving a drug product including:
  - unanticipated problems involving risks to subjects [21 CFR 56.108(b)(1)]  
  - serious or continuing noncompliance by an investigator with FDA regulations or with the IRB’s determinations [21 CFR 56.108(b)(2)]
Medius Devices

Division of Bioresearch Monitoring
Office of Compliance
Center for Device and Radiological Health (CDRH)
Phone: 301-796-5490
Fax: 301-847-8136
Web site: www.fda.gov/cdrh/comp/bimo.html

Contact the Division of Bioresearch Monitoring for questions about:

• Human subject protection regulations pertaining to medical devices [21 CFR Parts 50, 56, and 812]
• Informed consent, standard operating procedures, records and reports
• Serious or continuing noncompliance by an investigator with FDA regulations or with the IRB’s determinations involving a medical device [21 CFR 56.108(b)(2)]
• Reporting complaints related to human subject protection/Good Clinical Practice in FDA-regulated medical device trial

CFSAN-regulated products

Bioresearch Monitoring Program
Office of Center Director
Center for Food Safety and Applied Nutrition (CFSAN)
Phone: 240-402-1757
Fax: 301-436-2668

Contact the Bioresearch Monitoring Program for questions about:

• Human subject protection relating to CFSAN-regulated products. CFSAN-regulated products include:
  o food additives
  o color additives
  o infant formula
  o dietary supplements
• Human subject protection relating to petitions for nutrient content claims and health claims
• Reporting complaints related to the conduct of clinical trials of CFSAN-regulated products
New Animal Drugs

Premarket Compliance and Administrative Action Team
Center for Veterinary Medicine (CVM)
Phone: 240-276-9200
Fax: 240-276-9241

Contact the Premarket Compliance and Administrative Actions Team for questions about:

- Good Clinical Practice regulations pertaining to new animal drugs for investigational use (21 CFR Part 511)
- Reporting complaints related to the conduct of studies with new animal drugs for investigational use

Enforcement Information

Division of Compliance Policy
Office of Enforcement
Office of Regulatory Affairs
Telephone: 240-632-6800
Fax: 240-632-6810

Contact the Division of Compliance Policy for questions about:

- questions about the overall FDA Bioresearch Monitoring Program, and specifically the Good Laboratory Practice (GLP, nonclinical laboratories) Program
- general Bioresearch Monitoring program enforcement issue

Page Last Updated: 06/20/2014
## Office of Research Oversight (ORO)

**Central Office**  
**Mailing Address (including express mail):**  
810 Vermont Ave., NW (10R), Washington, DC 20420  
[Physical location: 1100 1st Street, NE, Washington, DC 20002]  
**Main Phone Number:** (202) 632-7620

<table>
<thead>
<tr>
<th>Position</th>
<th>Phone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Director, Tom Puglisi, PhD</td>
<td>202-632-7676</td>
</tr>
<tr>
<td>Deputy Executive Director, Peter Poon, JD, MA, CIPP/G</td>
<td>202-632-7687</td>
</tr>
<tr>
<td>Medical Officer / Associate Director for Policy &amp; Planning, James F. Burris, MD</td>
<td>202-632-8431</td>
</tr>
<tr>
<td>Executive Analyst, Shannon Williams, CIPP/G</td>
<td>202-632-7682</td>
</tr>
<tr>
<td>Research Misconduct Officer, Doug Bannerman, PhD</td>
<td>202-632-7688</td>
</tr>
<tr>
<td>Health Science Specialist, Melody Higgins, RN, MS, CCRP</td>
<td>202-632-7631</td>
</tr>
<tr>
<td>Health Science Specialist, Hannah Van Hook, RN, BS</td>
<td>202-632-7679</td>
</tr>
<tr>
<td>Staff Assistant, Penny Powell, COTR</td>
<td>202-632-7675</td>
</tr>
<tr>
<td>Staff Assistant, Ronnie Bautista, US Navy (Retired)</td>
<td>202-632-7625</td>
</tr>
</tbody>
</table>

**Research Compliance Education & Policy (RCEP) Program**  
[ORORCEP@va.gov](mailto:ORORCEP@va.gov)

<table>
<thead>
<tr>
<th>Position</th>
<th>Phone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate Director, Robert Brooks, MD, PhD, MBA</td>
<td>202-632-7622</td>
</tr>
<tr>
<td>Deputy Director, Yen Nguyen, PharmD, CCRC</td>
<td>202-632-7686</td>
</tr>
<tr>
<td>Veterinary Medical Officer, Dale H. Conaway, DVM, MS*</td>
<td>678-924-5773</td>
</tr>
<tr>
<td>Health Science Specialist, Priscilla Craig, COTR</td>
<td>202-632-7624</td>
</tr>
<tr>
<td>Health Science Specialist, Aileen Ward, RN, MSN, CCRP, CIP</td>
<td>202-632-7681</td>
</tr>
<tr>
<td>Management Analyst, Michael Grabenbauer, BBA, LATG, US Army (Retired)</td>
<td>202-632-7628</td>
</tr>
<tr>
<td>Staff Assistant, Dee Dee Chavers</td>
<td>202-632-7623</td>
</tr>
</tbody>
</table>

*Virtual position

**Research Information Security & Privacy (RISP) Program**  
[ORORIPP@va.gov](mailto:ORORIPP@va.gov)

<table>
<thead>
<tr>
<th>Position</th>
<th>Phone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate Director, Vacant</td>
<td>202-632-7678</td>
</tr>
<tr>
<td>Deputy Director, Brendan Keegan, PhD</td>
<td>202-632-7639</td>
</tr>
<tr>
<td>Health Science Specialist, Greg Gilbo, CISA, CISM, CRISC, CIPP/G</td>
<td>202-632-7627</td>
</tr>
<tr>
<td>Management Analyst, Sweden DeMatas, PsyD, CIPP/G*</td>
<td>206-484-1942</td>
</tr>
<tr>
<td>Management Analyst, Dona Wooding, CSP, CHP, CAP*</td>
<td>202-641-8374</td>
</tr>
</tbody>
</table>

*Virtual positions

**Research Safety & Animal Welfare (RSAW) Program**  
[AskORO@va.gov](mailto:AskORO@va.gov)

<table>
<thead>
<tr>
<th>Position</th>
<th>Phone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate Director, Susan Harper, DVM, MS, DACLAM, DACVPM</td>
<td>202-632-7630</td>
</tr>
<tr>
<td>Health Science Specialist, Jamie Boehner, MS, PhD</td>
<td>202-632-8017</td>
</tr>
<tr>
<td>Health Science Specialist, Jim Trout, PhD, COTR</td>
<td>202-632-7677</td>
</tr>
<tr>
<td>Position</td>
<td>Phone Number</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Industrial Hygienist, Vacant</td>
<td>202-632-7660</td>
</tr>
<tr>
<td>Veterinary Medical Officer, Carol Eisenhauer, DVM, DACLAM*</td>
<td>304-433-5625</td>
</tr>
<tr>
<td>Veterinary Medical Officer, Maria Lorenzo, DVM, MPH, DACLAM</td>
<td>202-632-7685</td>
</tr>
<tr>
<td>Veterinary Medical Officer, Joanna Walker, DVM</td>
<td>202-632-7680</td>
</tr>
<tr>
<td>*Virtual position.</td>
<td></td>
</tr>
</tbody>
</table>

**Midwestern Regional Office (578/10R)**

Building 1(10R), Room B-103, 5th Ave. & Roosevelt Rd., Hines, IL 60141

Fax Number: (708) 202-7250 | MidwestORO@va.gov

Director, Cindy Paulsen            708-202-7251
Health Science Specialist, Kathleen Franke, CIP       708-202-7266
Health Science Specialist, Peter Mestaz, MS, CIP       708-202-7256
Health Science Specialist, Dennis Runyan, DDS, MS       708-202-7262
Health Science Specialist, Jean Stocks, RN, BSN, CCRC    708-202-7259
Program Specialist, Dawn Arps          708-202-7254

**Northeastern Regional Office (518/10R)**

VAMC Bedford, 200 Springs Rd., Bedford, MA 01730

Fax Number: (781) 687-3858 | VHANortheastRegionalOfficeofResearchOversight@va.gov

Director, Richard D'Augusta, RPh, MPA, CHRC      781-687-4783
Health Science Specialist, Nympha D'Souza, MS, PhD, MPH       781-687-4782
Health Science Specialist, Duane Janke, MBA       781-687-4778
Health Science Specialist, Mark Long, MPA, CIP       781-687-4786
Health Science Specialist, Frank Minichiello, LCSW, FACHE    781-687-4785
Health Science Specialist, Sandra Wunschel, LICSW, FACHE   781-687-4787
Program Specialist, Ovidia Dragoli, CIM, COTR          781-687-4784

**Southern Regional Office (508/10R)**

3700 Crestwood Pkwy, NW, Suite 210 (10R), Duluth, GA 30096

Fax Number: (678) 924-5708 / Conference Room: (678) 924-5765 | ATGOROSRO@va.gov

Director, Ben Gao, PhD                  678-924-5752
Health Science Specialist, Damaris Alvelo-Ceron, PhD       678-924-5770
Health Science Specialist, Terri Carlton, MPH             678-924-5769
Health Science Specialist, Michelle Fronheiser, MBA, CIM, CIP 678-924-5771
Health Science Specialist, Ward Hobbs, MS, MA, CCRC       678-924-5751
Administrative Officer, Judy Wilson         678-924-5762
Western Regional Office (605/10R)
For US Mail: P.O. Box 8349, Moreno Valley, CA 92552-8349
For Express Delivery: ORO Western Region, 14560 2nd Street, Bldg. 2641, Suite B, Riverside, CA 92518
Fax Number: (909) 801-5176 | OROWesternRegion@va.gov

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
<th>Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Director, Medical Director</td>
<td>Paul Hammond, MD, DPhil</td>
<td>909-801-5167</td>
</tr>
<tr>
<td>Health Science Specialist</td>
<td>John Farley, PhD</td>
<td>909-801-5169</td>
</tr>
<tr>
<td>Health Science Specialist</td>
<td>Cynthia Kerenyi, MAM</td>
<td>909-801-5168</td>
</tr>
<tr>
<td>Health Science Specialist</td>
<td>Carrie Pennison, BA</td>
<td>909-801-5164</td>
</tr>
<tr>
<td>Health Science Specialist</td>
<td>Deborah Van Etten, BA</td>
<td>909-801-5180</td>
</tr>
<tr>
<td>Health Science Specialist</td>
<td>Jeff West</td>
<td>909-801-5165</td>
</tr>
</tbody>
</table>