

Institutional Review Board Guidebook

*** FOREWORD ***

The impetus for developing this Guidebook for Institutional Review Boards (IRBs) was a finding of need by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. In its 1981 report, *Protecting Human Subjects: The Adequacy and Uniformity of Federal Rules and their Implementation*, the Commission stated that it "is clear that researchers and IRB members desire help both in understanding the policies and principles that underlie the regulations governing research with human subjects, and in identifying the issues to which one should be sensitive in designing or reviewing research proposals".

A first edition of the Guidebook was produced in the early 1980s under contract for the President's Commission by Public Responsibility in Medicine and Research (PRIM&R). PRIM&R is a Boston-based, nonprofit organization that sponsors annual conferences on topics related to the protection of human subjects.

The present Guidebook is a revised, updated, and expanded second edition, prepared under contract by Robin Levin Penslar, Research Associate at the Poynter Center for the Study of Ethics and American Institutions, in consultation with the Office for Protection from Research Risks and its numerous advisors. The Poynter Center is an independent ethics center housed at Indiana University.

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A. INTRODUCTION

Most of the research reviewed by IRBs falls within the broad categories of biomedical or behavioral research. IRBs should be sensitive to specific aspects of biomedical and behavioral research in their review of protocols.

Biomedical research includes both studies designed primarily to increase the scientific base of information about normal or abnormal physiology and development and studies primarily intended to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. The terms "behavioral research" or "the behavioral sciences" may be used to refer either to studies of the behavior of individuals, or to studies of the behavior of aggregates such as groups, organizations, or societies. The broad objective of the behavioral and social sciences is similar to that of the biomedical sciences: to establish a body of demonstrable, replicable facts and theory that contributes to knowledge and to the amelioration of human problems.

It is neither possible nor necessary to draw a clean line between biomedical and behavioral research. Some biomedical research pertains to behavior (*e.g.*, in psychiatry, neurology, or epidemiology), and many of the methods used in behavioral research, such as observation and the questioning of subjects, are also used in biomedical research. Research may be designed to evaluate the behavioral changes that result from a biomedical intervention (*e.g.*, lessening of depression after taking a particular medication or changes in psychiatric disorders following hemodialysis) or to examine physiological responses to behavioral interventions (*e.g.*, lowering of blood pressure through biofeedback or weight loss through hypnosis). Some studies involve functions that are not easily defined as either behavioral or physiological (*e.g.*, sleep, exercise, or diet). Thus, although it is sometimes useful to refer to biomedical or behavioral and social research as if they involve distinct activities, there is considerable overlap among the three areas. (While the use of such terms as "behavioral and social research" may imply that social research is distinct from behavioral research, this distinction generally has little utility for the work of IRBs and is not applied here.) The questions that are of concern to IRBs stem not from the label attached to the research but from the nature of the interventions and the characteristics of the subjects in any given study. It is for this reason that institutions and federal agencies are concerned that IRB members be knowledgeable about the various types of research reviewed by that IRB.

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BIOMEDICAL RESEARCH

Biomedical research employs many methods and research designs. Studies designed to evaluate the safety, effectiveness, or usefulness of an intervention include research on therapies (*e.g.*, drugs, diet, exercise, surgical interventions, or medical devices), diagnostic procedures (*e.g.*, CAT scans or prenatal diagnosis through amniocentesis, chorionic villi testing, and fetoscopy), and preventive measures (*e.g.*, vaccines, diet, or fluoridated toothpaste). Research on normal human functioning and development can include studies of the human body while exercising, fasting, feeding, sleeping, or learning, or responding to such things as stress or sensory stimulation. Some studies compare the functioning of a particular physiological system at different stages of development (*e.g.*, infancy, childhood, adolescence, adulthood, or old age). Others are directed at defining normal childhood development so that deviations from normal can be identified. Sometimes research, particularly records research, is used to develop and refine hypotheses. Research on specific disease processes is often needed before improved methods of

prevention, diagnoses, and treatment can be developed (*e.g.*, research on the biochemical changes associated with AIDS or schizophrenia, or the neurological changes associated with senile dementia of the Alzheimer type). Research on the human genome and genetic markers is expected to create new avenues for understanding disease processes and their eventual control.

Subjects of some biomedical studies engage in ordinary tasks (*e.g.*, exercise, learn a series of words, or respond to various sensory stimuli) while measurements of physiological and bodily functions are made. Although many procedures used in biomedical research are similar to those used in routine physical examinations, at times more invasive procedures (*e.g.*, "spinal taps," skin or muscle biopsies, or X-rays used in conjunction with contrast dyes) must be used if a desired measurement is to be made. Although research designed to generate information about normal physiology or a disease process is not concerned with evaluating a medical intervention, it may still require the use of invasive procedures. When the research deals with subjects whose condition is not normal, the research can have either therapeutic or nontherapeutic purposes.

Other biomedical studies do not involve human subjects or are exempt from the human subjects regulations, and, therefore, do not require IRB review. This category includes research with animals and research on preexisting samples of materials (tissue, blood, or urine) collected for other purposes, where the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects [Federal Policy § ___.101(b)(4)]. It also includes research based on records, when the data are recorded in such a manner that the individuals to whom the records pertain cannot be identified, either directly or through identifiers linked to them [Federal Policy § ___.101(b)(4)]. [See Guidebook Chapter 4, "Considerations of Research Design."]

Some biomedical studies, particularly those conducted to evaluate new therapies or treatments, use such rigorous experimental methods as **random** assignment to treatment and control groups. Other studies, such as those directed at establishing the normal range of some element in the blood, may involve no experimental intervention and no assignment of subjects to groups. [See Guidebook Chapter 4, "Considerations of Research Design."]

The fact that much biomedical research is conducted for the purpose of evaluating new therapies or treatments leads to two problems for IRBs. The first is to some degree a problem of IRB jurisdiction; the second is a problem of risk/benefit assessment. The distinction between research and treatment can become blurred in patient care settings, as well as in some educational and training settings. This distinction raises questions of IRB jurisdiction over the research: Is the proposed activity one that requires IRB review (pursuant either to federal regulations or institutional policy)? A discussion of this issue appears in the Guidebook in Chapter 1, Section A, "Jurisdiction of the Institutional Review Board."

The second distinction between research and therapies that may pose a problem for IRBs concerns risk/benefit assessments in research on therapies. Often, the risks of a study may seem justified by a therapy provided as part of the study. IRBs should determine, however, whether the anticipated therapeutic benefits would be available to persons who are not participating in a study that presents additional risks. As is discussed in the Guidebook Section on risk/benefit analysis [Chapter 3, Section A], such benefits should not be used to justify risks presented by the research.

The IRB's general responsibilities in reviewing biomedical research are discussed in other chapters of the Guidebook. [See Chapter 3, "Basic IRB Review," and Chapter 4, "Considerations of Research Design."] Special concerns arising in the conduct of certain types of biomedical research are discussed in the following Sections of this chapter on "Drug Trials," "Vaccine Trials," "Medical Devices," "Use of Radioactive Materials and X-Rays," "HIV-Related Research," "Transplants," "Human Genetic Research," and "Alcohol and Drug Research." The additional IRB responsibilities that arise when the subjects of biomedical research are other than healthy, normal adults are set forth in Chapter 6, "Special Classes of Subjects."

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BEHAVIORAL RESEARCH

The scope and diversity of research areas in the behavioral and social sciences is quite broad. Some research is readily applicable to human affairs; other studies may broaden understanding without any apparent or immediate application. Some research is designed to test hypotheses derived from theory; other research is primarily descriptive. Still other research may be directed at evaluating an intervention or social program.

Theories and methods vary both across and within disciplines; the same problems may be approached by researchers trained in different disciplines. For example, some research psychologists work in laboratories studying the neurology, anatomy, and physiology that underlies perception, learning, instinctual behavior, and emotional responses. Other psychologists may perform **survey** research, observational studies, or small group experiments that differ little from work done by some sociologists. Within anthropology, physical anthropology overlaps with paleontology, anatomy, and genetics, while the social or cultural anthropologist studies the organization, institutions, and belief and value systems of societies or groups of people.

Behavioral research involving human subjects generates data by means of questionnaires, observation, studies of existing records, and experimental designs involving exposure to some type of stimulus or intervention. Many variations of these four basic methods are used. Questions may be asked in person, over the telephone, or by means of a questionnaire. Observation may or may not be covert, and the observer may or may not be a participant in the activity being studied. Records studied in research may be public (*e.g.*, vital statistics, motor vehicle registrations, or court records) or non-public and sensitive (*e.g.*, medical or educational records in which the subjects are identified). Experimental studies may be conducted in public places, in private settings (*e.g.*, a clinic or therapist's office), or in laboratories. Interventions

in such studies range from the innocuous, such as varying the package design of commercial products, to the potentially significant, such as varying behavior modification techniques in studying the treatment of alcoholism. Not all behavioral research involves human subjects. Studies of human migration are often undertaken using anonymous U.S. Census data, and much research in behavioral psychology is done with animals. In addition, many categories of behavioral research that do involve human subjects are exempt from the federal regulations for protection of human subjects. [See Federal Policy §___.101.] This exemption does not imply that investigators have no ethical responsibilities to subjects in such research; it means only that IRB review and approval of the research is not required by federal regulations.

Most behavioral research involves no physical intervention and no physical risk. However, some studies do present a risk of social harm (*e.g.*, harm to a subject's reputation, which is sometimes a danger if **confidentiality** is not maintained) or psychological harm, which may occur if the research involves deception or provides subjects with unwelcome and disturbing information about themselves. When deception is involved, the IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects will be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself may present an unreasonable risk of harm without a counterveiling benefit.) The IRB should also make sure that the proposed subject population is suitable. [See Guidebook Chapter 3, Section A, "Risk/Benefit Analysis."]

Some studies involve the possibility of a moral wrong, which is what some commentators have labeled the ethical problems posed by deception of subjects or invasions of their **privacy**. Although some psychologists have overemphasized the value and necessity of using deception, deception or incomplete disclosure may be the only scientifically valid approach for certain research. An example of such research would be a study designed to determine the effect of group pressure (*i.e.*, responses of others) on a subject's estimate of the length of a series of lines. In some groups, pseudo-subjects would be told in advance to give incorrect answers to questions about the length of the lines to determine the effect of such misinformation on the real subjects' responses. Obviously, if the subjects were told all about the research design and its purpose in advance, it would not be possible to do the research. IRBs need to determine whether any deception or invasion of privacy involved in a research protocol is justified.

Some social and behavioral researchers are concerned that IRB judgments at times seem to be influenced more by the subject matter of the study than by concerns about informed consent or risks to subjects. Researchers cite examples of studies that involve **minimal risk** and pose no consent questions, but that encounter difficulty with some IRBs, particularly IRBs in medical settings. Some researchers believe that IRBs are more likely to object to research on the behavior or values of the powerful (*e.g.*, physicians, professors, or managers) than to research using similar methods but on subjects of lower status (*e.g.*, patients, students, or workers). Other researchers believe that IRBs sometimes perceive research on controversial topics, such as deviant sexual behavior or fraud in science, as presenting ethical problems because of the nature of the activity being studied, rather than because of research methods, risks, or the rights of subjects. Still others complain of a less specific prejudice against social and behavioral research on the grounds that it is "soft" or concerned with trivial questions.

Some behavioral research involves human subjects in studies of heredity and human behavior, genetics, race and IQ, psychobiology, or sociobiology. Vigorous ethical debates about these studies arise out of the fear that scientific data may be used to justify social stratification and prejudice, or that certain groups will appear to be genetically inferior. The possible use — or misuse — of research findings, however, should not be a matter for IRB review, despite the importance of this question.

The incidence of such problems may well have decreased because the regulations exempt much social research and provide additional flexibility regarding informed consent. IRBs should resist placing restrictions on research because of its subject matter; IRBs should instead be concerned about research methods and the rights and welfare of research subjects. IRBs must differentiate disapproving a research proposal because of qualms about the subject being explored or its possible findings, such as genetic differences in intelligence, from disapproving research involving the performance of illegal or unethical acts. The former raises serious issues of academic freedom; the latter is quite different and appropriate. Whatever the propriety of institutional administrators prohibiting research to protect the institutions from being associated with controversial or sensitive subjects, it is generally agreed that this is not an appropriate concern for an IRB, whose function is to protect human subjects.

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FIELDWORK

Fieldwork, or ethnographic research, involves observation of and interaction with the persons or group being studied in the group's own environment, often for long periods of time. Since fieldwork is a research process that gains shape and substance as the study progresses, it is difficult, if not impossible, to specify detailed contents and objectives in a **protocol**.

After gaining access to the fieldwork setting, the ongoing demands of scientifically and morally sound research involve gaining the approval and trust of the persons being studied. These processes, as well as the research itself, involve complex, continuing interactions between researcher and hosts that cannot be reduced to an informed consent form. Thus, while the idea of consent is not inapplicable in fieldwork, IRBs and researchers need to adapt prevailing notions of acceptable protocols and consent procedures to the realities of fieldwork. IRBs should keep in mind the possibility of granting a waiver of informed consent.

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SOCIAL POLICY EXPERIMENTATION

Social policy experimentation involves interventions in social or economic systems for use in planning public policy. Such experimentation often involves studying the costs and benefits of alternative ways of providing health, educational, or welfare services at national, state, or local levels. Some of this research may be exempt from IRB review under § 101(b)(5) of the Federal Policy. That section exempts research and demonstration projects that are conducted by or subject to the approval of department or agency heads, and that are 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.

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B. DRUG TRIALS

INTRODUCTION

Drug trials provide the transition from promising basic or laboratory research to helpful therapeutic or diagnostic procedures for patients. New drugs that offer the hope of some beneficial response in afflicted patients are first tested in animal models. But animal trials do not necessarily demonstrate what the physiological, pharmacological, or toxicological effects of a new drug will be in human beings. Only by careful testing in human subjects can the safety and effectiveness of a new drug be evaluated. The Food and Drug Administration (FDA) is responsible for monitoring the testing of new drugs in humans, for determining whether a new drug can be marketed, and for observing drugs after marketing to be sure that they are safe, effective, and properly labeled [21 CFR 312 and 21 CFR 314].

See also Guidebook Chapter 4, Section H, "Clinical Trials," and Section J, "Assignment of Subjects to Experimental and Control Groups."

DEFINITIONS

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

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

Investigational New Drug or Device: A drug or device permitted by FDA to be tested in humans, but not yet determined to be safe and effective for a particular use in the general population, and not yet licensed for marketing.

Investigator: In clinical trials, an individual who actually conducts an investigation [21 CFR 312.3]. Any interventions (*e.g.*, drugs) involved in the study are administered to subjects under the immediate direction of the investigator. (*See also:* Principal Investigator.)

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

Phase 1 Drug Trial: Phase 1 trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.

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

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

Phase 4 Drug Trial: Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time [21 CFR §312.85].

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

Sponsor: A person or entity that initiates a clinical investigation of a drug — usually the drug manufacturer or research institution that developed the drug. The sponsor does not actually conduct the investigation but rather distributes the new drug to investigators and physicians for clinical trials. The drug is administered to subjects under the immediate direction of an investigator who is not also a sponsor. A clinical investigator may, however, serve as a sponsor-investigator. The sponsor assumes responsibility for investigating the new drug, including responsibility for compliance with applicable laws and regulations. The sponsor, for example, is responsible for obtaining FDA approval to conduct a trial and for reporting the results of the trial to the FDA.

Sponsor-Investigator: An individual who both initiates and actually conducts, alone or with others, a clinical investigation. Corporations, agencies or other institutions do not qualify as sponsor-investigators.

OVERVIEW

Once a chemical (drug) is identified as having a potential effect on a disease state, it is subjected to testing in animals. Initial animal tests are designed to see whether the chemical has any desired drug effects, what dosage levels are poisonous, what the safe dosage range might be in humans, and whether there is a reason to test the chemical in humans. Additional animal tests may be required as human tests progress. If initial animal tests indicate that the drug can be safely tested in humans and that the chemical may be therapeutically useful, the drug sponsor will submit an Investigational New Drug Application (IND) to the FDA. In the IND, the **sponsor** must describe the complete composition of the drug, its source, and how it is made. In addition, the sponsor must submit the results of all animal studies that support the drug's potential usefulness in humans and that define its toxicity in animals. The data should indicate that no human subject will be exposed to an unreasonable **risk**. The IND must also include a **protocol** describing the plan for testing in humans. To permit the FDA to review the materials and make sure subjects will not be exposed to unreasonable risks, the sponsor may not begin clinical tests for 30 days after submitting the IND. At the end of that period, the sponsor may begin the proposed clinical trial unless the FDA has asked for a delay because of a potential safety problem involving use of the drug.

Clinical trials are conducted by clinical investigators (usually physicians) who have entered into an agreement with a sponsor to conduct the study. All physicians administering an **investigational drug** agree to conditions regarding the conduct of the study outlined by FDA regulations. Clinical investigators agree to these conditions by signing an FDA form that certifies that the investigator has obtained IRB review and approval prior to conducting the study.

Investigational new drugs may be available outside of a clinical trial, through a treatment protocol, to patients with life-threatening or other serious diseases for which no satisfactory alternative drug or other therapy exists. Established by the FDA in 1987, the Treatment Investigational New Drug exemption (Treatment IND) is a treatment protocol that is added to an existing IND. The Treatment IND allows physicians to treat qualifying patients according to the protocol. Treatment INDs are discussed in greater detail in Guidebook Chapter 2, Section B, "Food and Drug Administration Regulations and Policies."

For further information concerning human subjects research to which FDA regulations apply, contact:

Mr. Richard M. Klein
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel: (301) 443-1382

IRB CONSIDERATIONS

In reviewing proposed drug research, IRBs must first consider whether the protocol is scientifically sound. Since this decision is not the IRB's primary concern, however, an IRB may rely on the FDA, institutions, scientific review committees, funding agencies (*e.g.*, NIH), or others for this determination. [*See* the Introduction to Guidebook Chapter 4, "Considerations of Research Design" for a discussion of this question.] Evaluating the risks and benefits of drug trials requires IRBs to consider many aspects of the study design, paying special attention to the study population, the trial phase, and mechanisms for data analysis and surveillance. Risk/benefit analysis and review of the procedure for obtaining **informed consent** must be performed in all IRB reviews. [*See* Guidebook Chapter 3, Section A, "Risk/Benefit Analysis," and Chapter 3, Section B, "Informed Consent."] In addition, subjects participating in studies involving investigational drugs must be told that the FDA may have access to their medical records as they pertain to the study.

The obligation of IRBs and investigators to assure that subjects understand the purposes, methods, and possible hazards of the research is more difficult to fulfill when prospective subjects are seriously ill and in need of therapy. The consent process may require additional efforts and attention for research involving particularly vulnerable subjects such as the seriously ill. [See Chapter 6, Section G, "Terminally Ill Patients."]

Phase 1 trials are historically safest because they usually involve administering a single dose to healthy volunteers. However, Phase 1 trials may pose the highest level of unknown risk because they involve the drug's first administration to humans. (With highly toxic drugs such as cancer chemotherapies, Phase 1 trials are usually conducted with cancer patients as subjects.) Insofar as possible, risks should be identified from previous laboratory experiments and animal trials. The FDA, which reviews Phase 1 trials submitted in the initial IND application, may have valuable information and recommendations on particular protocols.

Subjects in **Phase 2 trials** are usually patients with the condition that the new drug is intended to detect or treat. IRBs should recognize that although Phase 2 testing is preceded by earlier clinical trials, the physiological responses of healthy volunteers to a therapeutic drug may not be reliable indicators of how safe the drug is for persons who are ill, taking other medication, or have immunodeficiencies. Since the primary purpose of a Phase 2 trial is to test the drug's effectiveness in achieving its purpose, the responses of subjects receiving the drug are usually compared with those of subjects who are not receiving the drug (**control subjects**). Whether control subjects receive some existing therapy or a **placebo** is a research design issue with serious ethical implications. Where an alternate safe and effective drug is available for a serious condition being studied, it should generally be given to the control subjects; however, existing therapies may be inadequate because they are of limited effectiveness against the disease, they have relatively high levels of toxicity, or because they are inconvenient to administer. When determining the acceptability of a proposed research design, IRBs must examine the risks and effectiveness of existing therapies, as well as the risks associated with providing no therapy (or a placebo). [See Chapter 4, "Considerations of Research Design."]

While most drug trials involve agents that the FDA has not yet approved for marketing, some drugs may be the subject of further testing concurrent with or following FDA approval. Post-marketing investigations, also called **Phase 4 trials**, are conducted to develop further information about the article's safety or effectiveness. Such studies might, for example, seek to establish the safety or effectiveness of using the drug for a new indication, with a new dosage level or a new route of administration [21 CFR §312.85].

Phase 4 studies should be distinguished from use of a marketed product by a physician for an indication not in the approved labeling as part of the "practice of medicine." Investigational use of a marketed product differs from such uses by physicians in that the principal intent of the investigational use of a test article is to develop information about its safety or efficacy; the submission of an **IND** or **IDE** may therefore be required. The criteria for submission of an IND or IDE for investigational use of a marketed product is described in the FDA's *IRB Information Sheet* entitled, "Investigational Use of Marketed Products," (1989, pp. 70-71).

Throughout drug trials, the distinction between therapy and research must be maintained. A physician who participates in research by administering a new drug to consenting patients must ensure that the patients understand and remember that the drug is experimental, and that its benefits for the condition under study are unproven. Furthermore, whereas the principal investigator's primary allegiance is to the protocol, the physician's allegiance is to the patient. Where an individual is both an investigator and the subject's treating physician, these two allegiances may conflict. The subject must recognize that the person with whom he or she is dealing may have such conflicting interests. The IRB should be aware of the need to inform the patient of the potential conflict.

If the trial is to collect accurate and timely data concerning the drug's safety and effectiveness, procedures for identifying positive and negative responses to the drug should be in place, and all participating physicians should be well integrated into a reporting system. The principal investigator is responsible for keeping all subjects informed of material changes in the design and conduct of the research, and must communicate new information that might affect their willingness to continue as subjects [Federal Policy §___.116]. The IRB may assist the investigator in deciding when information from accumulating data should be disclosed to participating or prospective subjects. The disclosure of information gained during the conduct of the trial is especially important with patients entering a study when it is nearing completion.

As part of their determination of the appropriate methods for conducting continuing reviews of ongoing studies, IRBs should be aware of the arrangements made for monitoring the study results. In FDA-regulated clinical investigations, arrangements for data monitoring are the sponsor's responsibility. The sponsor may designate an independent person or group (often called a **data and safety monitoring board**) to assume this responsibility. An IRB may function in such a capacity; however, most IRBs do not have the necessary expertise. Independent monitoring is most appropriate when the study is **double-masked** (*i.e.*, neither the subjects nor the investigators know which drug a subject is receiving) or if the trial is multicentered. Ongoing monitoring of drug trials includes review of data on therapeutic effects, side effects and the effects of any changes in the study design. [See also Guidebook Chapter 3, Section E, "Monitoring and Observation."] Sponsors must notify the FDA and all participating investigators of any adverse experiences associated with the use of an investigational new drug that is both serious and unexpected [21 CFR 312.32].

Occasionally, hazards are discovered after a trial is concluded. If the drug has since been marketed, the FDA and the drug manufacturer are usually responsible for notifying users and physicians.

POINTS TO CONSIDER

1. Is the proposed research scientifically sound?
2. Has sufficient information been obtained from the literature, experimental and animal studies, and the FDA to define, as far as possible, the potential risks of and the precise need for studies involving human subjects?

3. Does the principal investigator have the appropriate qualifications, experience, and facilities to ensure that all aspects of the trial and follow-up will be conducted rigorously and with due regard for the safety and well-being of the subjects?
4. Have appropriate measures been adopted to ensure that subjects understand the objectives and consequences, particularly the risks, of their participation?
5. Are sufficient safeguards provided to ensure the **confidentiality** of data generated during research?
6. Are adequate procedures provided for the ongoing surveillance of the drug's effectiveness and safety, and for notifying subjects and physicians of significant risks?
7. Has appropriate FDA review and clearance been obtained?

APPLICABLE LAWS AND REGULATIONS

Federal Policy for the protection of human subjects

- 21 CFR 50 [FDA: Informed consent]
- 21 CFR 56 [FDA: IRB review and approval]
- 21 CFR 312 [FDA: Investigational new drugs]
- 21 CFR 52 [FDA: Sponsor and monitor (proposed)]
- 21 CFR 54 [FDA: Clinical investigators (proposed)]

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C. VACCINE TRIALS

INTRODUCTION

Vaccines are used to prevent infectious diseases. Successful vaccine trials have resulted in the development of safe and effective vaccines for polio, measles, rubella, hepatitis B, pneumococcal pneumonia, and other serious diseases. Currently, vaccines are being evaluated to prevent infectious diseases such as AIDS (or transmission of HIV), malaria, tuberculosis, trachoma, cytomegalovirus, herpes simplex, and influenza. Vaccines must undergo clinical testing prior to approval and licensure by the **FDA**. The regulations governing the conduct of clinical trials on investigational vaccines are the same as those governing the conduct of **investigational new drug** research [*see* Guidebook Chapter 5, Section B, "Drug Trials"]; however, the **risks** and **benefits** associated with vaccine trials may differ from those of drug trials.

A vaccine is a biologic; its use in trials involving human subjects is similar to the use of any drug. Vaccines do, however, differ from therapeutic drugs in two important ways. As used here, they are not designed to diagnose or cure disease in afflicted individuals; their purpose is to prevent a particular disease in healthy human beings. Vaccines are also used to protect people with a high statistical risk for contracting a particular disease or for suffering especially serious consequences from a disease. Vaccines trigger the body's normal immune response, producing antibodies that protect against future infection. Some vaccines (*e.g.*, those containing active microorganisms or live-attenuated vaccines) have a small but real disease-producing capacity. Thus, one rare risk of a new vaccine is the possibility of infecting a healthy subject with the very disease researchers are seeking to prevent. More often, however, subjects involved in vaccine trials temporarily suffer from some of the symptoms and effects of the disease (*e.g.*, polio, German measles) as they acquire immunity.

DEFINITIONS

- **Biologic:** Any therapeutic serum, toxin, anti-toxin, or analogous microbial product applicable to the prevention, treatment, or cure of diseases or injuries.
- **Purity:** The relative absence of extraneous matter in a vaccine that may or may not be harmful to the recipient or deleterious to the product.
- **Sterility:** The absence of viable contaminating microorganisms; aseptic state.
- **Vaccine:** A biologic product generally made from an infectious agent or its components — a virus, bacterium or other microorganism — that is killed (inactive) or live-attenuated (active, although weakened). Vaccines may also be biochemically synthesized or made through recombinant DNA techniques.

IRB CONSIDERATIONS

The development of vaccines is of considerable benefit to society, especially in the case of devastating or highly infectious diseases. The direct benefit to the individual subject receiving a new vaccine is the possibility of immunity (*i.e.*, protection against future disease). The benefits of such immunity will vary depending on: (1) the severity of the disease to be avoided; (2) the likelihood that the subject will be exposed to the infectious disease; and (3) in the case of certain diseases, the likelihood that the subject would suffer adverse consequences should he or she

contract the disease. Some populations will be at greater risk of contracting an infectious disease than others, either because they are more likely to be exposed to the disease or because they have an increased susceptibility to it. Among those who contract an infectious disease, there may be some sub-groups that are particularly vulnerable to adverse consequences (e.g., children, persons of advanced age, or persons suffering from other illnesses).

For most diseases, participation in vaccine trials carries the generally small risk of contracting the disease. [In some vaccine trials (e.g., HIV) there is no such risk. In the case of HIV vaccine research, the lack of risk is due to the manner in which the vaccine is derived.] The risks of participating in a vaccine trial also include adverse effects unrelated to the disease in question (e.g., slight fever, headache, muscle soreness, or muscle aches). Such side effects are usually short-lived, tolerable, and not life-threatening. Again, the degree of risk associated with participating in a vaccine trial varies depending on the subjects' vulnerability to the adverse side effects of the vaccine. Some subjects may have an allergic or anaphylactic (i.e., a decrease rather than an increase in immunity) reaction to the vaccine. Anaphylactic reactions to vaccines cause the recipient to be hypersusceptible to the disease. Such reactions are generally unpredictable, and may be serious or potentially life-threatening.

The IRB should be aware of other risks associated with vaccine trials, including the possibility that vaccines produced synthetically or using recombinant DNA techniques may present risks as yet unknown, that groups often most likely to benefit from receiving a vaccine are often the most vulnerable to coercion (e.g., institutionalized persons or children), and that subjects in control groups may erroneously assume that they have been immunized.

When determining whether the risks are reasonable in relation to the benefits, IRBs should consider the severity of the disease, the risk of contracting the disease, and any special vulnerability of the subject population to the potential adverse effects of the vaccine. The most difficult cases are those in which the subjects most likely to benefit from participating in the vaccine trial are also the subjects at the greatest risk of suffering from the vaccine's potential adverse effects.

Some of the risks inherent in vaccine trials can be minimized. Before a vaccine is approved for testing with human subjects, IRBs should receive satisfactory evidence that animal trials and laboratory tests have, to the extent possible, demonstrated its safety. Since the sponsor must submit such information to the FDA as part of its investigational new drug application (IND), IRBs can readily obtain evidence of safety as well.

Mechanisms for protecting human subjects from some risks can be built into the vaccine study design. For example, with careful screening, investigators can avoid enrolling persons who may be susceptible to certain adverse reactions. Furthermore, trials can be designed to involve subjects who are most likely to be exposed to the infectious agent and who stand to benefit most from the protection afforded by the vaccine. Selecting subjects in this way avoids exposing those who may not be in need of its protective benefits to the risks of the vaccine. In many situations, however, **Phase 1** trials should be designed to evaluate low risk subjects. For example, an effective hepatitis B vaccine already exists. It would therefore be appropriate to determine that an investigational vaccine for hepatitis B is immunogenic in humans prior to use in high risk subjects.

Vaccine trials require careful monitoring of human subjects for both immune status and adverse reactions. The monitoring reflects the dual goals of any trial to determine both the effectiveness and the safety of the investigational substance or device. Although subjects in vaccine trials should be advised beforehand of known or anticipated side effects, rare or unknown reactions may occur. FDA regulations require that subjects be provided with written instructions about whom to contact in the event of serious adverse reactions or research-related injury.

IRBs should also be aware that large-scale field trials of a vaccine may involve many thousands of subjects, making monitoring difficult. The IRB should make sure that the sponsor has made provisions for monitoring the progress of the research, the immune status of participants, and side effects reported. Maintaining careful records is important both for monitoring the safety and effectiveness of the vaccine and for locating subjects for follow-up. If a vaccine either does not immunize the subject or does so for too limited a time, subjects may erroneously assume they are protected and fail to seek necessary medical attention. In addition, members of a **control** group may (incorrectly) assume they are immune from the disease because they believe they have received an effective vaccine (which they have not). IRBs sometimes require that control group subjects be given the first opportunity to receive the vaccine once its safety and effectiveness have been established. If such arrangements are not part of the research design, at the end of the trial control subjects should be informed of both their status vis a vis the vaccine, and the outcome of the trial: e.g., that the vaccine was shown to be safe and effective, but that they either did not receive the vaccine or did not receive an effective dose of the vaccine.

For a discussion of ethical issues related to the clinical testing of AIDS vaccines, see Guidebook Chapter 5, Section F, "AIDS/HIV-Related Research."

POINTS TO CONSIDER

1. Has appropriate FDA clearance and an approved IND been obtained?
2. Is there evidence that the vaccine has been adequately tested in animal trials and in the laboratory?
3. Where appropriate, are subjects clearly told in the consent process that they might receive a placebo or ineffective dose of the vaccine, and thus may not be protected against the disease?

4. Does the protocol provide adequate plans to monitor all subjects for immune status and adverse reactions, respond to problems, and disseminate results?

5. Will subjects be informed about what to do and whom to contact in case of a serious adverse reaction or research-related injury?

APPLICABLE LAWS AND REGULATIONS

Federal Policy for the protection of human subjects

- 21 CFR 50 [FDA: Informed consent]
- 21 CFR 56 [FDA: IRB review and approval]
- 21 CFR 312 [FDA: Investigational new drug research]
- 21 CFR 600-800 [FDA: Standards for biological products]
- 21 CFR 630 [FDA: Standards for viral vaccines]

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D. MEDICAL DEVICES

INTRODUCTION

Comprehensive federal regulations governing investigations involving **medical devices** are comparatively new. In addition to their other duties, IRBs reviewing certain device investigations must also determine whether a device study presents a significant or nonsignificant risk to the human subjects participating in the study. When making determinations of significant versus nonsignificant risk, IRBs must consider not only the risks associated with use of the device itself, but also the risks associated with the investigational device study as a whole.

DEFINITIONS

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

General Controls: Certain FDA statutory provisions designed to control the safety of /marketed drugs and devices. The general controls include provisions on adulteration, misbranding, banned devices, good manufacturing practices, notification and record keeping, and other sections of the Medical Device Amendments to the Food, Drug and Cosmetic Act [21 U.S. Code §360(c) (Food, Drug and Cosmetic Act §513)].

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

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

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

Postamendments Devices: Medical devices marketed after enactment of the 1976 Medical Device Amendments.

Preamendments Devices: Medical devices marketed before the enactment of the 1976 Medical Device Amendments.

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

Premarket Approval: Process of scientific and regulatory review by the FDA to ensure the safety and effectiveness of Class III devices.

Significant Risk Device: An investigational medical device that presents a potential for serious risk to the health, safety, or welfare of the subject. Such a device is:

- intended for use as an implant and presents a potential for serious risk to the health, safety, or welfare of the

subject; or

- purported or represented to be of use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of the subject; or
- intended for a use that is 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 the subject; or
- otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

OVERVIEW

The 1976 Medical Device Amendments (the Amendments) to the Federal Food, Drug and Cosmetic Act (the Act) were passed to give the FDA additional authority to assure safety and effectiveness in devices intended for human use. New medical devices must be cleared by the FDA prior to being placed on the market. As part of the clearance process, all medical devices are classified into one of three categories by the FDA based on the extent of control necessary to ensure the safety and effectiveness of each device [21 U.S. Code §360(c) (Food, Drug and Cosmetic Act §513)].

Medical devices are classified as Class I, Class II, or Class III devices depending on several criteria. Devices are classified as Class I medical devices if their safety and effectiveness can be assured by the general controls of the Amendments. The general controls include the provisions of the Act pertaining to adulteration, misbranding, banned devices, notification, repair, replacement or refund, records and reports, and restricted devices. In addition, general controls require device manufacturers or other designated persons, unless specifically exempted, to register their establishment, list their device, submit a premarket notification application, and be in compliance with the good manufacturing practices (GMPs). If a device cannot be classified as a Class I device because the general controls are insufficient to provide reasonable assurance of the safety and effectiveness of the device, the device may qualify for Class II classification. A Class II device must comply with general controls, and, in addition, the sponsor must provide sufficient information about the device to establish special controls that are sufficient to provide such assurance. Examples of special controls include the promulgation of performance standards, postmarket surveillance, the establishment of patient registries, and the development and dissemination of guidelines.

Devices are classified as Class III devices when: (1) their safety and effectiveness cannot be reasonably assured through either general or special controls; and (2) they are life-sustaining, life-supporting, implanted in the body, or of substantial importance in preventing impairment to health.

A new device that a manufacturer claims is substantially equivalent to a currently legally marketed device may be marketed after the FDA is notified of the intent to market, and the agency concurs with the manufacturer's claim of equivalence to other marketed devices. If the FDA determines that the new device is not substantially equivalent to a **predicate device**, the new device is automatically placed in Class III, and the manufacturer must obtain **premarket approval** from the FDA. Alternatively, the sponsor (or others) may petition the FDA to reclassify the device into Class I or II.

Investigational devices are medical devices that are the object of clinical research to determine their safety or effectiveness. Clinical investigations are necessary to support a request for premarket approval. Studies involving human subjects that are undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the Investigational Device Exemption regulations [21 CFR 812] or Investigational Exemptions for Intraocular Lenses [21 CFR 813]. An approved IDE exempts a device from certain sections of the Act (*e.g.*, misbranding under §502; registration, listing, and premarket notification under §510; special controls under §513; premarket approval under §515; banned devices under §516; records and reports under §519; restricted devices under §520(e); good manufacturing practices under §520(f); and color additive requirements under §706).

The IDE regulation describes two types of device investigations: **significant risk device** studies and **nonsignificant risk device** studies. Clinical trials involving significant risk devices require both FDA and IRB approval; sponsors must meet the full IDE requirements, including obtaining an FDA-approved IDE. Approval of studies involving nonsignificant risk devices require only IRB approval; no IDE is required to be formally submitted to the FDA. However, the sponsor must comply with the abbreviated regulatory requirements for such devices [21 CFR 812.2(b)]. The FDA may overturn IRB determinations that a device presents no significant risk.

IRB CONSIDERATIONS

In reviewing studies involving medical devices, IRBs should recognize that they must make two determinations: (1) whether a device study presents significant or nonsignificant risk; and (2) whether the study should be approved. These questions should be considered separately because the issues involved in making these decisions are quite different. Determining whether a device study poses a significant risk is based solely on considerations of risk to subjects, while IRB approval of the study is based on many factors. The discussion in this Section first considers IRB determinations of significant risk.

The FDA reviews and approves IDEs for significant risk device studies; it exercises less regulatory control over nonsignificant risk device studies. The initial responsibility for making the nonsignificant risk assessment for studies lies with the sponsor. If the sponsor believes that a particular device study presents a nonsignificant risk, the sponsor should provide the IRB with the study proposal, an explanation of why the device study presents a nonsignificant risk, and any other supporting information, such as reports of prior investigations. The sponsor should also tell the IRB whether the FDA or any other IRB has made a risk assessment and what the results of those assessments were. The IRB reviews the information, and may or may not agree with the sponsor's determination. If the IRB finds that the device study presents a

nonsignificant risk, the investigation may begin without submission of an IDE application to the FDA. If the IRB disagrees with the sponsor's determination that a device study presents nonsignificant risk to human subjects, the sponsor must so notify the FDA, whether or not the sponsor ultimately conducts the study at that institution.

If the study comes to the attention of the FDA, the agency's Office of Device Evaluation may reach a different conclusion on the risk presented by a device study than that reached by the IRB. If the FDA overrules an IRB's decision that a device study presents nonsignificant risk, the sponsor must then submit an IDE application to the FDA. The IRB must then review the investigation as a significant risk device study, and the investigator will be subject to more stringent recordkeeping and reporting requirements.

In determining whether a device study presents a significant or a nonsignificant risk, both the risks of the device and the risks associated with the procedure for using the device (e.g., surgery for installing an implant) must be considered. The comparison of risks is the basis for the other decision the IRB must make: whether to approve the research.

The clinical investigator should provide the IRB with adequate information about a device's regulatory status and the results of any risk assessment the FDA may have made. The IRB may also ask the sponsor whether other IRBs have reviewed the study and what determinations were made. IRBs may also request the sponsor or clinical investigator to provide documentation of appropriate FDA clearances, and may consult the FDA for its opinion on risk.

In the past, clinical investigations of intraocular lenses (IOLs) differed from other medical device studies in that there were few restrictions on the total number of subjects in an IOL investigation. Unlimited "adjunct" studies were phased out when enough approved IOLs became commercially available. IOL studies are now limited in enrollment size, as are other medical device studies.

Clinical investigations involving IOLs that commenced before July 27, 1981, are exempt from investigational device requirements [21 CFR 812], since they are subject to specific regulations on intraocular lenses [21 CFR 813], which specify procedures for IRB review and informed consent.

The IRB's second responsibility is to decide whether to approve the proposed research. In general, full IRB review is required for both significant and nonsignificant risk studies. However, some studies involving nonsignificant risk devices may also be considered minimal risk studies, and thus may be reviewed through the expedited review procedure established by the IRB.

IRBs need to keep in mind the difference between the risk/benefit evaluation made in the context of approving the research and the IRB's assessment of whether use of the device poses significant or nonsignificant risk. The latter decision categorizes the degree of risk of harm based upon the seriousness of the harm that may result from the use of the device; the former is a balancing of those risks (plus the risks of the research process) against the potential benefits to be gained from conducting the research.

The criteria for deciding whether a medical device study should be approved are the same as those used to evaluate research involving any FDA-regulated product. The IRB should determine that risks to subjects are minimized and are reasonable in relation to anticipated benefits and knowledge to be gained, that subject selection is equitable, informed consent procedures and documentation are adequate, and that provisions for monitoring the study and protecting subjects' privacy and confidentiality of data are acceptable. As in other clinical investigations, an IRB's decision to approve the research must take into account the risks and benefits of the investigational device as compared with the other available therapies. However, the IRB should not simply consider the increase in risk over standard treatment, but rather the risk of the procedure as a whole.

For further information and guidance on studies involving medical devices, contact:

Dr. Michael J. Blackwell
Chief, IDE Section (HFZ-403)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850
Tel: (301) 427-1190

Mr. Richard M. Klein
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
Room 11-44, 5600 Fishers Lane
Rockville, MD 20857
Tel: (301) 443-1382

POINTS TO CONSIDER

1. What risks are presented by the device? Are they significant or nonsignificant?
2. Have other IRBs reviewed and made decisions regarding this device? (Such information should be available from the sponsor or clinical investigator.)
3. What is the status of the device with the FDA? Has the device been approved for marketing? Is the device approved for other indications? Is it now being studied for a different indication? Is an IDE needed for this device? If so, has it been approved?

APPLICABLE LAW AND REGULATIONS

Federal Policy for the protection of human subjects

The Food, Drug and Cosmetic Act, as amended [codified at U.S. Code, Title 21]

The Medical Device Amendments of 1976 [P.L. 94-295, 90 Stat. 539 (May 28, 1976)]

The Safe Medical Devices Act of 1990 [P.L. 101-629]

21 CFR 50 [FDA: Informed consent]

21 CFR 56 [FDA: IRB review and approval]

21 CFR 812 [FDA: Investigational device exemptions]

21 CFR 813 [FDA: Investigational exemptions for intraocular lenses]

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E. USE OF RADIOACTIVE MATERIALS AND X-RAYS

INTRODUCTION

Radiopharmaceuticals and X-rays are widely used in medicine today for both diagnostic and therapeutic purposes. Certain aspects of human physiology can only be studied through exposure to radiation, or can be studied more safely by radiation than by alternative methods.

The types of radiation used most frequently in medical investigations and treatments are X-rays, gamma rays, and beta radiation. In addition to passing X-rays through the body to produce an image, some procedures use contrast agents to outline or define the shape of internal structures, or to image metabolic processes. Nuclear medicine uses procedures in which radioactive materials (*i.e.*, radiopharmaceuticals) are injected, ingested, or inhaled into the body. Most medical institutions have a radiation safety committee responsible for evaluating the risks of medical projects involving radiation and limiting the radiation exposure of employees and patients. Nevertheless, IRBs should have an understanding of radiation and its biological effects so they can evaluate the relative risks and benefits of research proposals utilizing radioactive materials or X-rays.

DEFINITIONS

Radioactive Drug: Any substance defined as a drug in §201(b)(1) of the Federal Food, Drug and Cosmetic Act that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons [21 CFR 310.3(n)]. Included are any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of a radioactive drug and "radioactive biological products," as defined in 21 CFR 600.3(ee). Drugs such as carbon-containing compounds or potassium-containing salts containing trace quantities of naturally occurring radionuclides are not considered radioactive drugs.

Radioactive Drug Research Committee (RDRC): An FDA-approved institutional committee responsible for the use of radioactive drugs in human subjects for certain research purposes [21 CFR 361.1]. Research involving human subjects that proposes to use radioactive drugs must be approved by the RDRC and must meet various FDA requirements, including limitations on the pharmacological dose and the radiation dose. The research must be basic research, not intended for diagnosis or treatment of a disease. Furthermore, the exposure to radiation must be justified by the quality of the study and the importance of the information it seeks to obtain. The committee is also responsible for continuing review of the drug use to ensure that the research continues to comply with FDA requirements, including reporting obligations. The committee must include experts in nuclear medicine as well as other medical and scientific members.

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

Radiopharmaceuticals: Radioactive drugs that are labeled or tagged with a radioisotope. These materials are largely physiological or subpharmacological in action, and, in many cases, function much like materials found in the body. The principal risk associated with these materials is the consequent radiation exposure to the body or to specific organ systems when they are introduced into the body.

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

OVERVIEW

The quantity of natural background radiation to which we are exposed varies considerably (*e.g.*, radiation exposures are much lower at sea level than they are at higher altitudes). The average annual natural background radiation from all sources in the United States is approximately 100 to 125 millirems (mrem) per year, while some individual exposures may be more than 400 mrem per year. Diagnostic medical procedures are the most likely source of additional radiation exposure. Estimates suggest that medical procedures increase the total exposure by 50 to 70 mrem per person per year.

Experts disagree, however, over the fundamental concepts that affect how radiation risks from medical procedures and other sources are estimated. The disagreements include debate about the existence of a theoretical threshold level below which no harmful effects occur. The National Council for Radiation Protection and Measurement (NCRPM) takes the position that there is no absolutely safe radiation dose. Generally, only approximations of risk from exposure are available; they are based on extrapolations from known exposures to high levels of radiation. The NCRPM has recommended dose standards; the Nuclear Regulatory Commission (NRC) has established occupational dose limits. The occupational dose limits vary according to the part of the body exposed to radiation.

The NRC is responsible for those radioactive materials considered to be "source material," "byproduct material," or "special nuclear material" [10 CFR Parts 30, 40, and 70]. The NRC directly regulates these materials in 21 states; the other 29 states, known as "Agreement States," have entered into an agreement with the NRC to regulate uses within their states of byproduct material, source material, or special nuclear material involving less than certain quantities. Agreement States may have unique policies or standards concerning the use of radioactive materials in research that could, in some cases, be more restrictive than those of the NRC. Naturally-occurring or accelerator-produced radioactive materials (NARM), such as Thallium-201, are not covered by the Atomic Energy Act; therefore they are not regulated by the NRC. Those radioactive materials (NARM) may be dealt with under specific state regulations (in both Agreement States as well as non-Agreement States) governing the use of radioactive materials.

The FDA requires investigators to submit an Investigational New Drug Application (IND) for radioactive drugs, kits, or generators that are to be used for investigational diagnostic or therapeutic purposes (including testing to establish their safety and effectiveness). An exception is made for radioactive drugs to be used in certain research designed to study the metabolism of the drug or to gather information about human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes [21 CFR 361.1]. If the radiation dose will not exceed the limits set forth in these regulations, the study design meets other research criteria, and the protocol is approved by a Radioactive Drug Research Committee (RDRC), the investigator does not need to submit an IND. Current radiation limits for the use of such drugs in research (including radiation doses from X-ray procedures that would not have occurred but for the study) are as follows [21 CFR 361.1]:

- For an adult research subject, radiation to the whole body, active blood-forming organs, the lens of the eye, or the gonads may not exceed a single dose of 3 rems or an annual cumulative dose of 5 rems.
- The amount of radiation to other organs may not exceed a single dose of 5 rems or an annual cumulative dose of 15 rems.
- Permissible doses for children (persons under age 18) are 10 percent of those for adults. The FDA must approve studies involving children before the study begins.

[See also 21 CFR 312.2(b), providing certain exemptions from IND application requirements.]

In addition to the RDRC, most medical institutions also have an Institutional Radiation Safety Committee, which assesses the risks that may be associated with exposure to radiation, both for research subjects and employees. In some states or institutions, review by the Radiation Safety Committee is mandated by law or policy; in others, the committee's review is offered as an opinion to the IRB to help it assess the risks and benefits of a given study involving radiation exposure.

IRB CONSIDERATIONS

An IRB should distinguish between radiation exposure resulting from routine medical management of a patient and radiation exposure that is part of research, including a clinical investigation. Although the occupational dose limits may not necessarily be appropriate when applied in a research setting, they do provide some guidance when exposure to radiation for research purposes is contemplated.

The likelihood of adverse effects associated with radiation exposure is generally considered to be low, but adverse effects can be serious when they do occur. Some effects rarely present themselves until many years after the subject has been exposed to radiation. The two adverse effects most commonly associated with radiation exposure are certain types of cancer and genetic damage.

The increased risk of genetic damage is of particular concern because exposure to radiation may involve substantial risk to the subject's unborn offspring. When the proposed research poses risk of genetic damage, an IRB should pay particular attention to the subject selection criteria. The human embryo is known to be particularly susceptible to damage from exposure to radiation; research involving pregnant or possibly pregnant women has therefore been of particular concern. Pregnancy tests could be required where doubt exists as to the presence of pregnancy, or the subject might be asked to use an effective contraceptive method during the course of the research. [See Guidebook Chapter 3, Section C, "Selection of Subjects," and Chapter 6, Section B, "Women."] Recent studies have suggested that male sperm cells are also adversely affected by radiation. Thus, no radiation dose should be considered risk-free if it is directed toward, or absorbed by, the reproductive organs.

Research involving radiation may also pose risks to lab personnel, nursing staff, and family members. This increased risk usually results from exposure to nuclear sources of radiation used in a medical device or nuclear medicine or radiotherapy. For example, when nuclear-powered artificial heart implants were under consideration, a federal panel expressed concern over the possible exposure and resultant risk to the patient's spouse.

Additional risk may be associated with the intravascular administration of contrast agents used in X-ray procedures (e.g., intravenous pyelograms (IVP), venograms, and cardiac catheterizations). The risks vary depending on the dose of the contrast agents, the chemical nature of the contrast agent used, and the age and disease state of the subject. Conditions such as advanced age, renal disease, diabetes, cardiac, or cerebrovascular disease, asthma, or chronic obstructive pulmonary disease may greatly increase the risk associated with the proposed study. Unsuspected anaphylactic reactions may also, although rarely, occur.

Radiopharmaceuticals present relatively low risks of adverse reactions unrelated to their radioactivity. The principal risks associated with radiopharmaceuticals are posed by the radioisotope's energy, its half-life, the radiosensitivity of the organ system being studied, and the radiation dose to the target organ, adjacent organs, and the whole body. Other factors are, however, also relevant. For example, the dose of a labeled brain receptor agent or the status of a subject's brain receptors must be considered.

In addition to determining the level of risk associated with exposure to radiation, IRBs must be concerned with informed consent. Specifically, IRBs must determine what subjects should be told: how properly to communicate the uncertainty about the risk of harm posed by exposure to the level of radiation involved in the study. Since subjects must be given sufficient information on which to decide whether to participate, consent should be based on information that the subjects may reasonably be expected to want to know. The question for the IRB is how much risk must there be before a "reasonable volunteer" would want to know about it. Given the sensitivity of our society to the uncertainty surrounding the risks associated with radiation exposure, IRBs should require that subjects be told that participation in the research involves exposure to radiation.

Several ways of explaining the risks associated with exposure to radioactive materials to potential subjects have been suggested, but none are totally satisfactory. One method used is comparing the risk of death from radiation exposure to that of more familiar activities such as air travel or cigarette smoking. A second method compares the incidence of death per year from radiation exposure with the mortality rates of various occupations. Comparisons may also be made between the proposed research exposure and the dose received from cosmic and background radiation to which a subject is naturally exposed. The proposed research exposure may also be compared with the annual maximum permissible exposures suggested by the NCRPM for occupational workers. Finally, the research exposure can be compared with exposures from more familiar medical procedures, such as chest X-rays.

The major problem with expressing risks in comparative terms is that the actual risk from low levels of exposure is not known. This uncertainty should be communicated to research subjects. Even in cases where the risks from exposure are considered to be minimal and not reasonably foreseeable, the IRB may determine that the information concerning exposure and its possible effects is something that research subjects might reasonably want to know.

The IRB should ensure that the risks of radiation exposure are minimized. In an attempt to minimize radiation exposure, experts have developed a principle known as ALARA: **A**s **L**ow **A**s **R**easonably **A**chievable. IRBs should ensure that the ALARA principle is observed. [See also 21 CFR 361.1(b)(3) (limit on radiation dose).]

POINTS TO CONSIDER

1. Can the information to be gained from the research project be gathered using methods that do not expose subjects to more radiation than that to which they would naturally be exposed?
2. Could the research be performed on patients undergoing the procedures for diagnostic or therapeutic purposes?
3. Will the smallest exposure (dose) possible be used in the study?
4. Have investigators taken steps to avoid re-exposure? Are procedures in place to ensure that investigators will use a minimum number of re-exposures in the event that the study needs to be repeated?
5. Are adequate radiation safety measures being taken to protect research subjects and others who may be exposed to radiation?

6. Have the investigators taken adequate precautions to screen subjects and exclude those not essential to the research project and those at increased risk from exposure to radiation or contrast agents?

7. Will both men and women be informed of the risks to future offspring due to possible genetic damage?

8. Will women of childbearing potential be adequately informed of the risks to an embryo associated with radiation exposure in early pregnancy, and of the importance of disclosing a possible pregnancy to the investigator? Does the protocol make adequate provisions for detecting pregnancies?

APPLICABLE LAWS AND REGULATIONS

Federal Policy for the protection of human subjects

10 CFR 19 [NRC: Notices, instructions, and reports to workers; inspections]

10 CFR 20 [NRC: Standards for protection against radiation]

10 CFR 35 [NRC: Medical use of byproduct material]

21 CFR 50 [FDA: Informed consent]

21 CFR 56 [FDA: IRB review and approval]

21 CFR 361.1 [FDA: Radioactive drugs for certain research uses]

21 CFR 312 [FDA: Investigational new drug application]

State laws regarding radioactive materials licensure

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F. AIDS/HIV-RELATED RESEARCH

INTRODUCTION

The human immunodeficiency virus (HIV) is a pathogenic retrovirus that causes acquired immunodeficiency syndrome (AIDS) and its related diseases in humans. Because of its high rate of mortality, AIDS has become the center of worldwide attention; research into the development of safe and effective therapies, as well as methods of prevention of this fatal disease, is currently a national public health priority.

HIV-related research centers on both biomedical and behavioral questions. Biomedical research has been characterized as falling into five major scientific categories: "(1) the study of the distribution of HIV infection and AIDS in the population (epidemiology) and the pattern of disease progression (natural history); (2) the identification and characterization of the virus that causes AIDS (etiologic agent); (3) delineation of the mechanisms by which the virus destroys the immune system and produces disease (pathogenesis); (4) the development and testing of potential therapies for HIV infection and its complications; and (5) the development and evaluation of potential AIDS vaccines" [Hamburg and Fauci (1989), p. 22].

Behavioral research on HIV focuses on: (1) identifying the social, psychological, and behavioral conditions of disease transmission and prevention; (2) the effects of psychological state on immunosuppression; and (3) the role of psychology in alleviating the distress experienced by persons affected by HIV infection (including families, friends, and persons at risk).

IRB CONSIDERATIONS

Research designed to answer the many biomedical and behavioral questions presented by HIV poses numerous ethical concerns. Primary among them are considerations of **privacy**, **confidentiality**, and **justice** (fairness in the distribution of the benefits and risks of research). The subjects involved in HIV-related research, HIV-infected individuals, and persons at risk of HIV infection, are particularly vulnerable, both because of their disease status, and because the disease disproportionately affects certain populations: male homosexuals and bisexuals, intravenous drug users, minorities, and, increasingly, women and children. [See Guidebook Chapter 6, "Special Classes of Subjects."]

An overriding concern in HIV research is confidentiality. Subjects included in HIV-related studies are understandably concerned about the confidentiality of the data, since breaches in confidentiality could have severe adverse consequences such as loss of employment or insurance coverage, or criminal charges. OPRR guidance on HIV studies states that:

where identifiers are not required by the design of the study, they are not to be recorded. If identifiers are recorded, they should be separated, if possible, from data and stored securely, with linkage restored only when necessary to conduct the research. No lists should be retained identifying those who elected not to participate. Participants must be given a fair, clear explanation of how information about them will be handled.

As a general principle, information is not to be disclosed without the subject's consent. The protocol must clearly state who is entitled to see records with identifiers, both within and outside the project. This statement must take account of the possibility of

IRBs should also consider whether and how information from HIV-related studies will be recorded in subjects' medical records, and may decide to impose limits on the recording of such data. Before agreeing to participate in an HIV study, subjects should be informed of exactly what information will be recorded, and whether any state laws require the reporting of HIV infection or other disclosures of information. The research protocol should also deal with the possibility of attempts under compulsory legal process to force disclosure of records, how such attempts will be responded to, and whether individuals will be notified of such attempts. [See also the Guidebook Chapter 3, Section D, "Privacy and Confidentiality," which deals with certificates of confidentiality and subpoenas.] The protocol should specifically set forth how to respond to requests by third parties who have authorizations for disclosure of information signed by subjects. An extensive set of guidelines for confidentiality in research on HIV has been developed by a group of prominent scholars, practitioners, and community members, and may be helpful to IRBs considering HIV-related protocols. [See Bayer, Levine, and Murray (1984).]

The PHS has an established policy on the issuance of certificates of confidentiality to projects that are subject to the reporting of communicable diseases to state and local health departments. The policy applies to projects that intend routinely to determine whether its subjects have communicable diseases, and that are required to report them under state law. Certificates will be issued: (1) where the referring treating physicians assure the project that they have complied with reporting requirements; (2) the investigator has reached an agreement with the health department about how he or she will cooperate with the department to help serve the purposes of the reporting requirements (unless the investigator can show why such cooperation is precluded); and (3) only where disclosures of identifiable information about subjects comply with regulations on subject protection, and are explained clearly to subjects prior to their participation [Mason (August 9, 1991)]. [See also Guidebook Chapter 3, Section D, "Privacy and Confidentiality."]

The giving of voluntary consent, axiomatic to all research involving human subjects, applies equally in HIV-related research. Complicating the consent issue, however, is that HIV-related illness, particularly in its later stages, can cause dementia, thus affecting the ability of subjects to give consent or continue to consent to ongoing research. Research protocols should deal with this possibility; IRBs should ensure that subjects in this particularly vulnerable condition are adequately protected. [See also Guidebook Chapter 6, Section D, "Cognitively Impaired."]

Research on vaccines and treatments poses some of the most difficult questions, including the level of acceptable risk to subjects when the disease is fatal and no effective therapy is available; whether HIV-infected patients can be used as a placebo group that is not given experimental treatments; how subjects should be selected to receive experimental therapies; whether and under what circumstances healthy and at-risk but not-yet-HIV-infected persons can ethically be asked to participate in vaccine trials.

Clinical Trials of HIV-Related Therapies. Randomized clinical trials (RCTs) and the ethical problems surrounding their use is discussed in Guidebook Chapter 4, Section H and related Guidebook Sections. This Section will focus on questions of particular concern for research involving HIV-infected individuals.

Randomized, controlled clinical trials are considered the research design most likely to yield valid scientific results for the evaluation of the safety and effectiveness of experimental therapies. Ethical use of RCTs depends on the existence of both the ability to state a **null hypothesis** (also called "theoretical equipoise") and that there be no other therapy known to be more effective than the one being studied in the RCT. A report produced by a working group on clinical HIV research convened by the American Foundation for AIDS Research argues, however, that when no known effective alternative therapy exists, as is presently the case with HIV, it may be justified to consider the use of other forms of controls such as historical controls (that is, to compare the effects of the therapy in the trial population with the treatment experiences of patients with the same disease before use of the experimental therapy) [Levine, Dubler, and Levine (1991), pp. 3, 6]. The justification for this position is that the conditions of "clinical equipoise" (a situation in which there is a "current or likely dispute among expert members of the clinical community as to which of two or more therapies is superior in all relevant respects," and which is also necessary for an RCT to be ethical) are not satisfied [id.]. The working group issued a document that included 57 recommendations on the conduct of clinical research on HIV, which IRBs may wish to consult [id.].

The use of placebo controls is particularly problematic. As a general matter, where the disease is lethal or seriously debilitating, as in the case of HIV, the use of placebo controls in place of an active control is difficult to justify ethically, despite the possibility that the experimental therapy is harmful (e.g., toxic) rather than therapeutic. In the language of the *Belmont Report*, the question of the use of control groups in this situation is one of **beneficence**: Are potential benefits maximized in all arms of the trial? The fatal nature of the disease leaves patients in a desperate position in which many seek any promising treatment. It has been suggested that the question may be resolved in favor of placebo controls only under two conditions: (1) when there is either no known effective therapy that can be used as an active control, or subjects are persons who cannot tolerate a known effective therapy; and (2) the trial therapy is "so scarce that only a limited number of patients can receive it" [Levine, Dubler, and Levine (1991), p. 8]. A fair way to then assign subjects to the active and control arm(s) is through a lottery [id.] [See also Macklin and Friedland (1986), pp. 277-79, and Guidebook Chapter 4, Section H, "Clinical Trials," and related Guidebook Sections.]

Once there is sufficient evidence of either a beneficial therapeutic effect, unacceptable side effects, or indication that there is a very low probability of establishing statistically significant research results, the trial should be stopped or the protocol should be modified [Macklin and Friedland (1986), pp. 177-78]. Where an experimental therapy is shown to have a beneficial therapeutic effect, the control group should be offered access to the experimental therapy. Prospective subjects should be informed of the probability of being assigned to the control group, the risks associated with being assigned to either the treatment or control group, the criteria that will be used for determining a beneficial effect sufficient to discontinue the control arm of the trial, and the consequences of discontinuing the control arm (e.g., will control subjects be added to the experimental group, will they be given the experimental therapy on a treatment basis, will they be offered the experimental therapy only if they pay for its cost, or will they be dropped from the study without access to the experimental therapy). It should be made clear to

prospective subjects that the likelihood of the experimental therapy having harmful effects may well be as great as the likelihood of its having beneficial effects.

The selection and recruitment of subjects is also of concern. Subjects for clinical trials are often recruited on the recommendation of treating physicians. Unable or unwilling to obtain medical care, many individuals have been excluded from participation in trials. Others, not aware of the existence of trials, are also left out. Care should be taken to ensure the appropriate inclusion of women, children and adolescents, and minority groups in HIV-related clinical trials. Note also that IRBs must follow the additional protections provided in the DHHS regulations wherever applicable. [See Subpart B (fetuses, pregnant women, and human in vitro fertilization), Subpart C (prisoners), and Subpart D (children).]

When reviewing protocols involving HIV-infected or at-risk individuals or persons, IRBs should consider including (as consultants, if they are not already members) persons knowledgeable about and experienced in working with such subjects [Federal Policy §__.107]. Some investigatory groups have used "community advisory committees" as a means both of better understanding the concerns of the subject population and of educating the HIV-infected community about clinical research.

Vaccines. The testing of AIDS/HIV vaccines in human subjects raises substantial ethical issues. First and foremost is the question of risks and benefits. Limited availability of animal data means that many of the risks that might be associated with an AIDS/HIV vaccine (*e.g.*, vaccine-induced immunotoxicity) are unknown. Nonetheless, the importance of developing an AIDS/HIV vaccine is felt to outweigh these uncertainties. From the standpoint of protecting the welfare of human subjects, however, the lack of knowledge about risk and the potential for the existence of serious risk must be clearly communicated and consented to by prospective subjects.

While all viral vaccines pose risks, HIV vaccines may, in addition, increase the risk of acquiring the disease when subsequently exposed to HIV. Also, because of potential immune tolerance, subjects may not be able to be vaccinated with a different AIDS/HIV vaccine if the experimental one proves ineffective. Persons with whom the subject is in close contact may also be at risk of transmission of recombinant viruses (through the injection site). IRBs should consider the degree to which investigators have minimized these risks, and ensure that subjects are adequately informed of and consent to these and other potential physical risks.

Another issue about which subjects must be informed is the effect of participation in the trial on their HIV serostatus and the potential social ramifications of changes in HIV serostatus. Just as persons infected with HIV through more usual means of transmission (*e.g.*, sexual activity, the use of intravenous drugs, or blood transfusions) will test positive on antibody screening tests, so too will persons immunized with experimental AIDS/HIV vaccines. There may be limited access to diagnostic methods for distinguishing between persons who are HIV-infected and persons who have received HIV vaccinations. One way to help alleviate this problem is for trial sponsors to follow the lead of the National Institute of Allergy and Infectious Diseases (NIAID), and provide subjects with documentation certifying participation in the vaccine trial. Nonetheless, participation in AIDS/HIV vaccine trials in itself may carry a social stigma.

Informing Subjects of Their HIV Serostatus. Some research protocols involve screening blood samples for HIV seroprevalence or other procedures through which subjects' HIV serostatus will be discovered. In addition to ensuring that the confidentiality of this information and all research data is scrupulously provided for, and that subjects will be informed that they will be tested and of the risks and benefits involved, IRBs will need to consider the circumstances under which subjects should or must be told of their HIV serostatus. PHS policy requires that where HIV testing is conducted or supported by the PHS, individuals whose test results are associated with personal identifiers must be informed of their own test results and provided the opportunity to receive appropriate counseling unless the situation calls for an exception under the special circumstances set forth in the policy. Under the PHS policy, individuals may not be given the option "not to know" their test results, either at the time of consenting to be tested or thereafter. The acceptable "special circumstances" include such compelling and immediate reasons as an indication that a given individual would attempt suicide if informed that he or she was HIV seropositive; that extremely valuable knowledge might be gained from research involving subjects who would be expected to refuse to learn their HIV antibody results; or research activities conducted at foreign sites where cultural norms, the health resource capabilities, and official health policies of the host country preclude informing subjects of their HIV serostatus. Subjects should also be informed early in the consent process of any plans to notify subjects' sexual or needle-sharing partners. [See OPRR Reports ("Dear Colleague" letters dated December 26, 1984 and June 10, 1988).] Several commentators have taken issue with the position that subjects should be told of their serostatus regardless of their wishes. [See, *e.g.*, Novick (1986) and Dubler (1986); compare Landesman (1986).] While this issue may be controversial, opportunities for early intervention weigh in favor of policies that require informing subjects of their HIV serostatus.

Counseling. Whenever subjects will be informed of their HIV serostatus, appropriate pretest and post test counseling must be provided. Counselors should be qualified to provide HIV test counseling and partner notification services. IRBs should ensure that such provisions are made. [See OPRR Reports ("Dear Colleague" letters dated December 26, 1984 and June 10, 1988)]

See also Guidebook Chapter 2, Section B, "Food and Drug Administration Regulations and Policies" (discussing expanded availability of investigational agents), and Chapter 4, "Considerations of Research Design."

Behavioral Research. Research on behavioral questions related to HIV often centers on what behavioral factors contribute to disease transmission and dissemination, as well as other psychosocial factors related to HIV (*e.g.*, the relationship of stress to immunosuppression). The American Psychological Association has expressed concerns for subjects' privacy, protections against the intrusive nature of behavioral research (because research on risk factors and modes of disease transmission often probes intimate details of subjects' lives such as sexual practices and past history of illicit drug use), confidentiality, and the need to carefully debrief subjects.

Vulnerability of Subjects. In addition to the ethical issues raised by the conduct of HIV-related research itself, the involvement of HIV-infected subjects presents special concerns to which IRBs should be sensitive. As noted above, homosexual and bisexual men, intravenous drug users, minorities, and, increasingly, women and children constitute the bulk of the HIV-infected population. Their vulnerability as subjects arises primarily because their HIV status presents special concerns of confidentiality and privacy. Knowledge of a person's HIV status can lead to discriminatory practices on the part of employers, landlords, insurance companies, and others. That HIV disproportionately affects certain populations heightens the threat of inappropriate disclosure of HIV-related data. In addition, characteristics of the progression of AIDS, which can include both physical incapacity and loss of mental capacity, can impinge on subjects' ability to exercise their right to autonomy in the course of the research. IRBs can ensure that AIDS patients and other HIV-infected subjects are adequately protected by viewing each subject first and foremost as an individual. Researchers working with HIV-infected persons must be capable of dealing with social, emotional, and psychological, as well as physical factors. Taking such a multifaceted approach to working with this subject population is a means of incorporating the various necessary cultural and filial influences into the research relationship. Researchers should seek the advice and consultation of experts in these and other relevant fields as necessary.

Another factor that heightens the vulnerability of HIV-infected individuals is the lack of available treatment alternatives. At present, HIV infection is believed uniformly to progress to AIDS; no available treatment cures AIDS, although some therapies postpone the onset and severity of opportunistic infection. Prospective subjects in HIV-related studies may, therefore, agree to participate in research out of a hope for a cure, which may or may not be realistic. But while IRBs should protect subjects against exposure to excessive risk, they must also guard against paternalism. Despite the fatal nature of the disease, there may be risks to which individuals should not be asked to subject themselves; despite their vulnerability, however, prospective subjects should be given the opportunity to participate and obtain whatever benefits may be available. IRBs should consider protocols and make their evaluation of the requisite factors (*i.e.*, the level of risk involved, a positive risk/benefit ratio, equitable selection of subjects, informed consent, and protection of privacy and confidentiality) with this concern in mind. The additional protection that IRBs can provide is to ensure that the protocol, its goals, and the research benefits and risks are clearly and simply delineated and communicated to the subject. It is important that participation in the research not engender either false hopes or a sense of hopelessness. Furthermore, IRBs should try to ensure that access to health care does not serve as a lure for participation.

IRBs need to review participant eligibility requirements closely and extensively monitor the data collection and analysis process. The consent process should also be carefully considered, with special attention to provisions for determining mental capacity to consent and alternative means for obtaining consent, where necessary. [See Guidebook Chapter 6, Section D, "Cognitively Impaired."] The duration of any health care to be rendered through participation, including counseling, should be thoroughly reviewed with subjects. As noted above, subjects must be clearly and explicitly informed of any applicable law or policy that requires either partner notification or notification to health authorities of subjects' HIV serostatus or disease status.

Finally, many HIV-infected persons are economically and/or educationally disadvantaged, and may need adjunct services or other help to be able to participate in research. To ensure that all affected groups have an adequate opportunity to participate, IRBs should give some thought to how investigators might meet these needs, thereby encouraging a broader distribution of the risks and benefits of HIV-related research.

Availability of Drugs and Other Therapeutic Agents for AIDS and HIV-Related Conditions. The availability of experimental drugs and other therapeutic agents for the treatment of AIDS and other HIV-related conditions has been highly controversial. Two mechanisms, Treatment INDs, and a subset of Treatment INDs, Parallel Track programs, have been developed by the FDA to meet this concern. They are discussed in the Guidebook in Chapter 2, Section B, "Food and Drug Administration Regulations and Policies."

POINTS TO CONSIDER

1. Pre-screening clinical study participants for HIV antibody status: See the list of questions provided in *OPRR Reports*, "Points to Consider for Institutional Review Boards (IRBs) Regarding the Screening of Volunteers for HIV Antibody Status," (circa August, 1989).
2. Is the composition of the IRB membership appropriate for an adequate review of the protocol? Should the IRB seek consultation with laypersons, persons with AIDS or who are HIV-infected, or members of the HIV-affected community?
3. Are subjects' privacy and confidentiality adequately protected? Are certificates of confidentiality appropriate?
4. Does the consent process provide adequately for the special needs of subjects participating in HIV-related research, including subjects with impaired mental capacities and the difficulties of communicating the risks presented by drug and vaccine trials?
5. Will the informed consent process clearly inform the subject of all pertinent information (*e.g.*, the circumstances under which the investigator may terminate the subject's participation without the subject's consent; the circumstances under which the subject may withdraw from participation and the costs associated with withdrawal; the financial costs of participation; how medical care will be handled in the event of injury or onset of opportunistic illness; whether partner notification and/or disease status reporting to health authorities will occur)?
6. Is there a mechanism for dealing with changes in mental capacity and continuing consent? Who will give consent in the event of diminished mental capacity or lack of majority (in the case of children)? Is it necessary to obtain subjects' assent?
7. Are protections against coercion in place?

8. If the protocol involves a clinical trial, have appropriate FDA clearances and an approved IND been obtained?
9. Does the protocol provide for adequate monitoring of all subjects for adverse reactions? Are provisions made for early termination?
10. Will subjects be informed about what to do and whom to contact in case of a serious adverse reaction or research-related injury?
11. Will subjects involved in behavioral research be adequately debriefed? Are intrusions into subjects' privacy minimized?

APPLICABLE LAWS AND REGULATIONS

Federal Policy for the protection of human subjects

- 21 CFR 50 [FDA: Informed consent]
- 21 CFR 56 [FDA: IRB review and approval]
- 21 CFR 312 [FDA: New drugs for investigational use]
- 45 CFR 46, Subparts B-D [DHHS: Protection of human subjects]

Federal Register 57 (April 15, 1992): 13250-13259 [FDA: Parallel track policy]

State and local laws concerning the reporting of HIV-related information

Public Health Service policies related to AIDS research:

U.S. Public Health Service. National Institutes of Health. "Guidance for Institutional Review Boards for AIDS Studies" [Dear Colleague Letter]. *OPRR Reports* (December 26, 1984).

U.S. Public Health Service. National Institutes of Health. "Policy on Informing Those Tested About HIV Serostatus" [Dear Colleague Letter]. *OPRR Reports* (June 10, 1988).

U.S. Public Health Service. National Institutes of Health. "Points to Consider for Institutional Review Boards (IRBs) Regarding the Screening of Volunteers for HIV Antibody Status" [Dear Colleague Letter] *OPRR Reports* [circa August, 1989].

James O. Mason [Assistant Secretary for Health]. "Certificates of Confidentiality — Disease Reporting" [Memorandum]. (August 9, 1991.)

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G. TRANSPLANTS

INTRODUCTION

Numerous ethical issues confront IRBs considering research that involves the transplantation of organs or tissues into human subjects. Transplanted organs may be either natural or artificial; natural organs or tissue may be of either human or animal origin. Ethical issues include the physical and psychological risks to the donor and recipient, informed consent, coercion, and the selection of recipient-subjects (*i.e.*, the distribution of organs or tissue to needy recipients).

The ethical considerations surrounding the transplantation of organs concern two basic problems: the scientific basis of the procedure (*i.e.*, risk to the recipient-subject) and the procurement of organs for transplantation. The first problem raises issues with which IRBs are familiar: determining whether the proposed research poses an acceptable risk; balancing that risk with the potential benefits; ensuring that the patient-subject and the donor give their informed consent; and ensuring that the decision to participate is free from coercion and undue influence. The second problem has several facets, including the appropriate selection of recipient-subjects and the obtaining of organs. Equitable subject selection for research on transplantation raises unique questions because of the involvement of the donor in the process and because of the scarcity of appropriate materials (*e.g.*, organs, tissue, or bone marrow) for the transplant procedure. The use of fetal tissue in transplantation is dealt with in Guidebook Chapter 6, Section A, "Fetuses and Human In Vitro Fertilization."

OVERVIEW

Experimental transplants are performed using a number of techniques: An organ or tissue can be obtained from a living relative, a living nonrelative, or a deceased person (usually a nonrelative). Transplants can also be performed using organs or tissue from animals (called *xenografts*); portions of organs have also been transplanted from living relatives into patient-subjects. The use of artificial implants is another method of replacing diseased organs that has been pursued.

The transplant procedure requires the matching of various factors between donor and recipient (*e.g.*, blood and tissue types). To increase the likelihood of a match (*i.e.*, to decrease the likelihood that the organ or tissue will be rejected by the recipient's system), living relatives are a preferred source of organs or tissue. For some organs, such as a heart, such an arrangement is obviously impossible. Furthermore, the subject may not have a living relative who provides an appropriate match or who is willing to donate the organ or tissue.

IRB CONSIDERATIONS

Candidates for experimental transplant procedures are usually under threat of imminent death; experimental transplant procedures are a last hope for survival. The highly vulnerable status of potential subjects makes stringent review of proposed transplant research essential. Transplant investigations involving children as subjects are governed by Subpart D of the DHHS regulations [45 CFR 46.401-409]. [*See* Guidebook Chapter 6, Section C, "Children and Minors."]

The first issue with which IRBs must concern themselves is whether the risk of the transplant procedure is outweighed by the potential benefits of the research. [*See* Guidebook Chapter 3, Section A, "Risk/Benefit Analysis."] The benefits take two forms: intended therapeutic benefit for the individual subject and the benefit to society from the knowledge gained from the research. An important factor when considering the benefit to individual subjects is the availability and quality of therapeutic alternatives for potential subjects. The subjects' prospects for survival and quality of life, with or without the transplant, will be particularly relevant to the IRB's decision.

Transplants involving living donors present a second level of risk that must be evaluated: the risk of obtaining the organ from the donor. That risk entails the risk of the removal procedure itself, plus the long-term risks of living without the donated organ or tissue. When balancing those risks against the potential benefits, one can see that the relationship of the donor to the recipient may be relevant. The donor will not therapeutically benefit from the donation; quite the contrary. The benefit comes, rather from the direct good the donor gives the recipient. In this regard, the living related donor will benefit more directly than will the living nonrelated donor: He or she is increasing the likelihood that the relative (about whom he or she presumably cares more than would a nonrelated donor) will live longer.

As with any research involving human subjects, IRBs need to ensure that subjects give **informed consent** that is free from coercion or undue influence. Potential subjects for studies involving experimental transplants must be clearly informed of the highly experimental nature of the procedure, including the state of knowledge about the prospects for long-term viability of the organ or tissue.

Complicating the question of consent when the research involves transplants is the involvement of a donor. Where the donor is living, his or her consent must be obtained; the regulations concerning research subjects apply fully to the donor as well as to the recipient. Where the donor is deceased, his or her next of kin must be consulted: State and federal Required Request Laws mandate that the treating physician ask if the family wishes to donate organs from the patient upon his or her death; the deceased may also have indicated a desire to donate his or her organs in the event of death by, for instance, signing an organ donation card.

Technological innovations that allow for the preservation of cadavers and organs has led to concerns about treating brain dead persons as research objects. Some question exists whether deceased donors come within the jurisdiction of IRBs because the federal regulations define subjects as "living individual[s]" [Federal Policy §___.102(f)]. Nevertheless, the **President's Commission** [(1983), p. 41] suggested that IRBs consider requiring review of research on brain dead persons "to determine whether...it is consistent with 'commonly held convictions about respect for the dead.'" [*See also* Levine (1986), p. 78.] Considerable controversy surrounds the use of anencephalic infants as a source of organs for donation, with most commentators arguing against their use.

The involvement of living related donors also raises concerns of coercion and undue influence. The pressure on relatives to donate needed organs or tissues is unquestionably great; IRBs must carefully scrutinize the proposed consent process. Some investigators have provided for both medical and psychiatric evaluations and counseling as part of the donor consent process, as well as a waiting period (if feasible) before the transplantation, during which the donor may withdraw consent. Some investigators have also provided for a consent advocate for the donor who is not directly involved in the donor's operation. [*See, e.g.*, Singer, et. al. (1989).]

A further complication to the consent process for organ donors is the minor who is a potential donor for a relative — a sibling, for instance. Where the donor is a minor, the regulations concerning children and minors as research subjects apply [45 CFR 46.401-46.409]. Organ donations from minors raise concerns about the ability of the minor to comprehend the risks of donation, as well as the possibility of coercion or undue influence. [*See* Guidebook Chapter 6, Section C, "Children and Minors."] IRBs may want to consider requesting the guidance of a court of law before allowing a given donation to be made.

Experimental xenografts have been particularly controversial. The celebrated Baby Fae case, in which an infant received the transplanted heart of a baboon, raised serious questions about IRB review of research involving human subjects. Any research involving transplants should be carefully reviewed by an IRB regardless of the source of funding. The extremely risky nature of the procedure and the special vulnerability of the subjects demand that their welfare be scrupulously protected. Subjects must be clearly informed of the state of knowledge about the long-term viability of the transplant, of alternatives to the procedure, and of all possible physical and psychological effects that may result from the transplant and any other procedures that will be undertaken as a part of the transplant. Consent to the transplant must be carefully documented. [*See* Caplan (1985), p. 3343].

POINTS TO CONSIDER

1. Does the consent process adequately protect both the donor and the recipient? Is sufficient information provided regarding the risks of all procedures involved? Is adequate provision made for incompetent subjects by providing for trustworthy proxy decision makers?
2. Have both donors and recipients been adequately protected against coercion and undue influence?
3. Are special regulatory provisions applicable, *e.g.*, Subpart D governing children as subjects?

APPLICABLE LAWS AND REGULATIONS

Federal Policy § ____.111(a)(3) [Criteria for IRB approval of research: equitable selection of subjects]

Omnibus Budget Reconciliation Act of 1986 (Pub. L. 99-509) enacted sec. 1138, Social Security Act (Required Request Law)

The Uniform Anatomical Gift Act

The Uniform Definition of Death Act

State and local laws pertaining to organ donation

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Institutional Review Board Guidebook

*** CHAPTER VI * SPECIAL CLASSES OF SUBJECTS**

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INTRODUCTION

The federal regulations require that IRBs give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons [Federal Policy § __.111]. For research to which the DHHS regulations are applicable, the DHHS regulations set forth specific provisions on research involving fetuses, pregnant women, and human in vitro fertilization [45 CFR 46 Subpart B]; prisoners [45 CFR 46 Subpart C]; and children [45 CFR 46 Subpart D]. In general, these special regulations allow IRBs to approve research that is of minimal risk or that will benefit the subjects directly. Investigations involving these subjects that present significantly greater than minimal risk without direct benefit to them must be reviewed and approved by the Secretary of Health and Human Services, in consultation with appropriate experts.

Special Note Regarding Applicability of DHHS Regulations. Institutions with DHHS-approved Assurances on file must abide by the provisions of 45 CFR 46 Subparts A-D. Some of the other departments and agencies have incorporated all provisions of 45 CFR 46 into their policies and procedures as well. The exemptions at 45 CFR 46.101(b), however, do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization (*i.e.*, research to which Subparts B and C apply). Also, 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 involving children (*i.e.*, research to which Subpart D applies), except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed. [See Federal Policy § __.101, footnote 1.]

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A. FETUSES AND HUMAN IN VITRO FERTILIZATION

INTRODUCTION

Research involving the human fetus raises special concerns for IRB reviewers. The fetus has a unique and inextricable relationship to the mother. It cannot consent to be a research subject. These circumstances have aroused lengthy public debate on the ethics of fetal research, and led to special federal regulations that guide IRB deliberations about fetal research [45 CFR 46 Subpart B]. The fetus may also be an indirect subject of research when women who may be pregnant participate. Research involving pregnant women is also regulated by 45 CFR 46 Subpart B. [See Guidebook Chapter 6, Section B, "Women."]

DEFINITIONS

Dead Fetus: An expelled or delivered fetus that exhibits no heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord (if still attached) [45 CFR 46.203(f)]. Generally, some organs, tissues, and cells (referred to collectively as fetal tissue) remain alive for varying periods of time after the total organism is dead.

Fetal Material: The placenta, amniotic fluid, fetal membranes, and the umbilical cord.

Fetus: The product of conception from the time of implantation until delivery. If the delivered or expelled fetus is viable, it is designated an infant [45 CFR 46.203(c)]. (Hereafter, the term "fetus" will refer to a living fetus unless otherwise specified.) The term "fetus" generally refers to later phases of development; the term "embryo" is usually used for earlier phases of development.

Human In Vitro Fertilization: Any fertilization involving human sperm and ova that occurs outside the human body.

Minimal Risk: A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [Federal Policy § __.102(i)]. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

Nonviable Fetus: An expelled or delivered fetus which, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy. Although it may be presumed that an expelled or delivered fetus is nonviable at a gestational age less than 20 weeks and weight less than 500 grams [*Federal Register* 40 (August 8, 1975): 33552], a specific determination as to viability must be made by a physician in each instance.

Pregnancy: The period from confirmation of implantation of a fertilized egg within the uterus until the fetus has entirely left the uterus (*i.e.*, has been delivered). Implantation is confirmed through a presumptive sign of pregnancy such as missed menses or a positive pregnancy test [45 CFR 46.203(b)]. This "confirmation" may be in error, but, for research purposes, investigators would presume that a living fetus was present until evidence to the contrary was clear. Although fertilization occurs a week or more before implantation, the current inability to detect the fertilization event or the presence of a newly fertilized egg makes a definition of pregnancy based on implantation necessary.

Viable Infant: When referring to a delivered or expelled fetus, the term "viable infant" means likely to survive to the point of sustaining life independently, given the benefit of available medical therapy. This judgment is made by a physician. In accordance with DHHS regulations, the Secretary, HHS, may publish guidelines to assist in the determination of viability. Such guidelines were published in 1975, and specify an estimated gestational age of 20 weeks or more and a body weight of 500 grams or more as indices of fetal viability [*Federal Register* 40 (August 8, 1975): 33552]. These indices depend on the state of present technology and may be revised periodically.

OVERVIEW

In the early 1970s, considerable national concern was expressed about the ethics of fetal research and about reports of ethically questionable procedures involving human fetuses. Partly in response to these concerns, Congress established the **National Commission for the Protection of Human Subjects** in 1974, required that it study the subject of fetal research and make recommendations concerning such research to the Department of Health, Education and Welfare (the precursor of DHHS), and imposed a moratorium on federally funded fetal research until regulations based upon the Commission's recommendations were in place. Subsequent DHHS regulations on this subject implemented fully the recommendations of the National Commission. Congress may, from time to time, impose further limitations on research involving the human fetus; similarly, a number of states have laws affecting such research.

Although the Commission did not define the "personhood" of the fetus, it recognized the genetic heritage and vulnerability of the fetus, and affirmed that it should be treated respectfully and with dignity, regardless of its life prospects. The Commission also affirmed the legitimacy and importance of fetal research for improving the health of fetuses both in the present and the future. Risks to the fetus from any research procedure must not be more than minimal (*e.g.*, from ultrasound or changes in maternal diet). If the risks exceed the level considered minimal, they must be justified by anticipated benefit for the health of the mother or the particular fetus.

The concept of **minimal risk** is evaluative rather than objective; considerable room for interpretation exists. In an effort to impart some objectivity, regulations concerning competent adult subjects define minimal risk in terms of those risks encountered in everyday life or in routine physical or psychological examinations [Federal Policy § __.102(i)]. Determinations of minimal risk to a fetus, however, can challenge an IRB. If risk to the fetus is deemed to be more than minimal and without anticipated medical benefit to the mother or the fetus, special provisions apply.

IRB CONSIDERATIONS

In addition to the general requirements for review of research by the IRB, prior research with animal subjects, and, if feasible, research with nonpregnant persons should form the basis of the risk/benefit assessment for fetal research. The proposed research should seek information not obtainable in any other way. If abortion is involved, the investigators may have no part in either the decision to abort or decisions about the timing or the method to be used; no change in the abortion procedure that would present more than minimal risk to the fetus or its mother can be introduced for research purposes. No monetary or other inducements (*e.g.*, free care) may be offered to a woman to induce her to terminate her pregnancy for research purposes.

Ethics Advisory Board. The DHHS regulations mandate the establishment of a national **Ethics Advisory Board** whose responsibility is to render advice to the Secretary on various issues. Applications involving human in vitro fertilization must be reviewed by the Ethics Advisory Board before they can be funded [45 CFR 46.204]. Similarly, requests for modification or waiver of the regulatory requirements (*e.g.*, research involving greater than minimal risk where therapeutic benefit to the fetus is lacking) must be approved by the Board. If the Board approves the request, the Secretary may authorize support of the research if the knowledge to be gained can be obtained in no other way and is important

enough to justify the risk involved [45 CFR 46.211].

The Board's charter, however, expired in 1980 and has not been renewed as of this writing. Applications for federally-sponsored research involving human in vitro fertilization and embryo transfer may therefore not be funded until a Board is reestablished. Research protocols that require a waiver or modification of the regulatory requirements are similarly restricted. The Guidebook will provide updated information on the status of an Ethics Advisory Board as information becomes available.

Research Directed Toward the Fetus In Utero. Research in which the welfare of a fetus in utero must be considered may involve the fetus either directly or indirectly. The research may be directed toward the pregnant woman (in which case the fetus is indirectly involved), the fetus (in which case it is directly involved) or both. Where it is directed toward both the pregnant woman and the fetus in utero, the regulations pertaining to both subjects apply [45 CFR 46.207 (activities directed toward pregnant women as subjects) and 45 CFR 46.208 (activities directed toward fetuses in utero as subjects)]. Research directed toward the pregnant woman is discussed in Guidebook Chapter 6, Section B, "Women."

An IRB may approve research directed toward the fetus in utero if: (1) the purpose of the research is to meet the health needs of the fetus and is conducted in a way that will minimize risk (*e.g.*, a new technique for fetal transfusion for Rh incompatibility); or (2) the research poses no more than **minimal risk** to the fetus (*e.g.*, minor changes in maternal diet or use of ultrasonography) and the purpose of the activity is the development of important biomedical knowledge that is unobtainable by other means [45 CFR 46.208]. Many possibilities for intrauterine treatment of fetuses are presently being explored. The initial efforts in this field will inevitably be innovative and experimental. When proposals for research on fetal therapy come before an IRB, the risks should be justified by a reasonable possibility of benefitting the fetus (*e.g.*, increased chance of survival or avoidance of severe disability).

Research Involving the Fetus Ex Utero. If an ex utero fetus is judged viable (*i.e.*, likely to survive to the point of sustaining life independently, given the benefit of available medical therapy), it is then called an infant. At this point, an IRB must be guided by regulations and policies dealing with children. [See 45 CFR 46 Subpart D.] A fetus is judged nonviable if it cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy, and will therefore die. Research involving a nonviable fetus that would either artificially maintain vital functions or hasten their failure is forbidden. Ethical considerations call upon investigators to maintain the dignity of this dying human subject and to avoid unseemly intrusions in the process of dying for research purposes [45 CFR 46.209].

Research With Dead Fetuses, Fetal Material, and the Placenta. Research activities involving the dead fetus, macerated fetal material, or cells, tissue, or organs excised from a dead fetus are governed by state laws and regulations [45 CFR 46.210]. The National Commission recommended that, in addition to conforming to such laws, research involving dead fetuses be compatible with commonly held views about respect for the dead.

Fetal Tissue Transplantation Research. Research involving the use of human fetal tissue obtained from induced abortions into patients suffering from such disorders as Parkinson Disease and juvenile diabetes has been the subject of considerable debate in the biomedical community. A moratorium on federally-funded research involving the therapeutic transplantation into humans of fetal tissue obtained from induced abortions, which was imposed by the Assistant Secretary for Health in 1988, was lifted on January 22, 1993, by presidential memorandum [*Federal Register* 58:7457 (February 5, 1993)]. A panel convened by NIH to deliberate on the concerns that gave rise to the moratorium issued recommendations regarding the ethical use of fetal tissue from induced abortions in therapeutic transplantation research [U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health (1988b)]. The panel's report was approved by NIH in December 1988. NIH has issued interim guidelines for the support and conduct of therapeutic human fetal tissue transplantation research [*NIH Guide for Grants and Contracts* 22 (No. 11, March 19, 1993)]. The interim guidelines, which closely follow the panel's recommendations, provide as follows:

Separating Abortion from Research

- The decision to terminate a pregnancy and procedures of abortion should be kept independent from the retrieval and use of fetal tissue.
- The timing and method of abortion should not be influenced by the potential uses of fetal tissue for transplantation or medical research.

Prohibiting Payments and Other Inducements

- Payments and other forms of remuneration and compensation associated with the procurement of fetal tissue should be prohibited, except payment for reasonable expenses occasioned by the actual retrieval, storage, preparation, and transportation of the tissues.

Informed Consent

- Potential recipients of such tissues, as well as research and health care participants, should be properly informed about the source of the tissues in question.
- The decision and consent to abort must precede discussion of the possible use of the fetal tissue and any request for such consent that might be required for that use.
- Fetal tissue from induced abortions should not be used in medical research without the prior consent of the pregnant woman. Her

- decision to donate fetal remains is sufficient for the use of tissue, unless the father objects (except in cases of incest or rape).
- Consent should be obtained in compliance with state law and with the Uniform Anatomical Gift Act.

Prohibiting Directed Donations

- The pregnant woman should be prohibited from designating the transplant recipient of the fetal tissue.
- Anonymity between donor and recipient should be maintained, so that the donor does not know who will receive the tissue, and the identity of the donor is concealed from the recipient and transplant team.
- Experimental transplants performed with fetal tissue from induced abortions provided by a family member, friend, or acquaintance should be prohibited.

Abiding by State and Local Laws

- Researchers in states with statutes appearing to ban fetal tissue transplants should seek clarification of the law.

Ethical Review of Research

- Customary review procedures should apply to research involving transplantation of tissue from induced abortions.

Determining When Progress to Clinical Studies is Justified

- Sufficient evidence from animal experimentation is needed to justify proceeding to human clinical trials. Acceptable preliminary data must be presented to an appropriate Institutional Review Board, NIH Initial Review Group, and National Advisory Council before Public Health Service funds would be available.

Resources discussing the ethical issues involved in the use of human fetal tissue for transplantation are provided in the "Suggestions for Further Reading" section at the end of this chapter. Restrictions on the use of fetal material for research purposes is an evolving area of the law. In addition to any federal requirements concerning the use of fetal tissue in research, many states have adopted legislation governing the use of fetal tissue, including use for transplantation purposes. IRBs should be aware of and adhere to any legal requirements relevant to their review of protocols that include the use of fetal tissue.

Research in Anticipation of Abortion. There are conflicting views about whether research in anticipation of abortion is permissible. Some people believe such research exploits already difficult (some consider the situation morally unacceptable) circumstances; others feel that the opportunity to test drugs or procedures on fetuses whose mothers have already made a decision to abort poses little real risk to those fetuses, while the research may save other fetuses from considerable risk. For example, some drugs produce birth defects if taken during pregnancy because they pass through the placenta to the fetus, and tests performed on animals - even primates - are not always a reliable indicator of what will happen in humans. To evaluate this effect accurately, experimental drugs must be tested in women to see whether they cross the placenta. It has been suggested that such tests pose less risk to a fetus-to-be-aborted than to a fetus going to term, because there is not time for the harm (e.g., birth defect) to materialize prior to abortion. There are, however, two ethical problems in this situation. First, the woman may change her mind about having the abortion after taking the experimental drug. Second, regardless of life prospects, the fetus is an unconsenting subject.

The National Commission for the Protection of Human Subjects wrestled with this problem and concluded that there is no difference between the moral status of a fetus destined for abortion and that of a fetus to be carried to term. Therefore, only those research procedures that would be acceptable for a fetus going to term may be performed in anticipation of abortion. If the IRB determines that the risk is acceptable for fetuses that will be carried to term, it is acceptable to select only fetuses-to-be-aborted as subjects. By limiting the risk to what is acceptable for the fetus to be carried to term, the right of the mother to change her mind about abortion is protected; by selecting only those fetuses destined for abortion as subjects, risk to fetuses carried to term is minimized. In practical terms, research procedures that take place at the same time and during the same process as the abortion itself most fully meet these conditions (e.g., a fetoscopic procedure initiated after administering drugs to initiate abortion).

Consent for Research Involving Fetuses. In all research in which human fetuses are the subjects of research, the consent of the mother on behalf of the fetus is required. As a general rule, the consent of the father on behalf of the fetus is also required before a fetus may be enrolled in research. Exceptions to the requirement that the father provide consent are permitted if: (1) the father's identity or whereabouts cannot reasonably be ascertained; (2) the father is not reasonably available; or (3) the pregnancy resulted from rape [45 CFR 46.107(b) and 45 CFR 46.208(b)].

The drafters of the regulations reasoned that the father's consent should be obtained in cases where the father is known and reasonably available for several reasons: (1) as co-progenitor, the father has an interest second only to that of the mother in the well-being of the fetus; (2) the father will be held legally responsible for the health needs of the child, and since these health needs may be affected by participation in research, the father ought to have a voice in determining to what risks the fetus should be exposed; and (3) involvement of a fetus in research in cases where the parents are not in agreement concerning participation is likely to disrupt the family unit as a whole, an additional risk for the fetus.

The IRB should provide guidance to investigators to assist in determining when a father is "reasonably available." Some examples of situations in which a father is customarily judged not to be "reasonably available" will assist the IRB in providing direction to investigators:

- Paternity is uncertain. In such cases it is not necessary for the IRB or the research investigator to attempt to establish paternity.
- The father's whereabouts cannot be readily ascertained.
- The father does not acknowledge that he is the father of the fetus.
- The father has assumed no responsibility for the pregnancy and has manifested no interest in or has denied responsibility for the well-being of the fetus. [Note: It may be sufficient for an investigator to obtain a statement to this effect from the mother. No further assessment of the facts is required].

Investigators should document their reasons for deciding that a father was not "reasonably available" and should feel free to consult with the IRB in cases where applicability of the requirement for paternal consent is not clear.

In all studies, IRBs should ensure that the information provided to the parent(s) clearly distinguishes procedures performed for research purposes from procedures performed as a part of the standard care of medicine. Risks to the mother should be, so far as possible, distinguished from risks to the fetus; the limits of knowledge about the extent of those risks should be clearly presented.

Waiver of Specific Requirements by the Secretary. The Secretary, HHS, may modify or waive specific conditions or requirements of the regulations governing fetal research on the advice of a national Ethics Advisory Board and after an opportunity for public comment [45 CFR 46.211]. The primary considerations are whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant the modification or waiver, and whether the benefits of the research can be gained only if the modification or waiver is granted. [See discussion of the Ethics Advisory Board, above.]

The only waiver granted to date was in 1979 for research designed to assess the risk of fetoscopy as a method of prenatal diagnosis of genetic disorders. (It involved inserting a hollow tube into the uterus and extracting a small blood sample from the fetus for examination and testing.) Subjects were to be women who had already decided to undergo an abortion. Since the risk of the procedure was undetermined, it could not be said to be minimal; moreover, no medical benefit to the women or their fetuses was contemplated. Thus, the Department could not support the research without a waiver by the Secretary; that, in turn, required review and approval of the Ethics Advisory Board. The Board's report on this matter, with its conclusion that the research was ethically acceptable, was published in the *Federal Register* for public comment [*Federal Register* 44 (August 14, 1979): 47732]. The Secretary subsequently granted the waiver and provided support for the research.

Additional Restrictions on Fetal Research. Congress imposes additional restrictions on fetal research from time to time; IRBs should therefore consult with OPRR if they are unsure of the current status of such research.

Research Involving Human In Vitro Fertilization. DHHS regulations require all research involving human in vitro fertilization or embryo transfer to be reviewed by a national Ethics Advisory Board before it can be funded by the Department [45 CFR 46.204(d)]. The lapse in the Board has precluded federal funding of human in vitro fertilization research. The American College of Obstetricians and Gynecologists (ACOG) and the American Fertility Society (AFS) have recently established a National Advisory Board on Ethics in Reproduction, which plans to establish guidelines for research in this area. IRBs reviewing privately funded in vitro fertilization research might consider consulting with the new ACOG/AFS advisory board.

Levine (1986) provides an overview of the issues presented by in vitro fertilization, as well as resources for further reading. He notes that while the Ethics Advisory Board found research on in vitro fertilization ethically acceptable and set forth criteria for conducting such research [see Report (June 18, 1979)], the Board did not foresee many of the issues that have since been identified. One issue of importance to IRBs is what Levine calls "the problem of 'spare' embryos" [pp. 315-319]. IRBs should assure that investigators have clearly addressed what will happen to embryos that are not used in the particular embryo transfer procedure for which they were created (e.g., "they [will] be used for research purposes, they [will] be implanted in the uterus of another woman, or they [will] be destroyed"); investigators should ensure that participants are informed of and consent, in writing, to the resolution of this question. Investigators should also clarify to participants the ownership of the embryos that are not used in the procedure (e.g., that they "belong" to the laboratory and may not be removed by the parents, or that they "belong" to the biological mother). Levine describes how these questions were reviewed by the IRB at the Yale University School of Medicine [pp. 317-319].

POINTS TO CONSIDER

1. Is animal research an appropriate prerequisite? Has it been completed? Where appropriate and feasible, has research with nonpregnant women been completed?
2. If there is any risk to a fetus, is the information sought judged to be important? Could it be obtained by any other means?
3. Is risk to the fetus minimal?
4. In research with a nonviable fetus ex utero, is any intervention proposed that would shorten or prolong the natural course of dying?

5. Are the investigators involved in any decisions about an abortion process (e.g., timing or method) that is related to the research?
6. Is abortion encouraged for research purposes (e.g., are free care or services offered)?
7. Do any applicable federal, state, or local laws restrict such research?
8. From whom must consent be obtained?

APPLICABLE LAWS AND REGULATIONS

45 CFR 46 Subpart B

[DHHS: Additional protections pertaining to research, development, and related activities involving fetuses, pregnant women, and in vitro fertilization]

Federal Register 58:7457
(February 5, 1993)

[Fetal tissue transplantation research]

NIH Guide for Grants and Contracts 22

(No. 11, March 19, 1993) [NIH interim guidelines for the support and conduct of therapeutic human fetal tissue transplantation research]

Federal, state, and local laws governing research involving human fetuses or fetal material

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B. WOMEN

INTRODUCTION

Special regulatory requirements govern the participation of pregnant women in research [45 CFR 46 Subpart B]. Research involving women who are or may become pregnant receives special attention from IRBs because of women's additional health concerns during pregnancy and because of the need to avoid unnecessary risk to the fetus. Further, in the case of a pregnant woman, IRBs must determine when the informed consent of the father to the research is required. Special attention is justified because of the involvement of a third party (the fetus) who may be affected but cannot give consent and because of the need to prevent harm or injury to future members of society. Procedural protections beyond the basic requirements for protecting human subjects are prescribed in DHHS regulations for research involving pregnant women [45 CFR 46 Subpart B]. No specific DHHS regulations are directed toward research involving lactating women.

The inclusion of women in research studies is discussed in this Section and in Guidebook Chapter 3, Section C, "Selection of Subjects."

DEFINITIONS

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

Minimal Risk: A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [Federal Policy § __.102(i)]. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

Pregnancy: The period from confirmation of implantation of a fertilized egg within the uterus until the fetus has entirely left the uterus (*i.e.*, has been delivered). Implantation is confirmed through a presumptive sign of pregnancy such as missed menses or a positive pregnancy test [45 CFR 46.203(b)]. This "confirmation" may be in error, but, for research purposes, investigators would presume that a living fetus was present until evidence to the contrary was clear. Although fertilization occurs a week or more before implantation, the current inability to detect the fertilization event or the presence of a newly fertilized egg makes a definition of pregnancy based on implantation necessary.

IRB CONSIDERATIONS

Pregnant women may be involved in several categories of research. IRB duties differ in each category, but the primary objectives are assessing: (1) whether the research is directed toward the mother's health or toward the fetus; and (2) the risks to the woman and to the fetus or infant. Subsequent actions depend on those assessments. Research directed toward the fetus is discussed in Guidebook Chapter 6, Section A, "Fetuses and Human In Vitro Fertilization." For research activities directed toward pregnant women as subjects, the federal regulations provide that no pregnant woman may be involved as a subject unless either: (1) the purpose of the activity is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs; or (2) the risk to the fetus is minimal [45 CFR 46.207].

Inclusion of Women in Study Populations. NIH policy requires the inclusion of women and minorities in research study populations so that research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study. Specifically, the NIH policy states:

Applications for grants and cooperative agreements that involve human subjects are required to include minorities and both

genders in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study; special emphasis should be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy applies to all research involving human subjects and human materials, and applies to males and females of all ages. If one gender and/or minorities are excluded or are inadequately represented in this research, particularly in proposed population-based studies, a clear compelling rationale for exclusion or inadequate representation should be provided. The composition of the proposed study population must be described in terms of gender and racial/ethnic group, together with a rationale for its choice. In addition, gender and racial/ethnic issues should be addressed in developing a research design and sample size appropriate for the scientific objectives of the study.

Assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH...recognize [s] that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations (*i.e.*, American Indians or Alaskan Natives, Asians or Pacific Islanders, Blacks, Hispanics). Provide the rationale for studies on single minority population groups.

Applications for support of research involving human subjects must employ a study design with gender and/or minority representation (by age distribution, risk factors, incidence/prevalence, etc.) appropriate to the scientific objectives of the research. It is not an automatic requirement for the study design to provide statistical power to answer the questions posed for men and women and racial/ethnic groups separately; however, whenever there are scientific reasons to anticipate differences between men and women, and racial/ethnic groups, with regard to the hypothesis under investigation, applicants should include an evaluation of these gender and minority group differences in the proposed study. If adequate inclusion of one gender and/or minorities is impossible or inappropriate with respect to the purpose of the research because of the health of the subjects, or other reasons, or if in the only study population available, there is a disproportionate representation of one gender or minority/majority group, the rationale for the study population must be well explained and justified [PHS Grant Application form 398, pp. 21-22].

[See also publication and interpretation of the NIH policy in the *NIH Guide for Grants and Contracts* 20 (No. 32, August 23, 1991): 1-3.]

In addition, principal investigators of funded grants and cooperative agreements falling under the scope of the policy must report annually on the number of subjects planned and enrolled to date by ethnic origin and gender [Application for Continuation of a Public Health Service Grant, form 2590, pp. 7-9 and Form Page 7].

This information should also be available for IRB review, both for its initial review and for its annual review for continuation of projects. The role of the IRB in assuming responsibility for reviewing the adequacy of representation of women and minorities in studies has been controversial. IRBs around the country have deliberated the relevance of the inclusion of women and minorities in studies to their consideration of whether the welfare and safety of subjects are adequately protected. Their responses cross the entire spectrum of possibilities, from considering the question irrelevant to regarding it as one of utmost importance. Discussion is continuing at many levels in the federal government in an effort to develop IRB guidance policies. NIH expects to provide further guidance concerning the policy, which will be published in the *NIH Guide for Grants and Contracts* during 1993.

Discussion centers on issues of justice, beneficence, appropriate levels of inclusion, generalizability of study results, and liability of sponsors. The exclusion of women from studies raises considerations of justice because exclusion deprives women from the possibility of directly benefitting from participation (*e.g.*, receiving a potentially beneficial medical therapy).

Exclusion or inappropriate representation further raises issues of generalizability: If women are excluded or are not appropriately represented, the data generated by the study may not be generalizable beyond the male study population; women as a class will therefore not benefit. In considering the inclusion of women in the study, IRBs should note the limitations on generalizability that may result from study size or other factors. The ability to evaluate gender differences may depend on sample sizes that the investigator cannot reasonably attain.

Women of child-bearing potential may be excluded from studies not only because of concern for the welfare of the fetus, but also because of possible legal liability of sponsors and investigators for harm caused by investigational agents or other research activities. Consideration of the liability issue requires balancing the protection of women and potential fetuses against the benefits that would result from their inclusion (*i.e.*, direct benefits and the generalizability of data).

Until a consensus is reached on this question, IRBs should continue to consider representation of women in study protocols in their deliberations on the adequacy of protections of the safety and welfare of subjects.

In 1977 the FDA issued guidelines limiting the involvement of women of childbearing potential in Phase 1 and early Phase 2 clinical drug trials, with which IRBs should be familiar. [See *General Considerations for the Clinical Evaluation of Drugs* (1977) and *Guidelines for the Format and Content of the Clinical and Statistical Sections of New Drug Applications* (1988).] The FDA is reevaluating its policy on the exclusion of women of childbearing potential from such clinical studies [U.S. General Accounting Office (1992)], and has indicated that it will revise the 1977 guidelines to permit and encourage the inclusion of women of childbearing potential in research.

Studies in Which Pregnancy is Coincidental to Subject Selection. Any study in which women of childbearing potential are possible subjects may inadvertently include pregnant women. DHHS regulations require that, when appropriate, subjects be provided 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" as part of the informed consent process [Federal Policy § __.116(b)(1)]. IRBs must judge whether the mother's participation would pose any risk to the fetus or nursing infant. In some studies, IRBs may need to ensure that nonpregnant subjects are advised to avoid pregnancy or nursing for a time during or following the research. Furthermore, where appropriate, subjects should be advised to notify the investigator immediately should they become pregnant. In some instances there may be potential risk sufficient to justify requiring that pregnant women either be specifically excluded from the research or studied separately.

Studies Directed Primarily Toward the Mother's Health. Many women enter pregnancy with health problems or develop new ones during pregnancy. Some problems are affected positively or negatively by pregnancy; others are unaffected. A considerable amount of research is conducted on health problems that occur during pregnancy (e.g., arthritis, hypertension, diabetes); despite standard therapy, deterioration of maternal health may also necessitate experimental treatment. In research undertaken to meet the health problems of a pregnant woman, her needs generally take precedence over those of the fetus [45 CFR 46.207], except, perhaps, where the health benefit to the woman is minimal and risk to the fetus is high. If, for example, an experimental drug were considered necessary to improve a pregnant woman's condition, her consent alone would be sufficient to authorize its administration - even though it might have unknown or greater than **minimal risk** for the fetus. In reviewing such studies IRBs must attempt to ensure that the risk to the fetus is minimized, consistent with achieving the research objective.

Studies Directed Toward Pregnancy. Numerous studies are conducted that address the normal and abnormal processes of pregnancy, labor, and delivery. Some (e.g., studying the physiological mechanisms maintaining pregnancy or initiating labor) are not directed to the health of either the mother or fetus. Others (e.g., studying the effects of strict control of maternal diabetes on pregnancy outcome) involve research on improving maternal health and research on the fetus, thus requiring review for both sets of considerations. [See Guidebook Chapter 6, Section A, "Fetuses and Human In Vitro Fertilization."] The requirements for IRB approval will sometimes conflict, depending on how the research is categorized (e.g., whether or not it is directed toward improving maternal health determines the degree of fetal risk permitted and paternal consent requirements). In such instances, the IRB will have to determine which circumstances prevail and which requirements apply.

The primary requirement for approval in this category is an IRB determination that the risk to the fetus is "minimal." The broad definition of minimal risk places great responsibility for good judgment on IRB members. The definition suggests that if the estimated risk to the fetus is no more than that from established procedures routinely used in an uncomplicated pregnancy or in a pregnancy with complications comparable to those being studied, the risk is considered minimal. Ultrasound exams, maternal exercise comparable to job- or recreation-related levels, amniocentesis, and delivery in a sitting position might be considered minimally risky in most pregnancies. If the IRB cannot conclude that fetal risk is minimal, it may conditionally approve the research, subject to review and approval by the Secretary, HHS [45 CFR 46.211]. As with fetal research, the Secretary may modify or waive specific conditions or requirements of the regulations governing fetal research on the advice of a national Ethics Advisory Board and after an opportunity for public comment [45 CFR 46.211]. The primary consideration is whether the risks to the subjects are so outweighed by the sum of the benefit to the subjects and the importance of the knowledge to be gained as to warrant the modification or waiver. A further consideration is whether the benefits of the research can be gained without the modification or waiver.

Consent. Once the research is approved under the IRB's minimal risk standard, the IRB must make a judgment regarding the consent. DHHS regulations require both the woman's and the father's consent for research in this category unless: (1) the purpose of the research is to meet the health needs of the mother; (2) the father's identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape. Issues of consent are discussed in Chapter 6, Section A, "Fetuses and Human In Vitro Fertilization."

Lactating Women. Although there are no specific regulations for research involving lactating women, IRB review should include a focus on safety for the nursing infant (the mother's own child or one to whom she provides her milk). IRBs should require that investigators provide assurance that taking breast milk samples, maternal dietary modifications, drugs given to the mother, or other research manipulations will not unduly threaten the supply or nutritional content of colostrum or milk for nursing infants.

Studies to Develop or Evaluate Methods of Enhancing Conception or Contraception. These studies are closely related to research involving pregnant women and raise some of the same concerns. There are no special regulations for this category of research, but special IRB attention is needed. IRBs should ensure that there is an adequate explanation of the risks, benefits, reversibility, and alternatives; that backup protection against unintended pregnancy is provided when appropriate; and that the possibility of failure (and options available for dealing with unintended pregnancies) are satisfactorily described.

Research on Abortion Techniques. DHHS regulations do not deal directly with research on abortion techniques. In reviewing such research, risks to the woman would be a primary consideration. IRBs should keep in mind, however, that if a fetus survived the abortion and was viable, the infant might be severely damaged. IRBs must be aware of local requirements and the most current federal laws and policies before proceeding to review the proposed research.

Exemption from Review. Note that the exemptions from IRB review provided for in 45 CFR 46.101(b) [Federal Policy § __.101(b)] do not apply to research involving pregnant women [*Federal Register* 56 (June 18, 1991): 28013, note 1].

POINTS TO CONSIDER

1. For all studies, is there reason to exclude pregnant or lactating women? If so, how strict should the screening measures be?
2. For all studies involving pregnant women, have appropriate studies on animals and nonpregnant humans been conducted? Is any special monitoring of the informed consent process needed?
3. For studies directed toward maternal health, is the risk to the fetus the least possible consistent with the research objectives? Will the mother

be adequately informed of the potential risk to the fetus and of alternative treatments and their risks and benefits?

4. For studies of pregnancy, labor, or delivery, is the risk to the fetus "minimal?" Is the father's consent required?

5. For studies of lactating women, is the supply and content of breast milk adequately protected?

6. For studies of conception or contraception, are the risks, benefits, reversibility, and alternatives adequately explained? In contraceptive studies, is there adequate explanation of possible failure and of the options available for dealing with unintended pregnancies?

7. Will women be appropriately represented in the study? Does the study need to be designed to allow evaluation of gender differences?

APPLICABLE LAWS AND REGULATIONS

Federal policy for the protection of human subjects

21 CFR 50.25(b)(1)

[FDA: Informed consent]

45 CFR 46, Subpart B

[DHHS: Additional protections pertaining to research, development, and related activities involving fetuses, pregnant women, and in vitro fertilization]

Applicable regulations of the Department of Agriculture, the Army, and the Air Force

Federal laws that may limit research involving the living human fetus

State and local laws governing research involving human fetuses

NIH policy concerning inclusion of women and minorities in study populations. *NIH Guide for Grants and Contracts 20* (No. 32, August 23, 1991): 1-3. The policy also appears in the application packet for PHS Grants, form PHS 398, pp. 21-22, and in NIH Requests for Proposals (RFPs).

Application for Continuation of a Public Health Service Grant, form 2590, pp. 7-9 and Form Page 7.

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C. CHILDREN AND MINORS

INTRODUCTION

The ethical mandate of IRBs is to protect the rights and welfare of human research subjects. IRBs are obligated to ensure that research studies do not endanger the safety or well-being of human subjects or undermine public confidence in the conduct of research. The special vulnerability of children makes consideration of involving them as research subjects particularly important. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations are in place for reviewing research involving children. Title 45 CFR Part 46, Subpart D provides for "Additional Protections for Children Involved as Subjects of Research." Research that is contrary to the rights and welfare of child-subjects is prohibited. A good summary of the ethical considerations surrounding research involving children can be found in Levine (1989).

DEFINITIONS

Assent: A child's affirmative agreement to participate in research. Mere failure to object should not be construed as assent [45 CFR 46.402(b)].

Benefit: A valued or desired outcome; an advantage.

Children: Persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted [45 CFR 46.402(a)].

Emancipated Minor: A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage or procreation. (*See also:* Mature Minor.)

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

[45 CFR 46.402(3)].

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

Minimal Risk: A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [Federal Policy § __.102(i)]. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

Permission: The agreement of parent(s) or guardian to the participation of their child or ward in research [45 CFR 46.402(c)].

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

IRB CONSIDERATIONS

Analysis of Probable Risks, Possible Benefits, and Associated Discomforts. IRBs reviewing research involving children as subjects must consider the benefits, risks, and discomforts inherent in the proposed research and assess their justification in light of the expected benefits to the child-subject or to society as a whole. In calculating the degree of risk and benefit, the IRB should weigh the circumstances of the subjects under study, the magnitude of risks that may accrue from the research procedures, and the potential benefits the research may provide to the subjects or class of subjects.

The federal regulations require IRBs to classify research involving children into one of four categories and to document their discussions of the risks and benefits of the research study. The four categories of research involving children that may be approved by IRBs, based on degree of risk and benefit to individual subjects, are as follows:

1. Research not involving greater than minimal risk [45 CFR 46.404].
2. Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual subject. Research in this category is approvable provided: (a) the risk is justified by the anticipated benefit to the subject; and (b) the relationship of risk to benefit is at least as favorable as any available alternative approach [45 CFR 46.405].
3. Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Research in this category is approvable provided: (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 settings; and (c) the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition [45 CFR 46.406].
4. Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Research that is not approvable under 45 CFR 46.404, 46.405, or 46.406 may be conducted or funded by DHHS provided that the IRB, and the Secretary, after consultation with a panel of experts, finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a significant problem affecting the health and welfare of children. The panel of experts must also find that the research will be conducted in accordance with sound ethical principles [45 CFR 46.407].

In all cases, the IRB must determine that adequate provisions have been made for soliciting the assent of children and the permission of their parents or guardians [45 CFR 46.408].

Assessing Probable Risks. Central to IRBs' consideration of research involving children is the determination of what constitutes **minimal risk**. Procedures that usually present no more than minimal risk to a healthy child include: urinalyses, obtaining small blood samples, EEGs, allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. The assessment of the probability and magnitude of the risk, however, may be different in sick children and may vary depending on the diseases or conditions the subjects may have. For example, obtaining blood samples from a hemophiliac child may present more than minimal risk to the child. On the other hand, IRBs may consider that children suffering from chronic illnesses who are accustomed to invasive procedures are placed at minimal risk by involvement in similar research procedures, in contrast to children who have not had such experiences. The IRB must also consider the extent to which research procedures would be a burden to any child, regardless of whether the child is accustomed to the proposed procedures.

Procedures that exceed the limits of minimal risk may be difficult to define in the abstract, but should not be too difficult to identify on a case-by-case basis. Riskier procedures might include biopsy of internal organs, spinal taps, or the use of drugs whose risks to children have not yet been established. Behavioral interventions likely to cause psychological stress may also exceed minimal risk.

Assessing Possible Benefits. In assessing the possible **benefits** of research intervention, the IRB should consider the variability in health statuses among potential subjects. For example, a potential subject might be a normal, healthy child, or a child who has been exposed to a disease or a toxin (e.g., meningococcus or lead) where it is known that a percentage of the children exposed will actually experience untoward

consequences. A child may also be in an early state of disease, *e.g.*, an HIV-infected child, or may actually suffer from disease or other significant medical condition. Thus the IRB must take into account the current health status of a child and the likelihood of progression to a worsened state without research intervention.

Phase 1 Trials. The issue of Phase 1 drug studies deserves special consideration. The usual approach to designing drug studies involving children as subjects is for appropriate studies to be conducted first in animals, adults, and older children before young children are involved as research subjects. There are some studies, however, in which data may not be entirely generalizable from older populations, and in which the existence of life-threatening conditions for children are important considerations in the IRB's risk/benefit analysis. The requirement for previous testing in adults or older children may thus not be appropriate. Furthermore, some diseases specific to children may require that children be involved without data from older groups (*e.g.*, there is no adult model that mimics the state of HIV-infected newborns; Wilms' tumor and various cancers such as neuroblastoma affect infants who do not survive into older childhood.) In some cases "tandem" studies in older populations and children may be justifiable. For example, some Phase 1 studies in children might be based on only pharmacologic safety and toxicity data (completed Phase 1 and ongoing Phase 2) but without complete effectiveness data from trials in adults and older children. If the IRB approves a Phase 1 drug trial, the consent document must specify what is known about the probability that, and the degree to which, an intervention will be of possible benefit based on all of these data.

Consent Procedures. When children or minors are involved in research, the regulations require the **assent** of the child or minor and the **permission** of the parent(s), in place of the consent of the subjects.

Given that children have not reached their full intellectual and emotional capacities and are legally unable to give valid consent, involving children in research requires the permission of their parents or legally authorized representatives. The IRB must determine whether the permission of both parents is necessary, and the conditions under which one parent may be considered "not reasonably available" [45 CFR 46.408]. (Examples of circumstances in which parental permission may be inappropriate are discussed below.) In addition, the regulations require that the IRB 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 [45 CFR 46.408(a)].

The regulations provide that an IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 (minimal risk research) or 45 CFR 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects) [45 CFR 46.408(b)]. Where research is covered by 45 CFR 46.406 and 45 CFR 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 [45 CFR 46.408(b)].

While children may be legally incapable of giving informed consent, they nevertheless may possess the ability to assent to or dissent from participation. Out of respect for children as developing persons, children should be asked whether or not they wish to participate in the research, particularly if the research: (1) does not involve interventions likely to be of benefit to the subjects; and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others. The IRB must determine for each protocol - depending on such factors as the nature of the research and the age, status, and condition of the proposed subjects - whether all or some of the children are capable of assenting to participation. Where appropriate, IRBs may choose to review on a case-by-case basis whether assent should be sought from given individual subjects. The federal regulations do not require that assent be sought from children starting at a specific age, but that their assent should be sought when, in the judgment of the IRB, the children are capable of providing their assent. IRBs are to take into account the ages, maturity, and psychological state of the children involved [45 CFR 46.408(a)].

When the research offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research, the IRB may determine that the assent of the child is not necessary [45 CFR 46.408(a)]. Additionally, in such circumstances a child's dissent, which should normally be respected, may be overruled by the child's parents, at the IRB's discretion. When research involves the provision of experimental therapies for life-threatening diseases such as cancer, however, IRBs should be sensitive to the fact that parents may wish to try anything, even when the likelihood of success is marginal and the probability of extreme discomfort is high. Should the child not wish to undertake such experimental therapy, difficult decisions may have to be made. In general, if the child is a mature adolescent and death is imminent, the child's wishes should be respected.

When the IRB determines that the assent of the child is required, it must also determine that the provisions for obtaining and documenting assent are adequate [45 CFR 46.408(e)]. The child should be given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity, and condition. This explanation should include a discussion of any discomforts and inconveniences the child may experience if he or she agrees to participate.

For some research activities, IRBs may require that either an IRB member or an advocate for the child be present during the assent and permission procedures to verify the child's understanding and to support the child's preferences. The IRB may also require that the parent(s) or a close family member be present during the research, especially if a young child will be exposed to significant discomfort or inconvenience, or if the child will be required to spend time in an unfamiliar place.

The requirement for parental permission may be inappropriate in some cases. Examples include research involving older adolescents who, under applicable law, may consent on their own behalf for selected treatments (*e.g.*, treatment for venereal disease, drug abuse, or emotional disorders). In other research (*e.g.*, research on child abuse or neglect), there may be serious doubt as to whether the parents' interests adequately reflect the child's interests. In these cases, IRBs should devise alternative procedures for protecting the rights and interests of the children asked to participate, including, perhaps, the court appointment of special guardians.

Parental permission may sometimes be insufficient to protect the child's interests. In cases involving transplants (*e.g.*, of bone marrow or a kidney) between minor siblings, the parents' concern for the afflicted child may interfere with their consideration of the best interests of the healthy donor. Therefore, IRBs may want to consider asking for court review of the parents' decision. [See also Guidebook Chapter 5, Section G, "Transplants."]

The IRB should consult legal counsel about the applicability of any state laws affecting consent for the proposed research. The IRB should be aware of the age of majority in the state as well as laws or court decisions that might limit the right of parents to consent on behalf of their children in certain circumstances. Age and conditions of emancipation will differ from state to state. In some states the age at which a child can give consent to medical care differs depending on the medical condition involved (*e.g.*, venereal diseases). The federal regulations require that all research activities must comply not only with the regulations but also with the law of the state in which they are performed.

Exemption From Review. 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 covered by Subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed. The remaining exemptions in 45 CFR 46.101(b)(2) apply to research involving children.

Wards of the State. The special protections for children set forth in Subpart D include additional limitations on some research involving children who are wards of the state or any other agency, institution, or entity. Where the research involves greater than minimal risk to the subjects with no prospect of direct benefit to individual subjects (45 CFR 46.406), or requires HHS Secretarial approval (45 CFR 46.407), the research must either be related to their status as wards, or else be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards [45 CFR 46.409]. The IRB must require, for each child who is a ward, appointment of an advocate in addition to any other individual acting on behalf of the child as a guardian or *in loco parentis*.

IRBs should be particularly concerned with the involvement of HIV-infected children who are in foster care, but who are also not wards. Many of these children are from racial or ethnic minorities. IRBs need to give special attention to groups of children such as these who, while they need special protections, should not be denied the opportunity to participate in research that may potentially be of benefit to them.

Finally, whenever institutionalized children might be involved in research, care should be taken to ensure that they are not included as participants simply because of their availability to the investigator.

POINTS TO CONSIDER

1. Does the research have an identifiable prospect of direct benefit to the individual child participant? Can that benefit be achieved through alternative means?
2. Does the research have an identifiable prospect of risk to the individual child participant? What safeguards are proposed to minimize these risks? When procedures involving greater than minimal risk to children are anticipated, are convincing scientific and ethical justifications given?
3. Is the inclusion of normal volunteers justified?
4. Do studies involving placebo controls place the child at greater risk by withholding from selected subjects potentially therapeutic research drugs or interventions?
5. When possible, have appropriate studies been conducted on animals and adults first? Will older children be enrolled before younger ones?
6. What is the age of majority in the state? Can a child consent to medical care for certain conditions, and, if so, at what age? What legal limits are there on the right of parents to consent on behalf of their children?
7. Is permission of both parents necessary? Under what conditions may one of the parents be considered "not reasonably available?"
8. Will efforts be made to ensure that parents' permission to involve their children in research studies is free from coercion, exploitation, and/or unrealistic promises?
9. Are mechanisms in place to ensure that children are involved as research subjects in ways that do not undermine their dignity as young persons? Are provisions made that show respect for the developing rights of children, such as: (a) obtaining their assent, and, where appropriate, honoring their dissent; and (b) protecting their need for privacy and the confidentiality of information regarding them?
10. Are there special problems that call for the presence of a monitor or advocate during consent procedures?
11. Are special needs of adolescents such as counseling and confidentiality accounted for in the research design?
12. Are there any special problems such as confidentiality and reporting that might arise in sensitive research about child abuse or sexual practices of teenagers?
13. If conditions present in children have implications for other family members' health statuses, are appropriate mechanisms proposed for dealing with the larger family unit (*e.g.*, genetic risks or HIV infection)?

14. Should parents be required to be present during the conduct of the research? (Are proposed subjects to be very young? Are the procedures involved painful? Must subjects stay overnight in the hospital when they otherwise would not have to?)

APPLICABLE LAWS AND REGULATIONS

45 CFR 46 Subpart D [DHHS: Additional protections for children involved as subjects in research]

The IRB should consult legal counsel about any applicable state laws affecting research involving children as subjects, including laws affecting consent procedures.

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D. COGNITIVELY IMPAIRED PERSONS

INTRODUCTION

The predominant ethical concern in research involving individuals with psychiatric, cognitive, or developmental disorders, or who are substance abusers is that their disorders may compromise their capacity to understand the information presented and their ability to make a reasoned decision about participation. Many individuals with disabilities affecting their reasoning powers may be residents of institutions responsible for their total care and treatment. The impact of institutionalization may further compromise their ability to exercise free choice (voluntariness). (These concerns apply both to voluntary patients and those committed involuntarily.) The eagerness for release may induce an institutionalized person, especially one who is involuntarily confined, to participate in research out of a desire to appear "rational" and "cooperative" to those who will make decisions about his or her release.

It is important to protect the privacy of all subjects and the **confidentiality** of information gathered in research exploring emotionally sensitive topics. Many patients do not want even the fact of their institutionalization divulged.

DEFINITIONS

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

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

Competence may fluctuate as a function of the natural course of a mental illness, response to treatment, effects of medication, general physical health, and other factors. Therefore, mental status should be re-evaluated periodically. As a designation of legal status, competence or incompetence pertains to an adjudication in court proceedings that a person's abilities are so diminished that his or her decisions or actions (*e.g.*, writing a will) should have no legal effect. Such adjudications are often determined by inability to manage business or monetary affairs and do not necessarily reflect a person's ability to function in other situations.

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

Incompetence: Technically, a legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity.

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

IRB CONSIDERATIONS

IRBs that regularly review research involving vulnerable subjects (such as the mentally disabled) are required by DHHS and FDA regulations to consider including among their members one or more individuals who are knowledgeable about and experienced in working with those subjects [45 CFR 46.107; 21 CFR 56.107]. In addition, the IRB must be sure that additional safeguards are in place to protect the rights and welfare of these subjects [45 CFR 46.111(b); 21 CFR 56.111(b)]. Unlike research involving children, prisoners and fetuses, however, no additional DHHS regulations specifically govern research involving persons who are cognitively impaired.

The recommendations of the National Commission for the Protection of Human Subjects resemble the recommendations made with respect to children. [*See* Guidebook Chapter 6, Section C, "Children and Minors."] More recently, Annas and Glantz (1986) have argued that research

should involve cognitively impaired subjects only where: (1) they comprise the only appropriate subject population; (2) the research question focuses on an issue unique to subjects in this population; and (3) the research involves no more than minimal risk. Levenson and Hamric (1989) argue that research involving greater than minimal risk may be acceptable where the purpose of the research is therapeutic with respect to individual subjects and where the risk is commensurate with the degree of expected benefit.

Selection of Subjects. It is now generally accepted that research involving persons whose autonomy is compromised by disability or restraints on their personal freedom should bear some direct relationship to their condition or circumstances. Persons who are **institutionalized**, particularly if disabled, should not be chosen for studies that bear no relation to their situation just because it would be convenient for the researcher. An institutional setting can be advantageous to the conduct of research - the population is easily accessible, close supervision to prevent extraneous influences is possible, and medical monitoring and emergency services are available. Some not uncommon characteristics of the institutional setting, however, create circumstances that may compromise the voluntary nature of participation in research. For example, institutionalized individuals may have become emotionally dependent on their caretakers and may acquiesce too readily to requests for their "cooperation." Persons who are totally dependent on an institution may be vulnerable to perceived or actual pressures to conform to institutional wishes for fear of being denied services or privileges. If medical care, staff attention, or living conditions are inadequate, an invitation to move into a special unit or research ward may be appealing. Finally, with little or no opportunity to make decisions regarding their daily living, the ability of institutionalized subjects to make choices may be further diminished.

Nevertheless, IRBs should not make assumptions as to the effect of an institutional setting on **voluntariness** or **competence**. People do not automatically become incapable of competent and voluntary consent the moment they enter a mental institution. On the other hand, institutionalized individuals (particularly retarded persons) have been used as convenient research subjects in drug tests totally unrelated to their disorders or institutionalization. This exploitation of the vulnerable and the "voiceless" led the National Commission to recommend that, even in research on mental disabilities, subjects should be recruited from among noninstitutionalized populations whenever possible.

Degree of Risk. No clear consensus exists on the acceptable degree of risk when mentally compromised persons are involved in the research. One position holds that research that presents more than minimal risk should involve mentally compromised persons only if they will derive a direct and significant benefit from participation. The National Commission recommended that a minor increase over **minimal risk** may be permitted in research involving those institutionalized as mentally disabled, but only where the research is designed to evaluate an intervention of foreseeable benefit to their care. For research that does not involve beneficial interventions and that presents more than minimal risk, the National Commission recommended that the anticipated knowledge sought should be of vital importance for understanding or eventually alleviating the subject's disorder or condition. Finally, the National Commission recommended that there be additional ethical review at the national level for research projects the IRB believes should be supported - because the knowledge to be gained may be of major significance to the prevention, diagnosis, or treatment of mental disorders - but that would not otherwise be approved at the local level. The American College of Physicians has similarly recommended the creation of a national board to review research that involves more than minimal risk and that carries no direct benefit for the subjects [1989, p. 846]. Since the mechanism of a national board is not currently available, IRBs reviewing such research should consider obtaining assistance from expert consultants.

Limiting Risks. IRBs must be sure that investigators have included a description of appropriate psychological or medical screening criteria to prevent or reduce the chances of adverse reactions to the therapeutic and research procedures. When appropriate, IRBs might want to require that other health care providers be consulted to ensure that proposed research procedures will not be detrimental to ongoing therapeutic regimens. Specific diagnostic, symptomatic, and demographic criteria for subject recruitment should be described in the research proposal.

Any plan to hospitalize subjects or extend hospitalization for research purposes should be justified by the investigator. The effects of separation from supportive family or friends, of disruption in schooling or employment, and the question of responsibility for bearing any additional costs should be carefully considered by the IRB. Methods for assuring adequate protections for the **privacy** of the subjects and the **confidentiality** of the information gathered should also be described by the investigator. Individually identifiable information that is "sensitive" should be safeguarded, and requests for the release of such information to others, for research or auditing, should be allowed only when continued confidentiality is guaranteed.

Problems of Consent and Competence. Consent to research involving cognitively impaired subjects through any of the intramural programs of the National Institutes of Health (e.g., the National Institute of Mental Health, the National Institute of Neurological and Communicative Disorders and Stroke, the National Institute on Aging, and the National Institute on Alcohol Abuse and Alcoholism) is guided by NIH policy on consent to research with impaired human subjects. This policy sets out, in matrix form, conditions under which cognitively impaired subjects may participate in research of varying risk.

As a general rule, all adults, regardless of their diagnosis or condition, should be presumed competent to consent unless there is evidence of serious mental disability that would impair reasoning or judgment. Even those who do have a diagnosed mental disorder may be perfectly able to understand the matter of being a research volunteer, and quite capable of consenting to or refusing participation. Mental disability alone should not disqualify a person from consenting to participate in research; rather, there should be specific evidence of individuals' incapacity to understand and to make a choice before they are deemed unable to consent.

Persons formally adjudged incompetent have a court-appointed guardian who must be consulted and consent on their behalf. Officials of the institution in which incompetent patients reside (even if they are the patient's legal guardians) are not generally considered appropriate, since their supervisory duties may give rise to conflicting interests and loyalties. Family members or others financially responsible for the patient may also be subject to conflicting interests because of financial pressures, emotional distancing, or other ambivalent feelings common in such circumstances. IRBs should bear this in mind when determining appropriate consent procedures for cognitively impaired subjects.

Some individuals may be incompetent and have no legal guardian. One such example would be mentally retarded adults whose parents "voluntarily" institutionalized them as children and have never subsequently gone through formal proceedings to determine incompetence and have a guardian appointed. Another example would be geriatric patients with progressive cognitive disorders (e.g., senile dementia of the Alzheimer type). Typically, a spouse or adult child of such patients consents to their medical care, but no one is a "legally authorized representative." The extent to which family members may legally consent to the involvement of such patients in research (especially if no benefit to the subjects is anticipated) is not clear. According to a position paper published by the American College of Physicians (1989), surrogates of cognitively impaired persons should not consent to research that holds out no expected benefit if such research presents more than minimal risk of harm or discomfort. As mentioned earlier, the ACP also, however, recommended the creation of a national board to review research that involves more than minimal risk and that carries no direct benefit for the subjects [1989, p. 846].

Because no generally accepted criteria for determining competence to consent to research (for persons whose mental status is uncertain or fluctuating) exist, the role of the IRB in assessing the criteria proposed by the investigator is of major importance. The selection of an appropriate representative to consent on behalf of those unable to consent for themselves must be accomplished without clear guidance from statutes, case law, or regulations. Within the boundaries of existing legal precedents, IRBs can be creative in helping investigators formulate appropriate procedures in these uncertain areas. IRBs should be sure, however, to seek legal advice to determine the applicability of state laws that might affect the participation of legally incompetent persons in research. [See also Levine (1986), pp. 270-76.]

IRBs should be cautious about recommending legal proceedings to establish guardianship for the purpose of obtaining consent for research participation. Despite a temptation to recommend this course of action to "be on the safe side," depriving individuals of their freedom should not be taken lightly. Many states give guardians and conservators authority to make nearly all important decisions on behalf of the individual they represent. (These decisions are conditioned by an anticipated benefit to the individual.) The National Commission recommended that guardianships established for purposes of authorizing participation in research be limited to the provision and continuance (or withdrawal) of permission regarding the subject's participation in the research. The National Commission also urged that, despite the fact that consent may be obtained from a legally authorized representative or guardian, the feelings and expressed wishes of an incompetent person should still be respected. IRBs should consider whether to require investigators to solicit prospective subjects' "assent" (i.e., the willing and, to the extent possible, knowledgeable participation of those unable to give legally valid consent). IRBs should also determine whether an incompetent person's refusal to participate in research should override consent given by a legal guardian. The National Commission recommended that such decisions be based on the amount of risk involved in the research and the likelihood that the subjects will derive health benefits from their participation. [See *Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm*, Recommendations 2, 3, and 4.] The National Commission also recommended that in the case of research involving more than minimal risk, the objection of an adult subject who is incapable of consenting should be binding, unless the individual's participation is specifically authorized by a court of law, the intervention is expected to provide a direct health benefit to the subject, and the intervention is available only in the context of the research. [See *id.*, Recommendation 4.] Note, however, that where local law allows institutionalized persons the right to refuse therapy, objections to participation may not be overridden.

Procedures can sometimes be developed to enhance the possibility that subjects can consent for themselves. Criteria for determining **competence** might vary according to the degree of risk or discomfort presented by the research procedures and the extent to which therapeutic gains can be anticipated. The setting in which consent is sought and the person seeking it can also influence a potential subject's ability to comprehend or appreciate what is being asked. An uncomfortable chair, a room that is either too noisy or lacking in privacy, or a physician the patient dislikes may all create anxiety or resistance that would not exist if the information were presented by another person, at another time, or in another place. The National Commission recommended that, in certain cases, a consent auditor be appointed by the IRB to determine whether proposed subjects consent, assent, or object to their participation in research, especially if the research involves more than **minimal risk** and no foreseeable direct benefit.

POINTS TO CONSIDER

1. Does the IRB need to include a member knowledgeable about and experienced with the mentally disabled or cognitively impaired?
2. Does the research pertain to mental disabilities so that it is necessary to involve persons who are mentally disabled as subjects?
3. If the investigator proposes to involve institutionalized individuals, has he or she provided sufficient justification for using that population? Are noninstitutionalized subjects appropriate for the research and reasonably available? Does the research pertain to aspects of institutionalization?
4. Are adequate procedures proposed for evaluating the mental status of prospective subjects to determine whether they are capable of consenting? Are these procedures appropriate both to the subject population and the nature of the proposed research?
5. Is more than minimal risk involved? If so, is the risk justified by anticipated benefits to the participating subjects and the importance of the knowledge that may reasonably be expected to result?
6. Is it possible to identify persons authorized to give legally valid consent on behalf of any individuals judged incapable of consenting on their own behalf? Should assent of the prospective subjects also be required? If incapable of giving valid consent, can subjects' objection to participation be overridden? Under what circumstances?
7. Should an advocate or consent auditor be appointed to ensure that the preferences of potential subjects are elicited and respected? Should someone ensure the continuing agreement of subjects to participate, as the research progresses?

8. Should the patient's physician or other health care provider be consulted before any individual is invited to participate in the research? Is the research likely to interfere with ongoing therapy or regimens? Is it possible that the request to participate itself might provoke anxiety, stress, or other serious negative response?

APPLICABLE LAWS AND REGULATIONS

IRBs should be aware of any applicable law in their state, particularly those relating to consent by family members on behalf of persons incapable of consenting on their own. Note that consent to participation in research may differ from consent to medical treatment. In addition, it should be noted that some federal agencies (including components of the Department of Defense) prohibit the participation of mentally disabled persons in research conducted under their auspices.

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APPENDIX 1

GENERAL BIBLIOGRAPHY

The sources listed in this Section are important reference works that will be useful for every IRB. In-depth treatment of many of the subjects addressed in this Guidebook are provided (*e.g.*, informed consent, risk/benefit analysis, privacy and confidentiality, background on the IRB system). In addition, a number of the articles listed address issues of general interest to IRBs, but which are not discussed in the Guidebook (*e.g.*, conflicts of interest and the funding of research).

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- **Appendix 2: HHS, PHS and NIH Organizational Diagrams**
 - **Appendix 3: Department and Agency Persons to Contact**
 - **Appendix 4: The Federal Policy and 45 CFR 46**
 - **Appendix 5: Agency Documents - "OPRR Reports"**
 - **Appendix 6: The Nuremberg Code, Declaration of Helsinki, and Belmont Report**
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APPENDIX 6

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 probably [sic] cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

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WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

*Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
and the
41st World Medical Assembly
Hong Kong, September 1989*

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Assembly binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is

essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is a liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the

consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with clinical care (*Clinical research*)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any--should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human subjects (*Non-clinical biomedical research*)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers--either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

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APPENDIX 7

LOCAL IRB DOCUMENTS

**** *This appendix is intentionally blank to allow space in the three-ring binder version for institutions to add their own IRB documents.* ****

A place to insert documents pertaining to each institution and its IRB: the institutional assurance, current list of IRB members and staff, statements of meeting procedures, review procedures, the institution's standard forms, and so forth.

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Institutional Review Board Guidebook

* GLOSSARY *

GLOSSARY OF TERMS

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

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

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

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

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

ASSURANCE A formal written, binding commitment that is submitted to a federal agency in which an institution promises to comply with applicable regulations governing research with human subjects and stipulates the procedures through which compliance will be achieved [Federal Policy § ___.103].

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

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

AUTOPSY Examination by dissection of the body of an individual to determine cause of death and other medically relevant facts.

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

BENEFICENCE An ethical principle discussed in the Belmont Report that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: (1) do not harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm.

BENEFIT A valued or desired outcome; an advantage.

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

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

CADAVER The body of a deceased person.

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

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

CHILDREN Persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted [45 CFR 46.401(a)].

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

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

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

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

COHORT A group of subjects initially identified as having one or more characteristics in common who are followed over time. In social science research, this term may refer to any group of persons who are born at about the same time and share common historical or cultural experiences.

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

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

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

CONSENT *See: Informed Consent.*

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

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

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

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

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

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

DEAD FETUS An expelled or delivered fetus that exhibits no heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord (if still attached) [45 CFR 46.203(f)]. Generally, some organs, tissues, and cells (referred to collectively as fetal tissue) remain alive for varying periods of time after the total organism is dead.

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

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

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

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

DEVICE (MEDICAL) *See: Medical Device.*

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

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

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

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

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

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

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

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

EQUITABLE Fair or just; used in the context of selection of subjects to indicate that the benefits and burdens of research are fairly distributed [Federal Policy § __.111(a)(3)].

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

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

EXPANDED AVAILABILITY Policy and procedure that permits individuals who have serious or life-threatening diseases for which there are no alternative therapies to have access to investigational drugs and devices that may be beneficial to them.

Examples of expanded availability mechanisms include Treatment INDs, Parallel Track, and open study protocols.

EXPEDITED REVIEW Review of proposed research by the IRB chair or a designated voting member or group of voting members rather than by the entire IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research [Federal Policy § ___.110].

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

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

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

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

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

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

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

FETUS The product of conception from the time of implantation until delivery. If the delivered or expelled fetus is viable, it is designated an infant [45 CFR 46.203(c)]. The term "fetus" generally refers to later phases of development; the term "embryo" is usually used for earlier phases of development. (*See also: Embryo.*)

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

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

FULL BOARD REVIEW Review of proposed research at a convened meeting at which a majority of the membership of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those members present at the meeting [Federal Policy § ___.108].

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

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

GENERAL CONTROLS Certain FDA statutory provisions designed to control the safety of marketed drugs and devices. The general controls include provisions on adulteration, misbranding, banned devices, good manufacturing practices, notification and record keeping, and other sections of the Medical Device Amendments to the Food, Drug and Cosmetic Act [21 U.S. Code §360(c) (Food, Drug and Cosmetic Act §513)].

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

GENOTYPE The genetic constitution of an individual.

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

GUARDIAN An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care [45 CFR 46.402(3)].

HELSINKI DECLARATION *See: Declaration of Helsinki.*

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

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

HUMAN SUBJECTS Individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project. Under the federal regulations, human subjects are defined as: living individual(s) about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information [Federal Policy § __.102(f)].

IDE *See: Investigational Device Exemptions.*

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

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

IND *See: Investigational New Drug.*

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

INFORMED CONSENT A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the institution or agents thereof from liability for negligence [Federal Policy § 116; 21 CFR 50.20 and 50.25].

INSTITUTION (1) Any public or private entity or agency (including federal, state, and local agencies) [Federal Policy § __.102(b)].

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

INSTITUTIONAL REVIEW BOARD A specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral research [Federal Policy §§ __.102(g), __.108, __.109].

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

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

INVESTIGATIONAL DEVICE EXEMPTIONS (IDE) Exemptions from certain regulations found in the Medical Device Amendments that allow shipment of unapproved devices for use in clinical investigations [21 CFR 812.20].

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

INVESTIGATOR In clinical trials, an individual who actually conducts an investigation [21 CFR 312.3]. Any interventions (e.g., drugs) involved in the study are administered to subjects under the immediate direction of the investigator. (*See also: Principal Investigator.*)

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

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

IRB *See: Institutional Review Board.*

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

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

LEGALLY AUTHORIZED REPRESENTATIVE A person authorized either by statute or by court appointment to make decisions on behalf of another person. In human subjects research, an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research [Federal Policy § __.102(c)].

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

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

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

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

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

MEDICAL DEVICE AMENDMENTS (MDA) Amendments to the Federal Food, Drug and Cosmetic Act passed in 1976 to regulate the distribution of medical devices and diagnostic products.

MENTALLY DISABLED *See: Cognitively Impaired.*

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

MINIMAL RISK A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [Federal Policy § __.102(i)]. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

The definition of minimal risk for research involving prisoners differs somewhat from that given for noninstitutionalized adults. [See 45 CFR 46.303(d) and Guidebook Chapter 6, Section E, "Prisoners."]

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

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

NDA *See: New Drug Application.*

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

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

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

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

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

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

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

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

NONVIABLE FETUS An expelled or delivered fetus which, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy [45 CFR 46.203 (d) and (e)]. Although it may be presumed that an expelled or delivered fetus is nonviable at a gestational age less than 20 weeks and weight less than 500 grams [Federal Register 40 (August 8, 1975): 33552], a specific determination as to viability must be made by a physician in each instance. (*See also: Viable Infant.*)

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

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

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

OFFICE FOR PROTECTION FROM RESEARCH RISKS (OPRR) The office within the National Institutes of Health, an agency of the Public Health Service, Department of Health and Human Services, responsible for implementing DHHS regulations (45 CFR Part 46) governing research involving human subjects.

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

OPRR *See: Office for Protection from Research Risks.*

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

PERMISSION The agreement of parent(s) or guardian to the participation of their child or ward in research [45 CFR 46.402 (c)].

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

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

- **PHASE 1 DRUG TRIAL** Phase 1 trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients

with a particular disease, however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.

- **PHASE 2 DRUG TRIAL** Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects.
- **PHASE 3 DRUG TRIAL** Phase 3 trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, efficacy, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient-subjects.
- **PHASE 4 DRUG TRIAL** Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time [21 CFR §312.85].

PHENOTYPE The physical manifestation of a gene function.

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

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

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

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

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

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

PREGNANCY The period of time from confirmation of implantation of a fertilized egg within the uterus until the fetus has entirely left the uterus (*i.e.*, has been delivered). Implantation is confirmed through a presumptive sign of pregnancy such as missed menses or a positive pregnancy test [45 CFR 46.203(b)]. This "confirmation" may be in error, but, for research purposes, investigators would presume that a living fetus was present until evidence to the contrary was clear. Although fertilization occurs a week or more before implantation, the current inability to detect the fertilization event or the presence of a newly fertilized egg makes a definition of pregnancy based on implantation necessary.

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

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

PRINCIPAL INVESTIGATOR The scientist or scholar with primary responsibility for the design and conduct of a research

project. (See also: Investigator.)

PRISONER An individual involuntarily confined in a penal institution, including persons: (1) sentenced under a criminal or civil statute; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (*e.g.*, for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution [45 CFR 46.303(c)].

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

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

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

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

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

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

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

RADIOACTIVE DRUG Any substance defined as a drug in §201(b)(1) of the Federal Food, Drug and Cosmetic Act that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons [21 CFR 310.3(n)]. Included are any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of a radioactive drug and "radioactive biological products," as defined in 21 CFR 600.3(ee). Drugs such as carbon-containing compounds or potassium-containing salts containing trace quantities of naturally occurring radionuclides are not considered radioactive drugs.

RADIOACTIVE DRUG RESEARCH COMMITTEE (RDRC) An institutional committee responsible for the use of radioactive drugs in human subjects for research purposes. Research involving human subjects that proposes to use radioactive drugs must meet various FDA requirements, including limitations on the pharmacological dose and the radiation dose. Furthermore, the exposure to radiation must be justified by the quality of the study and the importance of the information it seeks to obtain. The committee is also responsible for continuing review of the drug use to ensure that the research continues to comply with FDA requirements, including reporting obligations. The committee must include experts in nuclear medicine and the use of radioactive drugs, as well as other medical and scientific members [21 CFR 36.1].

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

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

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

RECOMBINANT DNA TECHNOLOGY "The ability to chop up DNA, the stuff of which genes are made, and move the pieces, [which] permits the direct examination of the human genome," and the identification of the genetic components of a

wide variety of disorders [Holtzman (1989), p. 1]. Recombinant DNA technology is also used to develop diagnostic screens and tests, as well as drugs and biologics for treating diseases with genetic components. See Guidebook Chapter 5, Section H, "Human Genetic Research."

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

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

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

RESEARCH A systematic investigation (*i.e.*, the gathering and analysis of information) designed to develop or contribute to generalizable knowledge [Federal Policy § __.102(d)].

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

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

REVIEW (OF RESEARCH) The concurrent oversight of research on a periodic basis by an IRB. In addition to the at least annual reviews mandated by the federal regulations, reviews may, if deemed appropriate, also be conducted on a continuous or periodic basis [Federal Policy § __.108(e)].

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

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

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

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

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

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

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

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

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

reporting the results of the trial to the FDA.

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

STATISTICAL SIGNIFICANCE A determination of the probability of obtaining the particular distribution of the data on the assumption that the null hypothesis is true. Or, more simply put, the probability of coming to a false positive conclusion. [See *McLarty (1987), p. 2.*] If the probability is less than or equal to a predetermined value (*e.g.*, 0.05 or 0.01), then the null hypothesis is rejected at that significance level (0.05 or 0.01).

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

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

STUDY SECTION *See: Scientific Review Group.*

SUBJECTS (HUMAN) *See: Human Subjects.*

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

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

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

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

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

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

VIABLE INFANT When referring to a delivered or expelled fetus, the term "viable infant" means likely to survive to the point of sustaining life independently, given the benefit of available medical therapy [45 CFR 46.203(d)]. This judgment is made by a physician. In accordance with DHHS regulations, the Secretary, HHS, may publish guidelines to assist in the determination of viability. Such guidelines were published in 1975, and specify an estimated gestational age of 20 weeks or more and a body weight of 500 grams or more as indices of fetal viability [Federal Register 40 (August 8, 1975): 33552]. These indices depend on the state of present technology and may be revised periodically. (*See also: Nonviable Fetus.*)

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

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* PREFACE *

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A. PURPOSE OF THE GUIDEBOOK

It is hoped that the Guidebook will provide precisely what its title is intended to denote: guidance. **The Guidebook does not itself constitute regulations but rather has been prepared for the convenience and reference of IRB members and administrators.** The issues with which IRBs must concern themselves are many and complex. Simply becoming familiar with the regulations is difficult enough; understanding the concepts involved, how they relate to human subjects research, and how one might go about applying those concepts are complex matters, matters on which many talented and highly respected authors have written a great deal. (The bibliographies cite many materials that IRBs should find useful.) The Guidebook is not designed to tell IRBs whether or not specific protocols should be approved (unless the regulations specifically prohibit the proposed activity or method). It does point out issues to which IRBs should pay attention and presents, wherever possible, areas where ethicists and others concerned with these issues have arrived at a consensus on the ethical acceptability of a particular activity or method (e.g., in clinical trials, the use of placebo arms where a standard therapy is available).

The Guidebook is also intended to be a resource that will serve as the focal point of IRB administrators' and members' human subjects work. Constructed in a loose leaf format, the Guidebook holds the regulations, relevant institutional documents (e.g., the institution's assurance and operating policies and procedures), and relevant forms. In addition to the text dealing with specific topics, the Guidebook contains a glossary of terms and a bibliography of sources. The loose leaf format will permit the Office for Protection from Research Risks (OPRR) to distribute updated chapters as new areas of research emerge that have implications for human subjects research or as regulations are revised.

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B. INTENDED AUDIENCE

The Guidebook is addressed to new and continuing IRB members, researchers, and institutional administrators. Some will find portions of the material too simplistic; for others, these same portions will be an indispensable primer. Even the more advanced reader should find the Guidebook a useful reference.

The Guidebook, as a product of OPRR, deals primarily with the human subjects protection regulations promulgated by the Department of Health and Human Services (DHHS). Because a significant amount of the research subject to the DHHS regulations is also subject to parallel FDA regulations, the Guidebook also discusses the issues raised by similarities and differences between the two sets of regulations.

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C. HOW TO USE THE GUIDEBOOK

The Guidebook is divided into the following chapters:

Introduction. Provides a basic understanding of the background and purposes of the IRB review system. It should be particularly useful for new IRB members and investigators just beginning their clinical research. The Introduction includes a description of **The Belmont Report**, providing a summary of the principles set forth in this seminal policy statement on the protection of human subjects of research.

[Chapter 1.](#)

Institutional Administration. Directed primarily at institutional administrators and IRB chairpersons. It will also be of interest to others on the IRB, clinical investigators, and sponsors of research who wish to consider how the IRB relates to other institutional offices.

Chapter 2. **Regulations and Policies.** Assists in resolving uncertainties about the intent or interpretation of regulatory provisions. It should also be a useful reference for initial reviewers of research proposals.

Chapter 3. **Basic IRB Review.** Presents the major focal points of IRB review: informed consent, risk/benefit analysis, privacy and confidentiality, selection of subjects, and incentives for participation. It goes beyond the regulations in suggesting how the regulations might be applied in various situations.

Chapter 4. **Considerations of Research Design.** Provides descriptions of, and information on, the reasons for using certain experimental designs. The ethical issues raised by such uses are also explored.

Chapter 5. **Biomedical and Behavioral Research: An Overview.** Describes certain kinds of research by subject matter and their various goals and methods in a general, introductory way, pointing out the ethical concerns each raises and providing references for further reading. This chapter will be of most benefit to nonscientists on the IRB and to scientist-reviewers confronting a research proposal in an unfamiliar discipline.

Chapter 6. **Special Classes of Subjects.** Provides an analysis of the ethical issues that arise in research involving classes of particularly vulnerable research subjects. Regulations exist for some classes of subjects; for others, no regulations are in place.

Appendices.

- **Appendix 1: General Bibliography.** A list of suggested materials for an IRB library and references to other useful resources.
- **Appendix 2: HHS, PHS and NIH Organizational Diagrams.**
- **Appendix 3: Department and Agency Persons to Contact.**
- **Appendix 4: The Federal Policy and 45 CFR 46.**
- **Appendix 5: Agency Documents.**
- **Appendix 6: The Nuremberg Code, Declaration of Helsinki, and Belmont Report.**
- **Appendix 7: Local IRB Documents.** A place to insert documents pertaining to each institution and its IRB: the institutional assurance, current list of IRB members and staff, statements of meeting procedures, review procedures, the institution's standard forms, and so forth.

Glossary of Terms. Explains terms as they are used in the context of reviewing biomedical and behavioral research. Words that are printed in the text in boldface appear in the Glossary.

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D. CITATION FORM

When referring to federal regulations pertaining to the protection of human subjects, the Federal Policy citations are given, unless a particular department or agency's regulations are being discussed. Although the Guidebook deals primarily with DHHS human subjects regulations, the Federal Policy citation is used to indicate that the discussion applies to research conducted, supported, or otherwise regulated by any of the sixteen federal departments and agencies that have adopted the Federal Policy. Where DHHS regulations are being discussed specifically, the Code of Federal Regulations (CFR) citation is given. Thus, 45 CFR 46 Subpart A is generally referred to as Federal Policy '____.101-124, while 45 CFR 46 Subparts B, C, and D are referred to as 45 CFR 46.201-211, 45 CFR 46.301-306, and 45 CFR 46.401-409, respectively.

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E. SUGGESTED READING MATERIALS

The ideas and opinions expressed in the materials listed in the General Bibliography (Appendix 1) and in the Suggestions for Further Reading sections of each chapter of the Guidebook are those of their authors alone, and do not necessarily, with the exception of official government statements, represent the views or policies of the Department of Health and Human Services. These references are intended to provide IRBs with a wide range of perspectives to assist them in their understanding of the many complex issues presented by research involving human subjects.

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F. ABBREVIATIONS

The following is a list of the most common abbreviations used in the Guidebook. Definitions for these terms appear in the Glossary of Terms.

ADAMHA	Alcohol, Drug Abuse and Mental Health Administration
CDC	Centers for Disease Control and Prevention
DHEW	Department of Health, Education and Welfare
DHHS	Department of Health and Human Services
FDA	Food and Drug Administration
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
NDA	New Drug Application
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
OPRR	Office for Protection from Research Risks
PHS	Public Health Service
SAMHSA	Substance Abuse and Mental Health Services Administration

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Institutional Review Board Guidebook

* INTRODUCTION *

A. History of the Human Subjects Protection System
B. The Belmont Report || C. Suggestions for Further Reading

A. THE HISTORY OF THE HUMAN SUBJECTS PROTECTION SYSTEM

The modern story of human subjects protections begins 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. The first provision of the Code states that "the voluntary consent of the human subject is absolutely essential." Freely given consent to participation in research is thus the cornerstone of ethical experimentation involving human subjects. The Code goes on to provide the details implied by such a requirement: capacity to consent, freedom from coercion, and comprehension of the risks and benefits involved. Other provisions require the minimization of risk and harm, a favorable risk/benefit ratio, qualified investigators using appropriate research designs, and freedom for the subject to withdraw at any time. 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 by the 18th World Medical Assembly in Helsinki, Finland, in 1964, and subsequently revised by the 29th World Medical Assembly, Tokyo, Japan, 1975, and by the 41st World Medical Assembly, Hong Kong, 1989. The Declaration of Helsinki further distinguishes therapeutic from nontherapeutic research.

In the United States, regulations protecting human subjects first became effective on May 30, 1974. Promulgated by the Department of Health, Education and Welfare (DHEW), those regulations raised to regulatory status NIH's Policies for the Protection of Human Subjects, which were first issued in 1966. The regulations established the IRB as one mechanism through which human subjects would be protected.

In July of 1974, the passage of the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission met from 1974 to 1978. In keeping with its charge, the Commission issued reports and recommendations identifying the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and recommending guidelines to ensure that research is conducted in accordance with those principles. The Commission also recommended DHEW administrative action to require that the guidelines apply to research conducted or supported by DHEW. References for the Commission's reports are listed in Appendix 1 (General Bibliography). The Commission's report setting forth the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects is titled *The Belmont Report*, and is discussed in depth below.

In 1981, in response to the Commission's reports and recommendations, both the Department of Health and Human Services (DHHS, formerly DHEW) and the FDA promulgated significant revisions of their human subjects regulations. As Levine (1986) points out, these revisions "do not alter the general principles of IRB review as they had evolved over the preceding three decades. Rather, they are concerned with some of the details of what the IRB is expected to accomplish and some of the procedures it must follow" [p. 324].

The DHHS regulations are codified at Title 45 Part 46 of the Code of Federal Regulations. Those "basic" regulations became final on January 16, 1981, and were revised effective March 4, 1983, and June 18, 1991. The June 18, 1991, revision involved the adoption of the Federal Policy for the Protection of Human Subjects. The Federal Policy (or "Common Rule," as it is sometimes called) was promulgated by the sixteen federal agencies that conduct, support, or otherwise regulate human subjects research; the FDA also adopted certain of its provisions. As is implied by its title, the Federal Policy is designed to make uniform the human subjects protection system in all relevant federal agencies and departments. The Federal Policy is discussed in depth in Chapter 2, Section A(i).

Additional protections for various vulnerable populations have been adopted by DHHS, as follows:

Subpart B, "Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women and Human in Vitro Fertilization" became final on August 8, 1975, and was revised effective January 11, 1978, and November 3, 1978.

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

final on November 16, 1978.

Subpart D, "Additional Protections for Children Involved as Subjects in Research" became final on March 8, 1983, and was revised for a technical amendment on June 18, 1991.

FDA regulations on the protection of human subjects are codified at Title 21 Parts 50 and 56 of the Code of Federal Regulations. Part 50, which sets forth the requirements for informed consent, became final on May 30, 1980, and was revised effective January 27, 1981, March 3, 1989, and June 18, 1991. Subpart C, which provides special protections for prisoners, was adopted on July 7, 1981; the effective date of Subpart C has been stayed until further notice. Part 56, which sets forth the provisions for institutional review boards, was adopted on January 27, 1981, with revisions to some sections effective February 27, 1981, March 3, 1989, and June 18, 1991.

Additional FDA regulations that are relevant to IRB review of research are Parts 312 (Investigational New Drug Application), 812 (Investigational Device Exemptions) and 860 (Medical Device Classification Procedures).

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, which met from 1980 to 1983, produced numerous reports on various aspects of medical ethics and biomedical and behavioral research. Its mandate with respect to the protection of human subjects was, first, to review the federal rules and policies governing human subjects research, and second, to determine how well those rules were being implemented or enforced. References for the President's Commission's reports are listed in Appendix 1 (General Bibliography).

Several excellent sources trace the history of human subjects research and the development of the IRB system as a mechanism for the protection of human subjects. An account of the history of human subjects research and the human subjects protection system in the United States can be found in David J. Rothman's *Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision Making* (Chapters 1-5 and Epilogue) and in Dennis Maloney's *Protection of Human Research Subjects*. Rothman details the abuses to which human subjects were exposed, culminating in Henry Beecher's 1966 article, "Ethics and Clinical Research," published in the *New England Journal of Medicine*, and ultimately contributing to the impetus for the first NIH and FDA regulations. Other equally useful sources include Robert J. Levine's *Ethics and Regulation of Clinical Research* (Chapter 14), Joan E. Sieber's *Planning Ethically Responsible Research*, Robert M. Veatch's "Human Experimentation Committees: Professional or Representative?," and William J. Curran's "Government Regulation of the Use of Human Subjects in Medical Research: The Approaches of Two Federal Agencies."

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B. THE BELMONT REPORT

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted its report entitled "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The Report, named after the Belmont Conference Center at the Smithsonian Institution where the discussions which resulted in its formulation were begun, sets forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, **respect for persons**, **beneficence**, and **justice**, are now accepted as the three quintessential requirements for the ethical conduct of research involving human subjects.

Respect for persons involves a recognition of the personal dignity and autonomy of individuals, and special protection of those persons with diminished autonomy.

Beneficence entails an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm.

Justice requires that the benefits and burdens of research be distributed fairly.

The Report also describes how these principles apply to the conduct of research. Specifically, the principle of *respect for persons* underlies the need to obtain informed consent; the principle of *beneficence* underlies the need to engage in a risk/benefit analysis and to minimize risks; and the principle of *justice* requires that subjects be fairly selected. As was mandated by the congressional charge to the Commission, the Report also provides a distinction between "practice" and "research." The text of the *Belmont Report* is thus divided into two sections: (1) boundaries between practice and research; and (2) basic ethical principles. The full text of the *Belmont Report*, which describes each of the three principles and its application, is provided in the Guidebook in Appendix 6; a summary follows.

Boundaries Between Practice and Research

While recognizing that the distinction between research and therapy is often blurred, *practice* is described as "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." The Commission distinguishes *research* as designat[ing] 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. "The Report recognizes that "experimental"

procedures do not necessarily constitute research, and that research and practice may occur simultaneously. It suggests that the safety and effectiveness of such "experimental" procedures should be investigated early, and that institutional oversight mechanisms, such as medical practice committees, can ensure that this need is met by requiring that "major innovation[s] be incorporated into a formal research project."

Applying the Ethical Principles

Respect for Persons. Required by the moral principle of respect for persons (*see* definition, above), **informed consent** contains three elements: information, comprehension, and voluntariness. First, subjects must be given sufficient information on which to decide whether or not to participate, including the research procedure(s), 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. Responding to the question of what constitutes adequate information, the Report suggests that a "reasonable volunteer" standard be used: "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." Incomplete disclosure is justified only if it is clear that: (1) the goals of the research cannot be accomplished if full disclosure is made; (2) the undisclosed risks are minimal; and (3) when appropriate, subjects will be debriefed and provided the research results.

Second, subjects must be able to comprehend the information that is given to them. The presentation of information must be adapted to the subject's capacity to understand it; testing to ensure that subjects have understood may be warranted. Where persons with limited ability to comprehend are involved, they should be given the opportunity to choose whether or not to participate (to the extent they are able to do so), and their objections should not be overridden, unless the research entails providing them a therapy unavailable outside of the context of research. [See discussions on this issue in other sections of the Guidebook, including Chapter 6, "Special Classes of Subjects."] Each such class of persons should be considered on its own terms (*e.g.*, minors, persons with impaired mental capacities, the terminally ill, and the comatose). Respect for persons requires that the permission of third persons also be given in order to further protect them from harm.

Finally, consent to participate must be voluntarily given. The conditions under which an agreement to participate is made must be free from coercion and undue influence. IRBs should be especially sensitive to these factors when particularly vulnerable subjects are involved.

Beneficence. Closely related to the principle of beneficence (*see* definition, above), **risk/benefit assessments** "are concerned with the probabilities and magnitudes of possible harms and anticipated benefits." The Report breaks consideration of these issues down into defining the nature and scope of the risks and benefits, and systematically assessing the risks and benefits. All possible harms, not just physical or psychological pain or injury, should be considered. The principle of beneficence requires both protecting individual subjects against risk of harm and consideration of not only the benefits for the individual, but also the societal benefits that might be gained from the research.

In determining whether the balance of risks and benefits results in a favorable ratio, the decision should be based on thorough assessment of information with respect to all aspects of the research and systematic consideration of alternatives. The Report recommends close communication between the IRB and the investigator and IRB insistence upon precise answers to direct questions. The IRB should: (1) determine the "validity of the presuppositions of the research;" (2) distinguish the "nature, probability and magnitude of risk...with as much clarity as possible;" and (3) "determine whether the investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies."

Five basic principles or rules apply when making the risk/benefit assessment: (1) "brutal or inhumane treatment of human subjects is never morally justified;" (2) risks should be minimized, including the avoidance of using human subjects if at all possible; (3) IRBs must be scrupulous in insisting upon sufficient justification for research involving "significant risk of serious impairment" (*e.g.*, direct benefit to the subject or "manifest voluntariness of the participation"); (4) the appropriateness of involving vulnerable populations must be demonstrated; and (5) the proposed informed consent process must thoroughly and completely disclose relevant risks and benefits.

Justice. The principle of justice mandates that the **selection of research subjects** must be the result of fair selection procedures and must also result in fair selection outcomes. The "justness" of subject selection relates both to the subject as an individual and to the subject as a member of social, racial, sexual, or ethnic groups.

With respect to their status as individuals, subjects should not be selected either because they are favored by the researcher or because they are held in disdain (*e.g.*, involving "undesirable" persons in risky research). Further, "social justice" indicates 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."

Investigators, institutions, or IRBs may consider principles of distributive justice relevant to determining the appropriateness of proposed methods of selecting research subjects that may result in unjust distributions of the burdens and benefits of research. Such considerations may be appropriate to avoid the injustice that "arises from social, racial, sexual, and cultural biases institutionalized in society."

Subjects should not be selected simply because they are readily available in settings where research is conducted, or because they are "easy to manipulate as a result of their illness or socioeconomic condition." Care should be taken to avoid overburdening institutionalized persons who "are already burdened in many ways by their infirmities and environments." Nontherapeutic research that involves risk should use other, less burdened populations, unless the research "directly relate[s] to the specific conditions of the class involved."

SUGGESTIONS FOR FURTHER READING

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Institutional Review Board Guidebook

* CHAPTER I * *INSTITUTIONAL ADMINISTRATION*

- A. Jurisdiction of the Institutional Review Board**
B. Administration of the Institutional Review Board

Establishment of the Institutional Review Board
Membership
Record Keeping
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- C. Principal Investigators**
D. Compliance / Noncompliance
Suggestions for Further Reading

A. JURISDICTION OF THE INSTITUTIONAL REVIEW BOARD

The IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated. The IRB has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction as specified by both the federal regulations and local institutional policy. Research that has been reviewed and approved by an IRB may be subject to review and disapproval by officials of the institution. However, those officials may not approve research if it has been disapproved by the IRB [Federal Policy § __.112].

The IRB also functions independently of but in coordination with other committees. For example, an institution may have a research committee that reviews protocols to determine whether the institution should support the proposed research. The IRB, however, makes its independent determination whether to approve or disapprove the protocol based upon whether or not human subjects are adequately protected.

Whenever the IRB reviews a protocol, an initial question is whether the IRB has jurisdiction over approval of the research. That is, the IRB must ask, "Is the research subject to IRB review?" The federal regulations apply "to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency" that has adopted the human subjects regulations [Federal Policy § __.101(a)].

The first two questions the IRB faces is whether the activity involves *research*, and second, whether it involves *human subjects*. **Research** is defined by the regulations as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" [Federal Policy § __.102(d)]. **Human subjects** are defined by the regulations as "living individual(s) 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" [Federal Policy § __.102(f)]. (Section 102(f) goes on to define the meaning of such terms as "intervention" and "private information.")

In addition, some research that involves human subjects may be exempt from the regulations requiring IRB review [Federal Policy § __.101(b)]. Examples include educational testing and survey procedures where no identifying information will be recorded that can link subjects to the data, and disclosure of the data could not reasonably place the subjects at risk of civil or criminal liability or be damaging to the subjects' financial standing, employability, or reputation; and research that involves the use of existing data, documents, or specimens, where no identifying information will be recorded that can link subjects to the data.

Jurisdictional questions arise, however, in that the regulations also require that, as part of their Assurances, institutions agree to protect the welfare of all human subjects involved in research, whether or not the research is conducted or supported by a federal department or agency [Federal Policy § __.103(b)(1)]. While the regulations further specify that this requirement "need not be applicable to any research exempted...under § __.101(b)," many institutions' human subjects policies provide that all research, even research that is exempt from review under the federal regulations, is to be reviewed by the IRB. In such cases, the IRB has jurisdiction over all human subjects research, thereby providing broader protection for subjects than that required by the regulations. It is crucial that IRBs keep in mind that their authority to

approve, require modifications in, or disapprove research derives from both federal law and institutional policy.

Research that has been reviewed and approved by an IRB may be subject to further review and disapproval by officials of the institution. Those officials may not, however, approve research if it has been disapproved by the IRB [Federal Policy § ___.112]. Furthermore, approved research is subject to continuing IRB review and must be reevaluated at least annually (and more frequently, as specified by the IRB) [Federal Policy § ___.109(e)].

Research vs. Therapy. The fact that much biomedical research is conducted for the purpose of evaluating new therapies or treatments leads to two problems for IRBs. The first is to some degree a problem of IRB jurisdiction; the second is a problem of risk/benefit assessment.

The distinction between research and treatment can become blurred in patient care settings, as well as in some educational and training settings. This distinction raises questions of IRB jurisdiction over the research: Is the proposed activity one that requires IRB review (pursuant either to federal regulations or institutional policy)? Research itself is not therapeutic; for ill patients, research interventions may or may not be beneficial. Indeed, the purpose of evaluative research is to determine whether the test intervention is in fact therapeutic. The support of an activity by a research grant may sometimes provide a practical, if somewhat artificial, operational answer to the question of whether or not that activity is research. IRBs that review only activities whose review is mandated because of the source of funding (e.g., by DHHS regulations 45 CFR 46), can be confident that the intent of the activity is research rather than therapeutic (although subjects may obtain some therapeutic benefit from the research). But an IRB that reviews all research, regardless of the source of support, may sometimes face questions about whether or not a particular activity performed with therapeutic intent is, therefore, research and should be reviewed. Or it may face the difficult question of whether a formal research **protocol** should be developed (and reviewed by the IRB) for a new or non-validated procedure that is being used for therapeutic purposes within the institution. IRBs should be prepared to play such a role; some prominent commentators have pointed out the dangers of allowing new procedures to come into widespread use without having been systematically validated in well-controlled trials.

The second distinction between research and therapies that may pose a problem for IRBs concerns risk/benefit assessments in research on therapies. Often, the risks of a study may seem justified by a therapy provided as part of the study. IRBs should determine, however, whether the anticipated therapeutic benefits would be available to persons who are not participating in a study that presents additional risks. As is discussed in the Guidebook Section on risk/benefit analysis [Chapter 3, Section A], such benefits should not be used to justify risks presented by the research.

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B. ADMINISTRATION OF THE INSTITUTIONAL REVIEW BOARD

ESTABLISHMENT OF THE INSTITUTIONAL REVIEW BOARD

Each institution engaged in research involving human subjects that is supported by a department or agency to which the Federal Policy applies must establish an IRB to review and approve the research. Under the regulations, an institution can also establish more than one IRB, which may be necessary or appropriate, depending on the structure of the institution or the kinds of human subjects research that is performed at that institution. Alternatively, an institution can designate another institution's IRB to review its research upon approval of the appropriate department or agency. If the research is supported by DHHS, such designations must have the prior approval of the Office for Protection from Research Risks (OPRR, an office within NIH). [See also Guidebook Chapter 2, "Regulations and Policies."]

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MEMBERSHIP

Federal Policy Requirements. The Federal Policy [§ ___.107] provides that IRBs must have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB must be sufficiently qualified through the experience and expertise of its members and the diversity of their backgrounds, including considerations of their racial and cultural heritage and their sensitivity to issues such 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 must 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 must therefore include persons knowledgeable in these areas. No IRB, however, may consist entirely of members of one profession.

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, the IRB must consider the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects. Department of Education (ED) regulations require, in addition, that when an IRB reviews research for one of its programs that purposefully requires inclusion of handicapped children or mentally disabled persons as research subjects, the IRB must include at least one person primarily concerned with the welfare of these subjects [34 CFR 350.3(d)2; 34 CFR 356.3(c)(2)].

The IRB must include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. It must also 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.

The IRB must make every nondiscriminatory effort to ensure that it does not consist entirely of men or entirely of women. Selections must not, however, be made on the basis of gender.

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.

No IRB member may participate in the review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

A list of current IRB members must be submitted to OPRR and also kept with the IRB's records [Federal Policy §§ __.103(b)(3) and __.115(a)(5)]. The list must identify members by name, earned degrees, representative capacity, indications of experience (such as board certifications and licenses) sufficient to describe each member's chief anticipated contributions to IRB deliberations, and any employment or other relationship between each member and the institution (*e.g.*, full-time employee, stockholder, unpaid consultant, or board member). Any changes in IRB membership must be reported to the head of the department or agency supporting or conducting the research, unless the department or agency has accepted the existence of a DHHS-approved Assurance [see Federal Policy § __.103(a)]. In the latter case, changes in membership are to be reported to OPRR [Federal Policy §§ __.103(b)(3) and __.115(a)(5)].

IRB Considerations. An IRB can have as many members as necessary for it to perform its duties effectively. Care should be taken, however, to ensure that it does not become so large that its management becomes cumbersome.

The nonaffiliated member of the IRB should be drawn from the local community-at-large. Ministers, teachers, attorneys, business persons, or homemakers are possible candidates. The person selected should be knowledgeable about the local community and be willing to discuss issues and research from that perspective. Consideration should be given to the type of community from which the institution will draw its research subjects. If the community is rural and agricultural, perhaps a farmer would be appropriate, in addition to a minister and/or attorney. If the community is predominately African-American, Hispanic, or other minority, then it would be advisable to have a member of that particular minority (or those minorities, if there is more than one significant minority population) on the IRB. The nonaffiliated member(s) should not be vulnerable to intimidation by the professionals on the IRB, and their services should be fully utilized by the IRB.

An investigator can be a member of the IRB; however, there is a stipulation that must be adhered to without exception: The investigator-as-member cannot participate in the review and approval process for any project in which he or she has a present or potential conflict of interest. Where the investigator-member has a conflicting interest, he or she should be present only to provide information requested by the IRB. He or she should be absent from the meeting room during the discussion and voting phases of the review and approval process; IRB minutes should reflect whether or not these requirements have been met.

One of the most important actions to be taken in establishing an IRB is selecting the individual who will function as chair. The IRB chairperson should be a highly respected individual from within or outside the institution, fully capable of managing the IRB and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the institutional community will fall primarily on the shoulders of this individual. The IRB must be and must be perceived to be fair and impartial, immune from pressure either by the institution's administration, the investigators whose protocols are brought before it, or other professional and nonprofessional sources.

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RECORD KEEPING

The institution, or when appropriate the IRB, must prepare and maintain adequate documentation of IRB activities [Federal Policy § __.115]. In addition to the written IRB procedures and membership lists required by the Assurance process [Federal Policy § __.103], such documentation must include copies of all research proposals reviewed, minutes of IRB meetings, records of continuing review activities, copies of all correspondence between the IRB and investigators, and statements of significant new findings provided to subjects (as required by Federal Policy § __.116(b)(5)).

Minutes of IRB meetings must be kept in sufficient detail to record the following information: attendance at each meeting; actions taken by the IRB; the vote on actions taken (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 [Federal Policy § __.115(a)(2)].

IRB records must be retained for at least three years; records pertaining to research that is conducted must be retained for three years after completion of the research. All records must be accessible for inspection and copying by authorized representatives of the department or agency supporting or conducting the research at reasonable times and in a reasonable manner [Federal Policy § __.115(b)].

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INSTITUTIONAL RESPONSIBILITIES

Each institution engaged in research must establish one or more IRB, or designate one from another institution, to review and approve research involving human subjects performed at its facilities. Before any human subjects research can be conducted, the institution must provide the department or agency a written **Assurance** that it will comply with the requirements of the Policy; the Assurance must be approved by the department or agency; and the institution must certify to the department or agency head that the research has been reviewed and approved by an IRB established in accordance with the requirements of the Policy [Federal Policy § ___.103]. Note, however, that the FDA does not require the submission and approval of an Assurance. (See Guidebook Chapter 2, Section B for a comparison FDA and DHHS human subjects regulations.)

Specification of quality standards in the conduct of research is an important function of the institutional leadership. Insistence upon well-conceived and -conducted research should be evident both in written policies and in actions of institutional officials. Research that is conducted so poorly as to be invalid exposes subjects and the institution to unnecessary risk. Approval procedures should be devised such that the institution supports only well-designed and properly executed research.

The Assurance

An institution involved in biomedical or behavioral research should have in place a set of principles and guidelines that govern the institution, its faculty, and staff, in the discharge of its responsibilities for protecting the rights and welfare of human subjects taking part in research conducted at, or sponsored by, the institution, regardless of the source of funding [Federal Policy § ___.103(b)(1)]. Assurances applicable to federally supported or conducted research must, at a minimum, contain such a statement of principles, which may include an appropriate existing code, declaration, and/or statement of ethical principles as formulated by the institution. In the United States, most institutions cite *The Belmont Report*. Foreign institutions sometimes cite other codes, such as the Declaration of Helsinki.

This set of principles should be in the form of a document that is readily available to all staff or faculty personnel who have need of it and can be a part of the staff or faculty manual. It should be written in clear, concise, unambiguous language, understandable to its intended audience.

Staff, Space, and Supplies

The parent institution of the IRB should provide the IRB with sufficient meeting space and staff to support the IRB's review and record keeping duties [Federal Policy § ___.103(b)(2)].

Communication

The institutional leadership must assure that open channels of communication are maintained at all levels. It is important that staff, subjects, and other interested parties have a means of communicating information about the conduct of a research project directly to the appropriate institutional officials. It is vital that IRB members, department heads, and other officials with responsibility for oversight of research have open and ready access to the highest levels of authority within the institution.

Institutional Procedures and Guidelines

Federal Policy Requirements. As provided in its Assurance, an institution must prepare written procedures and guidelines to be followed by the IRB when conducting its initial and continuing review of research, and for reporting its findings and actions to the investigator and the administration of the institution. The procedures must provide guidance for determining which projects will require review more often than annually and which projects require verification from sources other than the investigator that no material changes have occurred since the last IRB review. The guidelines must also delineate procedures for ensuring prompt reporting to the IRB, by the investigator, of proposed changes in a research activity. They must also provide procedures 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 [Federal Policy § ___.103(b)(4)].

The institution must also have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of: (1) any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the Federal Policy or the requirements or determinations of the IRB; and (2) any suspension or termination of IRB approval [Federal Policy § ___.103(b)(5)].

The Authorized Institutional Official. Within the institution there must be a point of responsibility for the oversight of research and IRB functions. This point should be an official of the institution who has the legal authority to act and speak for the institution, and should be someone who can ensure that the institution will effectively fulfill its research oversight function. The authority can be delegated. The institution's president or chief executive officer (CEO) should appoint or delegate the appointment of the individual. If the CEO does not function as the Authorized Institutional Official, that person should be the equivalent of the director of research and development, a dean or assistant dean, or hospital administrator. Examples of individuals who should not be appointed, since they cannot speak or act for the institution are: department chair, director of oncology, research coordinator, and so forth. The person in this position may have the additional responsibility of selecting the chair of the IRB. Selection of appropriate personnel will assure the protection of the rights and welfare not only of research subjects, but also the institution itself. The designation of responsible officials must therefore be a considered action by the

institutional leadership.

Other Institutional Personnel. Training new personnel is a basic responsibility of any institution. In facilities that conduct research, all personnel should be aware of the applicable institutional policies and mechanisms for the approval of research and for reporting problems with research projects in progress. Personnel involved in the conduct of research should receive additional training in institutional expectations and specific regulations pertaining to research. Training designed to enhance the development of high quality proposals should be encouraged. IRB members and others charged with responsibility for reviewing and approving research should receive detailed training in the regulations, guidelines, and policies applicable to human subjects research. Attending workshops and other educational opportunities focused on IRB functions should be encouraged and supported to the extent possible. Training in good research practices and in methods for minimizing risk should be provided. Since research conducted by others may have a bearing on research projects conducted by or at the institution, journals and other research-related materials should be available to staff.

Internal Audits. Internal audit procedures assure the institution's administration that its policies and procedures are being adhered to and that they are proper in scope and content. Evaluation of activities and functions is an accepted management tool, and the monitoring of institutional high risk areas such as research is good policy. Audits allow the early identification and correction of problems. The institution must ensure that reporting of noncompliance is accomplished and that appropriate follow-up measures are taken [Federal Policy § ___.103]. *See also* Guidebook Chapter 1, Section D, "Compliance/Noncompliance."

POINTS TO CONSIDER

1. Do institutional policies comply with applicable regulations and promote appropriate review and approval?
2. Are the relevant institutional channels of communication sufficiently open?
3. Do adequate procedures for monitoring research and conducting audits of the research process exist?
4. Does the institution adequately provide for the training of personnel in policies and procedures related to research with human subjects?
5. Does the institution support educational activities related to the design, conduct, and approval of research?

APPLICABLE LAWS AND REGULATIONS

Federal Policy § ___.101 [To what does this policy apply?]

Federal Policy § ___.102 [Definitions]

Federal Policy § ___.103 [Assuring compliance with this policy C research conducted or supported by any federal department or agency]

Federal Policy § ___.107 [IRB membership]

Federal Policy § ___.108 [IRB functions and operations]

Federal Policy § ___.109 [IRB review of research]

Federal Policy § ___.110 [Expedited review procedures]

Federal Policy § ___.111 [Criteria for IRB approval of research]

Federal Policy § ___.112 [Review by institution]

Federal Policy § ___.115 [IRB records]

21 CFR 50 [FDA: Protection of human subjects (informed consent)]

21 CFR 56 [FDA: Institutional review boards]

34 CFR 97 [ED: Protection of human subjects]

34 CFR 350.3 [ED: What regulations apply to these programs (IRB membership)]

34 CFR 356.3 [ED: What regulations apply to these programs (IRB membership)]

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C. PRINCIPAL INVESTIGATORS

IRB CONSIDERATIONS

The qualifications of the principal investigator should be considered when reviewing proposals. The investigator's professional development should be taken into account and related to the degree of protocol complexity and risk to human subjects. IRBs may require less experienced research investigators to be sponsored by seasoned researchers. Proposals that require skills beyond those held by the principal investigator should be modified to meet the investigator's skills, have additional qualified personnel added, or be disapproved.

Research investigators shall prepare protocols giving complete descriptions of the proposed research. The research plan must include

provisions for the adequate protection of the rights and welfare of prospective subjects and ensure that pertinent laws and regulations are observed. Samples of informed consent documents must be included with protocols. Research investigators are responsible for obtaining informed consent and ensuring that no human subject will be involved in the research prior to obtaining the consent.

The research plan must address quality assurance standards set by the institution. In addition, applicable external standards for quality assurance must be met. External standards are of particular concern for research conducted in clinical facilities. Appropriate reviews for scientific merit must be conducted before the research is approved. Mechanisms for monitoring the progress of the research must be in place.

Research investigators, through their research design, determine whether the proposed research will involve human subjects. When it is not clear whether the research will involve human subjects, investigators should seek assistance from the IRB in making this determination [Federal Policy § ___.101(b)(1)-(6), ___.118, and ___.119]. Some IRBs, for example, require that all research protocols involving human subjects be submitted to the IRB for review. The IRB then determines whether the research is exempted from IRB review under the applicable regulations and institutional policies, and whether full or expedited IRB review is appropriate.

Researchers are responsible for complying with all IRB decisions, conditions, and requirements. Research investigators are responsible for reporting the progress of the research to the IRB and/or appropriate institutional officials as often as and in the manner prescribed by the IRB but no less than once per year [Federal Policy § ___.109(e)].

POINTS TO CONSIDER

1. Does the principal investigator have the appropriate qualifications, experience, and facilities to ensure that all aspects of the project and follow-up will be conducted rigorously and with due regard for the safety and well-being of the subjects?
2. Are adequate procedures in place through which the researcher will monitor the project and report problems to the IRB?
3. What is the investigator's past record with regard to approved research?

APPLICABLE LAWS AND REGULATIONS

Federal Policy § ___.101 [To what does this policy apply?]

Federal Policy § ___.102 [Definitions]

Federal Policy § ___.109 [IRB review of research]

Federal Policy § ___.111 [Criteria for IRB approval of research]

Federal Policy § ___.116 [General requirements for informed consent]

Federal Policy § ___.119 [Research undertaken without the intention of involving human subjects]

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D. COMPLIANCE / NONCOMPLIANCE

INTRODUCTION

Two basic approaches exist for ensuring compliance with human subjects regulations. FDA uses a system of inspections and audits; other DHHS components rely prospectively on assurances of compliance that are negotiated with institutions by OPRR. This divergence in approach reflects the respective agencies' mandates: FDA is regulatory (it regulates the pharmaceutical, biologic, and device industry, whether or not those substances or devices are used for research purposes, as well as the marketing and use of investigational drugs); other DHHS agencies, such as NIH, are research-supporting. FDA regulations provide specific administrative action and sanctions for noncompliance [21 CFR 56.120-24], which DHHS regulations [45 CFR 46] do not. [See, however, 45 CFR 46.123(a).] This Section deals primarily with compliance under DHHS regulations.

An **Assurance** is a written document negotiated with OPRR on behalf of the Secretary, HHS, that sets forth the means by which an institution will comply with DHHS regulations. Assurances are given as a condition of receipt of DHHS support for research involving human subjects. An Assurance approved by OPRR commits the institution and its personnel to full compliance with the DHHS human subjects regulations. Assurances are required by §46.103 of the Federal Policy (not adopted by FDA). That Section provides the required contents of the Assurance. [See Guidebook Chapter 2, Section A(iii), "Assurances."] While recognizing both individual and institutional responsibility for compliance with the regulations, OPRR generally negotiates Assurances only with institutions, which are ultimately responsible for ensuring that the regulatory requirements are met. Investigators and IRBs, however, also retain responsibility for complying with the regulations.

IRB CONSIDERATIONS

The Regulations

DHHS regulations (and those of any other department or agency that has adopted the Federal Policy) require that institutions follow written procedures for ensuring that serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB will be

reported to the IRB, appropriate institutional officials, and the head of the department or agency supporting the research [45 CFR 46.103(b)(5)]. FDA requires that such reports be made to the IRB, appropriate institutional officials, and the FDA [21 CFR 56.108(b)]. Each institution is responsible for establishing the mechanism through which instances of noncompliance will be reported to the department or agency. FDA interprets §56.108(b) to require that the IRB itself notify FDA of instances of noncompliance if such reporting would not otherwise occur [*Federal Register* 56 (June 18, 1991): 28026].

Suggested Internal Methods for Ensuring Compliance

To ensure compliance with the regulations, many institutions adopt internal audit or self-assessment procedures and practices designed to assure proper protocol and consent document preparation, protocol submission, review and approval by the IRB, and timely monitoring of protocol implementation. One example is the use of expiration date stamps on consent documents and protocols to ensure that the federal requirement of at least annual IRB review of each protocol is met. A second example is the use of standardized language, endorsed by the institution, which meets the minimal regulatory requirements and which is customized and elaborated upon by the investigator in creating an appropriate informed consent document.

External Audits and Site Visits

Regulatory compliance is similarly fostered by routine site visits and audits conducted by federal officials. The FDA monitors IRB compliance through a program of regular on-site inspections of IRB minutes and records. OPRR conducts occasional site visits to institutions to assess the adequacy of their procedures for protecting human research subjects. In addition, sponsors of research, such as the National Cancer Institute, and cooperative group research organizations, such as the Eastern Cooperative Oncology Group (ECOG), regularly audit their research performance sites. These audits normally include an examination of IRB minutes and records for conformance with applicable regulations. The results of these audits are shared with OPRR and FDA. On-site assessments are designed principally to instruct and educate.

Investigations Into Alleged Noncompliance

As warranted, both the FDA and OPRR conduct inquiries or investigations into alleged noncompliance with federal regulations. The need for site visits in connection with inquiries and investigations depends upon the seriousness and urgency of the circumstances, and whether on-site involvement is the most effective means of resolving the questions of noncompliance that have been raised.

Federal inquiries and investigations into alleged noncompliance with the regulations are not undertaken lightly. Experience has shown that these efforts are usually initiated in response to credible reports of inappropriate involvement of human subjects in research. Such reports can come from any source: IRB members, investigators, subjects, institutional personnel, or the media.

The FDA follows specific regulatory and administrative procedures regarding its determination of non-compliance, the imposition of sanctions, and appeal mechanisms. [See 21 CFR 56.121-124; FDA Compliance Program Guidance Manual, Chapter 48 - Bioresearch Monitoring - Human Drugs: Institutional Review Board (issued November 1988).]

DHHS regulations do not specify administrative actions for noncompliance with the human subjects regulations, except to state that material failure to comply with the regulations can result in termination or suspension of support for department or agency projects, and that DHHS will take terminations or suspensions of funding due to noncompliance into consideration when making future funding decisions [45 CFR 46.123]. OPRR compliance oversight procedures (called "compliance oversight evaluations") are described in a February 5, 1993 memorandum from the Director of OPRR, which is included in the Guidebook in Appendix 5. In part, the memorandum describes OPRR procedures as follows:

When OPRR initiates a compliance oversight evaluation, appropriate institutional officials are so advised, and they are informed as to the likely administrative course of events. Activities expected of the institution are carefully explained initially and at appropriate times during the course of the evaluation. Except in rare circumstances when sound ethics dictates the need to act immediately, OPRR takes no action against any institution without first affording the institution an opportunity to offer information which might refute or mitigate adverse determinations. In all cases, appropriate institutional officials are afforded an opportunity to comment in writing before OPRR issues its findings.

Under HHS regulations at 45 CFR 5, documents related to compliance oversight evaluations may be subject to the provisions of the Freedom of Information Act (FOIA). In most cases, such documents are exempt from the disclosure provisions of the FOIA while the evaluation is in progress, and OPRR treats them with confidentiality. However, OPRR routinely advises appropriate [D]HHS officials concerning the status of its evaluations and may be required to inform members of Congress. Most documents related to compliance oversight evaluations become publicly available under the FOIA when OPRR issues its findings.

Under HHS regulations at 45 CFR 5b, records which can be retrieved by an individual's name or other personal identifier are subject to the provisions of the Federal Privacy Act. Information regarding OPRR's compliance oversight activities is maintained only in a system of records identifying the institution under evaluation. Records can be retrieved by institutional name or Assurance number. OPRR maintains no system of records related to compliance oversight activities through which records can be retrieved by individuals' names or other personal identifiers....

OPRR's compliance oversight evaluations may result in one or more of the following outcomes:

(1) OPRR may determine that protections under an institution's Assurance of Compliance are in compliance with the HHS Regulations or the PHS Policy....

(2) OPRR may determine that protections under an institution's Assurance of Compliance are in compliance with the HHS Regulations or the PHS Policy...but that recommended improvements to those protections have been identified.

(3) OPRR may restrict its approval of an institution's Assurance of Compliance. Affected research projects cannot be supported by HHS until the terms of the restriction have been satisfied. Examples of such restrictions include, but are not limited to:

(a) suspending the Assurance's applicability relative to some or all research projects until specified protections have been implemented;

(b) requiring prior OPRR review of some or all research projects to be conducted under the Assurance;

(c) requiring that some or all investigators conducting research under the Assurance receive appropriate human subject or animal welfare education;

(d) requiring special reporting to OPRR.

(4) OPRR may withdraw its approval of an institution's Assurance of Compliance. Affected research projects cannot be supported by any HHS component until an appropriate Assurance is approved by OPRR.

(5) OPRR may recommend to appropriate HHS officials or PHS agency heads

(a) that an institution or an investigator be temporarily suspended or permanently removed from participating in specific projects, and/or

(b) that peer review groups be notified of an institution's or an investigator's past noncompliance prior to review of new projects.

(6) OPRR may recommend to HHS that institutions or investigators be declared ineligible to participate in HHS-supported research (Debarment). If OPRR makes this recommendation, the Debarment process will be initiated in accordance with the procedures specified at 45 CFR 76.

Noncompliance by Investigators, IRBs, and Institutions

Investigators. Research investigators are the most frequent source of noncompliance with human subjects regulations. The most common lapses in investigator compliance include unreported changes in protocols, misuse or nonuse of the informed consent document, and failure to submit protocols to the IRB in a timely fashion. Problems such as these are often caused by communication difficulties. With investigator goodwill, these cases can be resolved by the IRB without jeopardizing the welfare of research subjects.

Occasionally, an investigator will either avoid or ignore an IRB. Such cases present a more serious challenge to the IRB and to the institution. Regardless of investigator intent, unapproved research involving human subjects places those subjects at an unacceptable risk. When unapproved research is discovered, the IRB and the institution should act promptly to halt the research, assure remedial action regarding any breach of regulatory or institutional human subject protection requirements, and address the question of the investigator's fitness to conduct human subject research. Beyond the obvious need to protect the rights and welfare of research subjects, the credibility of the IRB is clearly at stake. In addition, any serious or continuing noncompliance with DHHS human subjects regulations or the determinations of the IRB must be promptly reported to OPRR (or the department or agency head) [Federal Policy § __.103(b)(5)].

IRBs. IRB noncompliance occurs whenever the IRB deviates from the duties imposed upon it by the federal regulations. Such deviations include the inadequate review of research protocols by failing to ensure that the consent document and process provide sufficient information to allow prospective subjects to make an informed decision whether to participate in the research; failing to ensure that the research design includes adequate monitoring of the data and any additional safeguards necessary to protect the welfare of particularly vulnerable subjects; and failing to conduct continuing review of research at intervals appropriate to the degree of risk. IRBs also breach their regulatory responsibilities by failing to maintain adequate records of IRB business and to hold their meetings with a majority of members present, including a nonscientific member. A demonstrated inability to carry out IRB responsibilities in accordance with DHHS regulations can be cause for the suspension or withdrawal of approval of an institution's Assurance.

Institutions. Although institutions are accountable for the actions of individual investigators and the IRB, institutional noncompliance is more broadly described as a systemic failure of the institution to implement practices and procedures contained in the institution's Assurance. Prime examples are the failure of the institution to ensure that the IRB is appropriately constituted and functions in accordance with the regulations, that the IRB receives appropriate institutional support and staffing, and that investigators meet their obligations to the IRB. Systemic failure to abide by the terms and conditions of an institution's Assurance will result in withdrawal of approval of the Assurance.

APPLICABLE LAWS AND REGULATIONS

Federal Policy for the Protection of Human Subjects

- 21 CFR 56.108(b) [FDA: IRB functions and operations]
- 21 CFR 56.120-124 [FDA: Administrative actions for noncompliance]

Federal Register 56 (June 18, 1991): 28026 [FDA]

- 45 CFR 46.103 [DHHS: Assuring compliance with this policy]
- 45 CFR 46.123 [DHHS: Early termination of research support]

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SUGGESTIONS FOR FURTHER READING

A. Jurisdiction of the Institutional Review Board

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- **Lind**, Stuart E. "The Institutional Review Board: An Evolving Ethics Committee." *The Journal of Clinical Ethics* 3 (No. 4, Winter 1992): 278-282. See also commentaries in the same issue by Troyen A. Brennan ("Researcher as Witness," dealing with health services research, pp. 308-309) and John B. Dossetor ("An Ethics Issue for Cadaver Renal Transplantation," p. 309-311).
- **Weiss**, Gary B., and Winslade, William J. "Is Post-Marketing Drug Follow-Up Research or Advertising?" *IRB* 9 (No. 4, July/August 1987): 10-11.

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- **Cowan**, Dale H., and Bertsch, Eva "Innovative Therapy: The Responsibility of Hospitals." *Journal of Legal Medicine* 5 (No. 2, June 1984): 219-251.
- **DeRenzo**, Evan G., and Wichman, Alison. "A Pilot Project: Bioethics Consultants as Non-Voting Members of IRBs at the National Institutes of Health." *IRB* 12 (No. 6, November/December 1990): 6-8.
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- **McCarthy**, Charles R. "Experience with Boards and Commissions Concerned with Research Ethics in the United States." In *Research Ethics*, edited by Kare Berg and Knut Erik Tranoy, pp. 111-122. New York: Alan R. Liss, 1983.
- **Porter**, Joan P. "What Are the Ideal Characteristics of Unaffiliated/Nonscientist IRB Members?" *IRB* 8 (No. 3, May/June 1986): 1-6.
- **Porter**, Joan P. "How Unaffiliated/Nonscientist Members of Institutional Review Boards See Their Roles." *IRB* 9 (No. 6, November/December 1987): 1-6.
- **Porter**, Joan P. "The Federal Policy for the Protection of Human Subjects." *IRB* 13 (No. 5, September/October 1991): 8-9.
- **Ryan**, Mary Kay. "General Organization of the IRB." In *Human Subjects Research: A Handbook for Institutional Review Boards*, edited by Robert A. Greenwald, Mary Kay Ryan, and James E. Mulvihill, pp. 29-38. New York: Plenum Press, 1982.
- **Ryan**, Mary Kay. "IRB Procedures." In *Human Subjects Research: A Handbook for Institutional Review Boards*, edited by Robert A. Greenwald, Mary Kay Ryan, and James E. Mulvihill, pp. 63-77. New York: Plenum Press, 1982.
- **Stopp**, G. Harry. "The Internal IRB Structure: Models in Academic Settings." *IRB* 7 (No. 6, November/December 1985): 9.

C. Principal Investigators

- **Appelbaum**, Paul S., and Rosenbaum, Alan. "Tarasoff and the Researcher: Does the Duty to Protect Apply in the Research Setting?" *American Psychologist* 44 (No. 6, June 1989): 885-894.

D. Compliance/Noncompliance

- **U.S. Department of Health and Human Services**. Public Health Service. Food and Drug Administration. *Compliance Program Guidance Manual: Chapter 48 - Bioresearch Monitoring - Human Drugs - Institutional Review Board*, November 1988. [Mimeo].

- Ellis, Gary B. [Director, OPRR]. "Compliance Oversight Procedures" [Memorandum]. (February 5, 1993).

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Chapter I: Institutional Administration

Institutional Review Board Guidebook

*** CHAPTER II * REGULATIONS AND POLICIES**

A. Department of Health and Human Services Regulations, Policies, and Assurances

- **The Federal Policy**
- **45 CFR 46: Most Frequently Asked Questions**
- **Assurances**

B. Food and Drug Administration Regulations and Policies

- **Introduction**
- **Comparing FDA and DHHS Human Subjects Regulations**

Waiver of IRB Review
Waiver of Consent Requirements
Emergency Use of a Test Article
Expanded Availability of Investigational Drugs

Treatment Investigational New Drug Exemption
Single Patient Use
Parallel Track

Suggestions for Further Reading

A. DEPARTMENT OF HEALTH AND HUMAN SERVICES REGULATIONS, POLICIES, AND ASSURANCES

i. THE FEDERAL POLICY

OVERVIEW

Until 1991, federal departments and agencies that conduct, support, or regulate research used a variety of policies and procedures to protect human research subjects. To eliminate confusion and promote uniformity, each of these departments and agencies has adopted as regulation a common Federal Policy for the protection of human research subjects. The Federal Policy applies to research involving human subjects that is conducted, supported, or otherwise subject to regulation by any of the following sixteen federal departments and agencies:

Department of Agriculture
Department of Energy
National Aeronautics and Space Administration
Department of Commerce
Consumer Product Safety Commission
International Development Cooperation Agency
Agency for International Development
Department of Housing and Urban Development
Department of Justice
Department of Defense
Department of Education
Department of Veterans Affairs
Environmental Protection Agency

Department of Health and Human Services
National Science Foundation
Department of Transportation
Central Intelligence Agency

The FDA has concurred in the Federal Policy, but has not adopted the Policy in its entirety. Instead, the FDA has made selected changes to its IRB and informed consent regulations that correspond to the Federal Policy. [See *Federal Register* 56 (June 18, 1991): 28025-28029.]

Where a protocol is subject to review under more than one department or agency's regulations, the requirements of each set of regulations must be met. This situation may arise, for example, with **Treatment INDs**, or when applying the provisions on waiver of documentation of informed consent, in cases where both the FDA and DHHS have jurisdiction over the research. (See, e.g., Guidebook Chapter 2, Section B, "Food and Drug Administration Regulations and Policies," discussing Treatment INDs, and Chapter 2, Section A(ii), "45 CFR 46: Most Frequently Asked Questions," question 10.)

The adoption of the Federal Policy by these departments and agencies implements a recommendation of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (established by Act of Congress on November 9, 1978) that all federal departments and agencies "adopt as a common core the regulations governing research with human subjects issued by the Department of Health and Human Services (codified at 45 CFR 46), as periodically amended or revised, while permitting additions needed by any department or agency that are not inconsistent with these core provisions." The resulting Federal Policy was drafted by the Ad Hoc Committee for the Protection of Human Research Subjects and the Interagency Human Subject Coordinating Committee, appointed under the auspices of the Federal Coordinating Council for Science, Engineering and Technology.

The Federal Policy is based on Subpart A of the DHHS regulations for the protection of human research subjects, adopted by DHHS in 1981. The Federal Policy now replaces Subpart A of the 1981 DHHS regulations; Subparts B and C remain unchanged; Subpart D has been modified to accommodate renumbering changes in Subpart A. [See 45 CFR 46.401(b).] Regulations for DHHS and the other departments and agencies listed above are now, in effect, identical (not including the FDA, which has regulations that differ in some significant respects, or the CIA, which follows the DHHS human subjects regulations through an Executive Order, but has not itself adopted specific human subjects regulations). Adoption of the Federal Policy incorporates DHHS's basic considerations for the protection of human subjects; the provisions of Subparts B, C, and D of the DHHS regulations are applicable to research supported or conducted by these departments and agencies at institutions that have MPAs approved by and on file with OPRR.

IRBs familiar with DHHS regulations prior to adoption of the Federal Policy will want to note the following changes (this list is not, however, exhaustive; IRB members must familiarize themselves with the Federal Policy in its entirety):

§101(b): **Exemptions.** Some of the previous exemptions have been combined, rephrased, and renumbered; there is also a new exemption for "taste testing." Institutions claiming exemptions should be careful to cite appropriate exemptions in grant applications and contract proposals.

§101(h): **Research in foreign countries.** This is a new provision that allows a department or agency head to determine that if procedures prescribed by a foreign institution afford protections at least equivalent to those in the regulations, the department or agency head may approve the substitution of foreign procedures in lieu of the procedural requirements in the regulations. Claims that foreign sites employ "at least equivalent" protections should be forwarded to OPRR. [Note that this provision was not adopted by the FDA. See description in Chapter 2, Section B(ii), "Comparing FDA and DHHS Regulations."]

§102: **Definitions.** The wording in the definition of "minimal risk" has been slightly altered [§102(i)]. Definitions for "IRB" and "IRB approval" have been added [§102(g) and (h)].

§103: **Assurances.** There are several minor modifications in this Section, primarily because federal departments and agencies must accept DHHS-approved Multiple Project Assurances (MPAs).

§103(f): **Certification.** The regulations no longer explicitly list a "grace period" of 60 days for receipt of certification of IRB review and approval from MPA institutions. The National Institutes of Health and other Public Health Service agencies extended the current policy of providing a "grace period" for competing applications and proposals via administrative announcement.

§107: **IRB Membership.** Several wording changes have been made, but the modifications from the 1981 language do not represent a change in the care with which institutions select IRB members. See, particularly, §107(a) and (b) for wording changes from the 1981 regulations. (See also, Department of Education Interim Final Regulations published at *Federal Register* 56 (June 18, 1991): 28029-28032.)

§114: **Cooperative research.** Significant wording changes clarify the definition of cooperative research and the responsibilities of the institutions involved. Joint review or other arrangements geared toward avoiding duplication of effort are desirable, but must be approved by the department or agency head. Each participating institution remains responsible for safeguarding the rights and welfare of human subjects and for complying with the regulations.

For information concerning the Federal Policy and DHHS regulations, contact:

Dr. Gary B. Ellis
Office for Protection from Research Risks
National Institutes of Health
6100 Executive Blvd.
Suite 3B01, MSC 7507
Rockville, MD 20892-7507
Tel: (301) 496-7005

For information concerning the Federal Policy and FDA regulations, contact:

Dr. Paul W. Goebel, Jr.
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel: (301) 827-1685

A description of major differences between DHHS and FDA regulations on research involving human subjects is given in Chapter 2, Section B, "Comparing FDA and DHHS Regulations."

APPLICABLE LAWS AND REGULATIONS

Federal Register 56 (June 18, 1991): 28002-28032 [Federal Policy for the Protection of Human Subjects; Notices and Rules]

Codification of the Federal Policy for each of the departments and agencies adopting it is as follows:

7 CFR Part 1c [Department of Agriculture]
10 CFR Part 745 [Department of Energy]
14 CFR Part 1230 [National Aeronautics and Space Administration]
15 CFR Part 27 [Department of Commerce]
16 CFR Part 1028 [Consumer Product Safety Commission]
22 CFR Part 225 [International Development Cooperation Agency]

[Agency for International Development]

24 CFR Part 60 [Department of Housing and Urban Development] 28 CFR Part 46 [Department of Justice] 32 CFR Part 219 [Department of Defense] 34 CFR Part 97 [Department of Education] 38 CFR Part 16 [Department of Veterans Affairs] 40 CFR Part 26 [Environmental Protection Agency] 45 CFR Part 46 [Department of Health and Human Services] 45 CFR Part 690 [National Science Foundation] 49 CFR Part 11 [Department of Transportation]

FDA regulations pertaining to research with human subjects are codified at:

21 CFR Part 50 [Protection of Human Subjects] 21 CFR Part 56 [Institutional Review Boards]

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ii. 45 CFR 46: MOST FREQUENTLY ASKED QUESTIONS

DHHS receives many requests for assistance in interpreting and applying its human subjects research regulations, which are codified at 45 CFR 46. This Section provides answers to the twenty-eight most frequently asked questions.

1. Question: What is OPRR's function in the DHHS regulations?

Answer: The Office for Protection from Research Risks (OPRR) is a unit within the Department of Health and Human Services (DHHS) that implements the regulations on behalf of the Secretary, HHS. It is located in the Office of the Director, Office of Extramural Research, National Institutes of Health (NIH), Bethesda, Maryland.

The Public Health Service Act required DHHS to issue regulations for the protection of human subjects of research and to implement a program of instruction and guidance in ethical issues associated with such research. The regulations are codified at

2. Question: How is 45 CFR 46 implemented?

Answer: DHHS regulations require institutions to assure their compliance with 45 CFR 46 before initiating participation in DHHS-conducted or - supported research involving human subjects. The terms of these written institutional assurances are negotiated with OPRR and constitute binding commitments to comply with the provisions of 45 CFR 46. Each negotiated commitment is called an **Assurance** document and is entered into by the institution and OPRR, representing DHHS. There is more than one type of Assurance document, depending on the nature of the research and other considerations. Each Assurance document stipulates the method(s) by which the institution will protect the rights and welfare of research subjects in accordance with the regulations [45 CFR 46.103]. [See Guidebook, Chapter 2, Section A(iii), "Assurances."]

3. Question: To what activities does 45 CFR 46 apply?

Answer: The regulations for the protection of human participants in research apply to all research involving human participants that is conducted or supported, in whole or in part, by DHHS in foreign or domestic settings. Note that **any** support provided by DHHS, *e.g.*, supplying a drug for research purposes, may trigger applicability of the regulations [45 CFR 46.101].

4. Question: If an IRB reviews a protocol that is closed to accruals before the institution initiates involvement in the research, must the IRB retain its records on the project for three years beyond the completion of the research [45 CFR 46.115]?

Answer: While most records (*e.g.*, the protocols) need not be retained, some, (*e.g.*, any IRB minutes in which the project is discussed) should be preserved. Institutional policy, however, may stipulate that all IRB records are to be kept for three years.

5. Question: Must an IRB perform continuing reviews of protocols in which patient accruals have been closed and the research interventions are completed, but investigators are still collecting follow-up data?

Answer: Yes. So long as data are being collected for an organized research project, the IRB must continue to review the status of the protocols and the details of the continuing data gathering activity. If the continuing research meets the requirements for expedited review, the expedited review process may be used, if desired by the IRB.

6. Question: Why would a standard cooperative research protocol or a standard informed consent document need review at the local level when it has already been reviewed by another national organization (*e.g.*, the National Institutes of Health, the National Cancer Institute, or a cooperative research group), or even by the IRB of another institution with an approved Assurance?

Answer: Cooperative protocol requirements may be standard, but the research setting is not standard across institutions. In addition, one should not assume that because a protocol or informed consent document has been reviewed by another entity, it necessarily conforms to pertinent regulations, local laws, or the local research setting. For example, local laws, institutional policies and constraints, professional and community standards, and population differences are all factors that can influence the research setting. [See 45 CFR 46.103(d), 46.107(a), and 46.111(a)(3), noting the relevance of the particular setting in which the research is to take place.]

7. Question: Certain research involving prisoners or children can be approved only upon review by the Secretary, HHS, in consultation with a panel of experts (specified in the regulations) [45 CFR 46.306(2)(c)-(d) (prisoners) and 46.407 (children).] Also, certain research involving fetuses, pregnant women, and human in vitro fertilization requires review by an Ethics Advisory Board established by the Secretary [45 CFR 46.204 and 46.211]. When a MPA-holding institution reviews research that is neither supported nor conducted by DHHS, does it have to meet these special review requirements?

Answer: The institution's Assurance requires the institution to protect the rights and welfare of human research subjects whether or not the research is supported or conducted by DHHS [Federal Policy § __.103(b)(1)]. Further, institutions are encouraged to treat all research involving human subjects with the same level of review, regardless of the source of funding. In the case of research that would receive a second level of review if it were DHHS-supported, institutions should appoint a special review panel composed of the same kinds and quality of experts who would likely have advised the Secretary.

8. Question: What role does an advocate play in the review of research involving children who are wards of the state?

Answer: An advocate for a child who is a ward of the state has a fiduciary relationship (one of trust and confidence) to the child. In other words, the advocate must act with the child's interest as the primary consideration.

9. Question: Why must foreign sites abide by DHHS regulations? Why isn't the Declaration of Helsinki or another international code acceptable?

Answer: DHHS wants to ensure that all DHHS-supported or -conducted research involving human subjects provides subjects

with protections that are at least equivalent to those afforded by DHHS regulations. Many international guidelines, such as the Declaration of Helsinki, provide general principles and are a good place to start, but do not describe the specific procedures through which those principles are to be realized. Through its negotiations with the foreign institution, OPRR ensures that those Assurances provide procedures that are equivalent to those required by 45 CFR 46.

10. Question: FDA will consider waiving local IRB review for Treatment INDs (if waiver is in the best interests of the subjects and adequate alternative mechanisms for human subject protection are provided, *e.g.*, to avoid duplication when a national review body has already reviewed the Treatment IND). [See 21 CFR 312.34; FDA, "IRB Information Sheet: Waiver of IRB Requirements" (February 1989).] Do DHHS regulations require local IRB review for Treatment INDs, even when FDA does not?

Answer: If both the FDA and DHHS have jurisdiction over the research activities, IRBs must meet the requirements of both sets of regulations. Where the FDA has granted a waiver of local IRB review, DHHS regulations would still require local IRB review if: (1) an MPA-holding institution that has agreed to follow DHHS regulations for all research is involved; or (2) the research is supported by a DHHS component. Furthermore, grant of an FDA waiver of local IRB review gives permission to the local IRB to forego review; local IRBs retain the right to review the research if they so choose. The Secretary may grant a waiver of DHHS regulations, and will consider waiving some part of 45 CFR 46 for Parallel Track protocols. [See Guidebook Chapter 2, Section B, "Food and Drug Administration Regulations and Policies."]

11. Question: Exemption 4 [45 CFR 46.101(b)(4)] covers research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens. When are data, documents, records, and specimens considered to be **existing** for the purposes of this exemption? Can an investigator use, for instance, blood specimens that have been drawn for another purpose?

Answer: To qualify for this exemption the data, documents, records, or specimens must be in existence *before* the project begins. An example might be helpful. Suppose Investigator A wishes to screen blood samples at a rural hospital for incidence of HIV infection. She does not want to draw specimens specifically for this purpose; rather she proposes to use specimens that were drawn for some other purpose but which remain in the hospital laboratory. If Investigator A proposes to use specimens that had been drawn prior to the initiation of her research and are, for some reason, "on the shelf," the protocol will qualify as exempt under 46.101(b)(4), assuming the other requirements of 46.101(b)(4) are met (*i.e.*, the sources are either publicly available or the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects). If she proposes to use specimens that will be drawn after the start date of her project for reasons unrelated to her research, the protocol is not exempt from IRB review, even though the specimens will be drawn regardless of her use of the excess blood. The protocol may, however, qualify for expedited review.

In the behavioral sciences, suppose Investigator B wishes to examine court records of involuntary commitments to psychological institutions. If he uses court records that were on file before the initiation of his research, the protocol will qualify as exempt under 46.101(b)(4). If he proposes to use records filed after the initiation of the project, the protocol is not exempt from IRB review, although it may qualify for expedited review.

The principle behind this policy is that the rights of individuals should be respected; subjects must consent to participation in research. When specimens and other data or records have yet to be collected, consent may be more easily sought. Where circumstances warrant, however, the investigator may seek a waiver of informed consent in accordance with the regulations [Federal Policy § __.116(d)].

12. Question: If an investigator is conducting a "masked" study, are the exemptions of 46.101(b) applicable, since no identifiers will be used?

Answer: It is a misnomer that subjects are not identified in masked studies. Research records do reflect the identity of subjects, either directly or through identifiers (codes) that can be linked to them. What is "masked" in a single-masked study is the identity of the intervention the subject receives: the subject does not know whether she is receiving the investigational intervention or a standard intervention. In a double-masked study, neither the subject nor the investigator knows which intervention the subject receives.

13. Question: Do the exemptions apply to Subparts B (fetuses, pregnant women, and human in vitro fertilization) and C (prisoners)?

Answer: No. In addition, with respect to research involving children (Subpart D), the exemption provided in 46.101(b)(2) for research involving survey or interview procedures or observation of public behavior does not apply, except for research involving observations of public behavior when the investigator(s) does not participate in the activities being observed.

14. Question: Can an IRB use an expedited procedure for the review of administrative changes to Cooperative Oncology Group (COG) protocols and related documents when the risks are minimal or less than minimal (*e.g.*, for follow-up calls when gathering initial data by telephone, collecting changes in addresses and telephone numbers, or altering the specification of individuals assigned to particular tasks in the protocol) [45 CFR 46.110]?

Answer: Yes. Such reviews would constitute review of minor changes in previously-approved protocols. It is important, however, to distinguish between those changes that are and are not truly "minor." Any change that would materially affect the

assessment of risks and benefits should not be considered minor.

15. Question: Can IRBs use an expedited review procedure when applying for a Single Project Assurance (SPA) from OPRR [45 CFR 46.110]?

Answer: No. Since SPAs are used by institutions that do not regularly engage in DHHS-supported research involving human subjects, special care must be taken to ensure that the subjects' welfare is fully considered. Institutions holding MPAs have established records of experience in reviewing human subjects research that SPA institutions may not have. OPRR policy is therefore to require that all research activities requiring an SPA be reviewed by the full IRB.

16. Question: Must investigators provide subjects with all of the information listed in 45 CFR 46.115(a) (basic elements) and (b) (additional elements) as part of the informed consent process unless the IRB specifically provides otherwise?

Answer: The additional elements of informed consent listed in 45 CFR 46.115(b) are required when they are appropriate to the research being conducted. It is necessary for the IRB to determine explicitly their inapplicability.

17. Question: Why are Multiple Project Assurances (MPAs) sometimes restricted?

Answer: OPRR will sometimes indicate that an IRB at an MPA-holding institution must acquire additional expertise before certain research activities can be reviewed and certified by issuing a restriction code. Restriction codes appear as a suffix to the MPA number (e.g., M2345-01XM). If the institution has only one IRB, the restriction applies to the overall MPA. If there is more than one IRB, each IRB has associated with it a unique restrictive suffix code. This policy may result in institutions holding MPAs that are not restricted overall because of offsetting capabilities of two or more IRBs.

An "XM" suffix indicates that the IRB has an insufficient number of members with expertise in medicine. An IRB with an XM restriction on its MPA cannot certify proposed research activities requiring medical expertise to assess risks, benefits, and the adequacy of safeguards. To certify such research, the IRB membership must include at least two voting members who possess appropriate medically-related degrees. OPRR will remove the restriction when the IRB notifies OPRR of the addition of the appropriate number of medical members and provides OPRR with a revised IRB membership list.

An "XB" suffix indicates that the IRB has an insufficient number of members with expertise in the behavioral sciences. Requirements parallel to those described for IRBs reviewing medical research exist for IRBs reviewing behavioral research. In contrast with the education requirements for members with medical expertise, members with expertise in the behavioral sciences must either possess degrees in the behavioral sciences or have related experience in behavioral research activities.

18. Question: What considerations should institutions address when arranging for review of research involving human subjects? For example:

- a. Must an institution establish its own IRB?
- b. Must there be "compelling reasons" for using another institution's IRB rather than one's own IRB?
- c. Must the reviewing IRB be "local" (within the geographic proximity of the research participants)?
- d. When using another institution's IRB for the review of research, must there be a representative or consultant appointed to the IRB from the institution requesting the review so that he or she can provide information about the local conditions where the research is to take place?

Answer: The answer to each of (a)-(d) is "not necessarily." The federal regulations allow institutions to use joint reviews, reliance on the review of another qualified IRB, or similar arrangements to avoid duplication of effort [45 CFR 46.114, relating to cooperative research projects]. Similarly, institutions at which it is not practical to set up an IRB, but which are not participating in cooperative research as required by §46.114, may be permitted to use another IRB acceptable to OPRR. Institutions wishing to use another institution's IRB for DHHS-supported research should contact OPRR for details.

Institutions should bear in mind several considerations when contemplating the use of another institution's IRB to review its protocols. Specifically, local laws, institutional policies and constraints, professional and community standards, and population differences are all relevant factors to IRB deliberations. Review by an institution in another geographical, cultural, or professional setting may not take into account pertinent local factors defined by the research setting. [See 46.103(d), 46.107(a), and 46.111(a)(3).] For example:

- the two institutions may draw from culturally dissimilar subject populations;
- the two institutions may be located in different states or other geographical subdivisions whose legal or regulatory constraints differ; or
- the two institutions' operational policies, procedures, constraints, or commitments may differ in ways that would substantively affect the assessment of protocols.

When an institution wishes to use another institution's IRB to review its protocols, OPRR requires documentation to verify for

itself whether the IRB is able to determine the acceptability of proposed research in terms of the institutional commitments of the institution at which the research will take place. [See 45 CFR 46.107(a).] If OPRR is not convinced that the IRB is properly constituted for making these judgments, OPRR may require that institutional representatives or other persons act as consultants for the IRB's review.

For further information, contact: Division of Human Subject Protection (DHSP): (301) 496-7041.

See also Guidebook Chapter 2, Section A(iii), "Assurances."

19. Question: Section 46.114 of the DHHS regulations allows for reliance upon "the review of another qualified IRB." Does "qualified" mean that the other institution must have an Assurance on file with OPRR?

Answer: Usually, yes. However, possession of an MPA or other OPRR-approved Assurance does not guarantee acceptability of the IRB for a given research activity. Each situation is unique and requires evaluation by OPRR. Contact the Assurance Branch, DHSP for details [(301) 496-7041].

20. Question: What options are typically available to an institution seeking to avoid duplication of IRB effort in the conduct of cooperative projects?

Answer: In addition to having each institution conduct its own review, several options exist, each of which OPRR has found to comply with the letter and intent of both 45 CFR 46.114 and the regulations as a whole.

First, institutions that are close enough geographically to contribute membership to a common IRB can share in bearing the costs of operation while simultaneously providing review for protocols that may be used by investigators at some of all of the sites. This approach results in the establishment of one IRB that can be cited as the IRB of record by all institutions that contribute to its membership.

A second approach is for one IRB to host reviews for other nearby institutions, with consultative representation from each institution present for all initial and continuing reviews of cooperative protocols. In this approach only the host institution has its own IRB. The other institutions rely on another's IRB, but in such a way as not to defeat the intent of 45 CFR 46.

21. Question: How can independent investigators (*i.e.*, investigators not associated with an Assurance-holding institution) who wish to engage in cooperative research in their private practices obtain local IRB approval for their research?

Answer: One possible approach is for the independent investigator to seek permission from OPRR (and the institution) to rely upon the IRB of a local institution with an applicable OPRR-approved Assurance for the research in question. If no such local institution is available or permission is denied, the independent investigator must identify another IRB that holds an appropriate Assurance for reviewing the research. It will be important for the investigator to ensure that the IRB he or she selects can evaluate the research in accordance with the needs of the research setting (*e.g.*, local laws, professional and community standards, and cultural differences due to different geographical or research settings).

22. Question: What is the difference between "compassionate" use, "emergency" use, and "Treatment INDs?"

Answer: The term "compassionate use" has been used in the past to refer to the provision of investigational drugs outside of an ongoing clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term "compassionate use" does not, however, appear in FDA or DHHS regulations; its plausible application to various access mechanisms causes more confusion than it does assistance. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of formal clinical trials.

First, the FDA human subjects regulations allow for a test article to be used in emergency situations without prior IRB approval provided that the emergency use is reported to the IRB within five working days; subsequent use of the test article must be reviewed by the IRB [21 CFR 56.104]. An emergency is defined as a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. [See Guidebook Chapter 2, Section B, "Food and Drug Administration Regulations and Policies."]

Second, various FDA regulations and policies allow certain persons not enrolled in clinical trials to obtain access to investigational drugs:

- A Treatment IND is a treatment protocol that is added to an existing investigational new drug application (IND), which allows physicians to treat qualifying patients according to the protocol, and which provides additional data on the drug's safety and effectiveness. Treatment INDs are available for patients with life-threatening or other serious diseases for which no satisfactory alternative drug or other therapy exists [21 CFR 312.34].
- A "single patient use" allows a physician to obtain access to an investigational drug for the treatment of a single patient.

Usually, the patient is in a desperate situation and unresponsive to other therapies, or in a situation where no approved or generally recognized treatment is available. Further, there is usually little evidence that the proposed therapy is useful, but may be plausible on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor under a treatment protocol, or through the FDA, by first obtaining the drug from the sponsor, and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment use [21 CFR 312.35].

- The Parallel Track mechanism makes available promising investigational agents as quickly as possible to persons with AIDS and other HIV-related diseases while generating data on the safety and effectiveness of the drug [Federal Register 57 (April 15, 1992): 13250-13259]. Under the FDA policy, persons with AIDS and HIV-related diseases who are not able to take standard therapy or for whom standard therapy is no longer effective, and who are not able to participate in ongoing controlled clinical trials would have access to promising investigational drugs. Applications for consideration of experimental therapies for Parallel Track expanded availability must be submitted to the FDA as amendments to existing INDs.

See Guidebook Chapter 2, Section B, "Food and Drug Administration Regulations and Policies" for a more detailed description of these mechanisms.

23. Question: Why does DHHS not allow for an emergency exception to IRB review as does the FDA? [See 21 CFR 50.23 and 56.104(c), and Guidebook Chapter 2, Section B, "Food and Drug Administration Regulations and Policies."]

Answer: DHHS regulations require that research involving human participants receive full IRB review and approval, except where expedited review is specifically permitted, prior to initiation of the research [45 CFR 46.103(b)]. Physicians do, however, retain the authority to provide emergency medical care to their patients [45 CFR 46.116(f)]. On May 15, 1991, OPRR issued the following statement clarifying emergency treatment of a patient by a physician when that patient is also a research subject:

Whenever emergency care is initiated without prior IRB review and approval, the patient may not be considered to be a research subject. Such emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity. Simply stated: [D]HHS regulations for the protection of human subjects do not permit research activities to be started, even in [an] emergency, without prior IRB review and approval.

If the emergency care involves drugs, devices, or biologics that are considered to be investigational by the Food and Drug Administration (FDA), then it may be necessary to meet FDA requirements to use the investigational article for emergency purposes.

Thus, the distinction for DHHS-supported or -conducted research is that while the physician may, without prior IRB approval, treat the patient/subject using a test article (if the situation meets the FDA requirements), the subject may not be considered a research subject; data derived from use of the test article may not be used in the study.

24. Question: The FDA regulations allow an exception from the general requirements for informed consent for life-threatening situations where the subject's consent or that of his or her legal representative cannot be obtained because of an inability to communicate with any of the requisite parties. Why don't the DHHS regulations provide for waiver of consent requirements in such emergency circumstances?

Answer: DHHS regulations permit the waiver of informed consent requirements only in the case of research that presents no more than minimal risk [45 CFR 46.116]. As with emergency use of a test article without prior IRB approval, physicians retain the authority to provide emergency medical care to their patients. [See Question 23.] Unless, however, prior consent has been obtained, or the IRB waives the consent requirement after determining that the research presents a minimal risk, the patient cannot be considered a research subject; any data derived from the emergency use of the test article cannot be used in the study.

25. Question: What must be reported to DHHS?

Answer: Any of the following occurrences:

- IRB membership changes;
- serious or continuing noncompliance with 45 CFR 46 [§46.103(b)(5)(i)];
- any unanticipated problems involving risks to subjects or others [45 CFR 46.103(b)(5)(i)]; or
- any suspension or termination of IRB approval for a project [45 CFR 46.103(b)(5)(ii) and 46.113].

26. Question: Must the IRB itself report instances of noncompliance with the regulations to DHHS?

Answer: Not necessarily. Each institution must have in place written procedures that ensure that instances of serious or continuing noncompliance will be reported to the IRB, appropriate institutional officials, and the head of the department or agency supporting the research (here, DHHS) [45 CFR 46.103(b)(5)]. The IRB is only responsible for doing the reporting if it is

required to do so under the institution's written procedures. [NOTE: FDA requires that the IRB report to FDA if such reporting would not otherwise occur (*Federal Register* 56 (June 18, 1991): 28026).]

27. **Question:** Can treatment of a single patient constitute "research?"

Answer: Yes, if there is a clear intent before treating the patient to use systematically collected data that would not ordinarily be collected in the course of clinical practice in reporting and publishing a case study. Treating with a research intent should be distinguished from the use of innovative treatment practices.

28. **Question:** If the research is subject to both DHHS and FDA human subjects regulations, which regulations should the IRB follow?

Answer: Where a protocol is subject to review under more than one department or agency's regulations, the requirements of each set of regulations must be met. This situation may arise, for example, with Treatment INDs, or when applying the provisions on waiver of documentation of informed consent, in cases where both the FDA and DHHS have jurisdiction over the research. [See, e.g., Guidebook Chapter 2, Section B, "Food and Drug Administration Regulations and Policies," discussing Treatment INDs, and Guidebook Chapter 3, Section D, "Privacy and Confidentiality," under the heading "Confidentiality of Research Data" (discussing waiver of documentation of informed consent where the data are sensitive and the existence of a consent form may place the subject at risk).]

See also Guidebook Chapter 2, Section B, "Food and Drug Administration Regulations and Policies."

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iii. ASSURANCES

An **Assurance** is an agreement or contract between the institution and OPRR, on behalf of the Secretary, HHS, stipulating the method(s) by which the institution will protect the welfare of research subjects in accordance with the regulations. The Assurance, approval of which is a condition of receipt of DHHS support for research involving human subjects, spells out the institution's responsibilities for meeting the requirements of 45 CFR 46 [45 CFR 46.103].

The existing types of Assurances include:

a. **Multiple Project Assurance (MPA).** A standing agreement on file with OPRR that is approved for five-year intervals. An MPA is designed for institutions that are engaged in a significant amount of health-related research (*i.e.*, institutions that usually have several federally-funded research projects under way at any given time.) Institutions with an MPA on file may also negotiate an **Inter-Institutional Amendment (IIA)**. An IIA covers DHHS-sponsored research conducted at a neighboring affiliated institution by employees of an institution with an MPA on file with OPRR.

b. **Single Project Assurance (SPA).** An agreement covering a single research project involving human subjects. An SPA is often used for institutions that do not have an MPA on file with OPRR. A modified SPA is used when an institution plans to use another institution's IRB to review its human subjects research. The reviewing institution must either have an MPA on file with OPRR or submit an SPA for this project for OPRR approval. The institution proposing to do the research submits a modified SPA; the institution whose IRB will have responsibility for reviewing the research submits an SPA, unless it has an MPA on file. OPRR must approve this arrangement; contact the Assurance Branch prior to submission of the Assurance [(301) 496-7041].

c. **Cooperative Project Assurance (CPA).** An agreement covering participation in OPRR-recognized Cooperative Protocol Research Programs (CPRPs). CPRPs involve multi-protocol, multi-site research in which data from standardized protocols are pooled across institutions. These protocols are approved and monitored by DHHS Protocol Review Committees, which are recognized by OPRR as satisfactorily addressing the adequacy of human subject protections. Once approved, the CPA is valid for participation in *all* OPRR-recognized CPRPs.

d. **Cooperative Research.** In the past, a variety of Assurances were used for certain cooperative research projects. Examples include:

- i. **Clinical Community Oncology Program (CCOP)**
- ii. **Cooperative Oncology Group Program (COG)**
- iii. **Community Program for Clinical Research on AIDS (CPCRA)**

These Assurances are being replaced with CPAs as they expire. Contact OPRR for information regarding these and other subject-specific cooperative Assurances [Assurance Branch, DHSP (301) 496-7041].

B. FOOD AND DRUG ADMINISTRATION REGULATIONS AND POLICIES

i. INTRODUCTION

The Food and Drug Administration (FDA) regulates but does not, for the most part, support or conduct research. Its regulatory mandate, therefore, differs substantially from other DHHS agencies and other departments and agencies that conduct and support a significant amount of research. While the structural and functional requirements for IRBs in the FDA regulations are identical to DHHS regulations, the substantive provisions differ in several significant respects. IRBs should note that **where a protocol is subject to review under both FDA and DHHS human subjects regulations, both sets of regulations apply, and the requirements of both sets of regulations must be met.** This situation may arise, for example, with Treatment Investigational New Drug Exemptions (*see* discussion of Treatment INDs, below) or when applying the provisions on waiver of documentation of informed consent, in cases where both the FDA and DHHS have jurisdiction over the research.

FDA regulations pertaining to human subjects research are codified at 21 CFR 50 [Protection of Human Subjects (containing the informed consent requirements)] and 21 CFR 56 [Institutional Review Boards].

In addition to the information provided in this Section, see the various FDA Information Sheets and guidelines (*e.g.*, *IRB Information Sheets*, *Clinical Investigator Information Sheets*, *Guideline for the Monitoring of Clinical Investigations*, and *Compliance Program Guidance Manual: Chapter 48, Bioresearch Monitoring - Human Drugs, Institutional Review Board*). For further information on FDA human subjects research regulations, contact:

Mr. Richard M. Klein
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(301) 443-1382

ii. COMPARING FDA AND DHHS HUMAN SUBJECTS REGULATIONS

The DHHS regulations (45 CFR 46) apply to research involving human subjects conducted by DHHS or supported in whole or in part by DHHS. The FDA regulations (21 CFR 50 and 56) apply to all research involving products regulated by the FDA, including research and marketing permits for drugs, biological products, or medical devices for human use, food and color additives, or electronic products. Federal funds do not need to be involved. When research involving products regulated by the FDA is funded by DHHS, both DHHS and FDA regulations apply. This Section describes significant differences between FDA and DHHS regulations, including departures from the new Federal Policy.

COMPARISON OF REGULATIONS

IRB Regulations

§312.120 (FDA)
§46.101(h) (DHHS)

The FDA regulations provide criteria for accepting foreign clinical studies not conducted under an Investigational New Drug Application (IND). The DHHS regulations allow a department or agency head to determine that if procedures prescribed by a foreign institution afford protections at least equivalent to DHHS regulations, the department or agency head may approve the substitution of foreign procedures. [*See also* 21 CFR 812.1.]

§56.102 (FDA)
§46.102 (DHHS)

FDA definitions are included for terms specific to the type of research covered by the FDA regulations (test article, application for research or marketing permit, clinical investigation). A definition for emergency use is provided. The definition of "IRB approval," added as a result of the Federal Policy, substitutes the term "clinical investigation" for the term "research" used in the

Federal Policy [§56.102(m)]. FDA also adopted the Federal Policy's new wording for the definition of "minimal risk" ("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") [§56.102(i)].

§46.103 (DHHS)

DHHS requires that institutions provide an Assurance of Compliance with human subjects regulations, which is negotiated with OPRR. FDA does not require Assurances of Compliance, but does require that IRBs have written policies and procedures.

§56.104 (FDA)

Unlike DHHS, FDA exempts from prospective IRB review the "emergency use" of a test article in specific situations. FDA added the Federal Policy's new "taste testing" exemption at §56.104(d).

§56.105 (FDA)

FDA provides for sponsors and sponsor-investigators to request a waiver of IRB review requirements (not informed consent requirements). DHHS regulations do not have a similar provision.

§56.108 (FDA)

§46.108 (DHHS)

DHHS requires prompt reporting of unanticipated problems to the Secretary. FDA does not specify that a similar report be made by the IRB to the FDA Commissioner, but that the IRB have and follow written procedures to ensure that such reporting is done by the sponsor and clinical investigator.

§56.109 (FDA)

§46.109 (DHHS)

§46.117(c) (DHHS)

Unlike DHHS, FDA does not provide that an IRB may waive the requirement for signed consent when the principal risk is a breach of confidentiality because FDA does not regulate studies that would fall into that category of research. (Both regulations allow for IRB waiver of documentation of informed consent in instances of minimal risk.)

§56.110 (FDA)

§46.110 (DHHS)

FDA does not include research on behavior or characteristics of groups or individuals such as studies of perception, cognition, game theory, or test development (DHHS activity #9) in its list of research activities that may be reviewed through expedited review procedures, because those types of studies are not regulated by FDA.

§56.114 (FDA)

§46.114 (DHHS)

FDA regulations do not discuss administrative matters dealing with grants and contracts because they are irrelevant to the scope of the Agency's regulation. (Both regulations make allowances for review of multi-institutional studies.)

§56.115 (FDA)

§46.115 (DHHS)

DHHS, but not FDA, requires the IRB or institution to report changes in membership. FDA has neither an assurance mechanism nor files of IRB membership; there is therefore no reason for FDA to be informed about changes in membership.

§56.115(c) (FDA)

FDA may refuse to consider a study in support of a research or marketing permit if the IRB or the institution refuses to allow FDA to inspect IRB records. DHHS has no such provision because it does not issue research or marketing permits.

§§56.120-124 (FDA)

FDA regulations provide sanctions for noncompliance with regulations. There is no parallel DHHS regulation, other than

§46.123, which permits early termination of research support and evaluation of applications and proposals in light of prior noncompliance.

Informed Consent Regulations

§50.3(l)

FDA adopted the Federal Policy's new wording for the definition of "minimal risk" ("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") [§56.102(i)].

§50.23 (FDA)

FDA, but not DHHS, provides explicit guidance for an exemption from the informed consent requirements in emergency situations. The provision is based on a statutory requirement in the Medical Device Amendments of 1976, and may be used in investigations involving drugs, devices, and other FDA-regulated products in situations described in §50.23.

§46.116(c) and (d) (DHHS)

DHHS provides for waiving or altering elements of informed consent under certain conditions. FDA has no such provision because the types of studies that would qualify for waiver or alteration are either not regulated by FDA or are covered by the emergency treatment provisions of §50.23.

§50.25(a)(5) (FDA)

§46.116(a)(5) (DHHS)

FDA explicitly requires that subjects be informed that FDA may inspect the records of the study because FDA may occasionally examine a subject's medical records as they pertain to the study. While DHHS has the right to inspect records of studies it funds, it does not impose the same informed consent requirement because of the infrequency with which the Department actually inspects subject records.

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WAIVER OF IRB REVIEW

FDA regulations allow the agency to waive any of the requirements contained in Part 56 of the regulations (governing IRBs), including the requirement of IRB review, for specific research activities or for classes of research activities otherwise covered by the regulations. Sponsors or sponsor-investigators must apply directly to FDA for such waivers [21 CFR 56.105]. The waiver provision does not apply to informed consent requirements (*see* description, below). [*See also* "Treatment INDs," below.] For emergency situations, the regulations on emergency use of a test article [§56.104, '50.23], rather than waiver of IRB review apply. Even if a waiver from the FDA requirement of IRB review is requested and granted, an institution may still require IRB review of the study.

Requests for a waiver associated with an IND should be submitted to the Division in the Center for Drug Evaluation and Research (CDER) or to the Division in the Center for Biologic Evaluation and Research (CBER) responsible for reviewing the IND. If the identity of the responsible Division is unknown, the waiver request may be sent to:

Mr. William Lampkin
Bioresearch Monitoring Staff
Office of the Associate Commissioner for Regulatory Affairs (HFC-30)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(301) 443-2390

See also FDA Information Sheets: "Waiver of IRB Requirements" and "Emergency Use of an Investigational Drug."

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WAIVER OF CONSENT REQUIREMENTS

Unlike the Federal Policy, FDA regulations do not permit modifications or waivers of the informed consent requirements, except for emergency use of test articles, which are exempt from prior IRB review (*see* description, below). [*See also*, Guidebook Chapter 3, Section B, "Informed Consent."]

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EMERGENCY USE OF A TEST ARTICLE

Emergency use is defined as the use of a test article (*e.g.*, investigational drug or biologic) 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 for the use. The investigator is still required to obtain informed consent under these circumstances.

FDA exempts from IRB review the emergency use of a test article so long as the emergency use is reported to the IRB within five working days of its occurrence. Any subsequent use of the test article is subject to IRB review [21 CFR 50.23; 21 CFR 56.104(c)]. "Subsequent use" means any use of the test article that occurs after its initial emergency use. When an IRB receives a report by a clinical investigator of an emergency use, the IRB must examine each case to assure itself and the institution that the emergency use was justified.

Although 21 CFR 56.104 is designed to permit only a single emergency use of a test article for the treatment of one patient by one physician within an institution, the regulation is not intended to limit the authority of a physician to provide emergency care in a life-threatening situation. Should a situation arise which would require the emergency use of the test article for a second patient, either by the same or a second physician, for the same test article, subsequent emergency use should not be withheld for the purpose of gaining IRB approval. If it appears probable that similar emergencies will require subsequent use of the test article at the institution, every effort should be made either to sign on to the sponsor's protocol or to develop a protocol for future emergency use of the article at the institution. Either of these protocols would need to be prospectively reviewed and approved by the IRB for future use of the test article.

In emergency circumstances, it may not be feasible to obtain informed consent prior to using the test article. The regulations therefore provide an exemption from the informed consent requirement for such situations. Emergencies qualifying for this exemption are defined as: (1) life-threatening situations necessitating use of the test article; (2) where the subject is unable to provide effective consent; (3) there is insufficient time in which to obtain consent from the subject's legal representative; and (4) there is no available alternative method of approved or generally recognized therapy of equal or greater likelihood of saving the subject's life [21 CFR 50.23(a)(1)-(4)].

Special procedures for documenting the infeasibility of obtaining consent apply as follows: The investigator and a physician who is not participating in the clinical investigation must certify in writing the existence of all four conditions listed above before use of the test article [21 CFR 50.23(a)]. If in the investigator's opinion immediate use of the test article is necessary to save the life of the subject and there is insufficient time to obtain the independent determination required by §50.23(a) before using the test article, the investigator is to make his or her own written determinations, then obtain the written review and independent evaluation of a physician who is not participating in the clinical investigation within five working days after the use of the test article [21 CFR 50.23(b)]. The documentation required by either §50.23(a) or §50.23(b) must be submitted to the IRB within five working days after the use of the test article [21 CFR 50.23(c)].

The use of a test article in an investigation designed to be conducted under emergency conditions (*e.g.*, emergency room research) usually does not qualify for the emergency use exemption.

For drug products, contact:

Document Management Reporting Branch (HFD-53)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(301) 443-4320

For biologic products, contact:

Division of Biological Investigational New Drugs (HFN-823)
Center for Biologic Evaluation and Research
Food and Drug Administration
8800 Rockville Pike
Bethesda, MD 20857
(301) 443-4864

(Nights and weekends: (202) 857-8400 - FDA Division of Emergency and Epidemiological Operations)

See also, FDA Information Sheets: "Emergency Use of an Investigational Drug" and "Guidance for the Emergency Use of Unapproved

EXPANDED AVAILABILITY OF INVESTIGATIONAL DRUGS

Treatment Investigational New Drug Exemption (Treatment INDs). The use of investigational drugs is usually limited to subjects enrolled in clinical studies covered by INDs. In 1987, the FDA established new procedures under which promising investigational new drugs may be made available to patients with life-threatening or other serious diseases for which no satisfactory alternative drug or other therapies exist. The purpose of the Treatment IND exemption is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible (before marketing begins) and to obtain additional data on the drug's safety and effectiveness. A Treatment IND is a treatment protocol that is added to an existing investigational new drug application (IND). It allows physicians to treat qualifying patients according to the protocol.

FDA permits Treatment INDs only for drugs that show some promise of therapeutic benefit. Two standards exist: For serious diseases, applications for Treatment INDs must show sufficient evidence of safety and effectiveness to support the use. Ordinarily, this standard means that a drug may be made available for treatment use either during Phase 3 investigations or after all clinical trials have been completed. For immediately life-threatening diseases, the evidence, taken as a whole, must show (*i.e.*, there must be sufficient data reasonably to conclude) that the drug *may be* effective for its intended use in its intended patient population *and* would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury. Under this standard, investigational drugs for treating immediately life-threatening diseases may be made available for treatment use earlier than Phase 3, but ordinarily not earlier than Phase 2 [21 CFR 312.34(a), 312.34(b)(2), and 312.34(b)(3)].

Treatment INDs must be reviewed by an IRB prior to their submission and must comply with the regulations governing informed consent (21 CFR Part 50) and IRBs (21 CFR Part 56) [21 CFR 312.34(c)]. The FDA will, however, consider waiving *local* IRB review for Treatment INDs, if waiver is in the best interests of the subjects and adequate alternative mechanisms for human subject protection are provided (*e.g.*, to avoid duplication when a national review body has already reviewed the Treatment IND). The effect of the FDA waiver is to give permission to the local IRB to forego review; local IRBs may, as a matter of institutional policy, choose to review protocols for which an FDA waiver has been obtained by the sponsor or sponsor-investigator. Note also that if both the FDA and DHHS have jurisdiction over the Treatment IND activities, local IRB review will be required despite the FDA waiver. DHHS regulations apply if: (1) an MPA-holding institution that has agreed to review the research according to DHHS regulations is involved in the research; or (2) the research is supported by a DHHS department or agency [45 CFR 46.101, 45 CFR 46.103].

The sponsor and investigators must also comply with all applicable provisions of 21 CFR Part 312, including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports.

A description of Treatment INDs and the requirements for receiving approval for treatment use is contained in the FDA's *Clinical Investigator Information Sheet* titled "Treatment Use of Investigational Drugs" (May 1989).

Charging for Treatment Use of Investigational Drugs. Ordinarily, sponsors or investigators may not charge for investigational drugs involved in clinical trials. FDA considers the cost of distributing drugs for investigational purposes to be part of the normal cost of doing business (unless the sponsor can show that charging subjects for the cost of the drug is necessary to enable the sponsor to undertake the clinical trial) [21 CFR 312.7(d)(1)]. Treatment use, however, is not part of a clinical trial and is therefore not considered to be a normal cost of doing business. Rather, the Treatment IND was created to encourage drug manufacturers to make potentially lifesaving drugs available before they receive FDA approval. Before charging for investigational drugs, the sponsor must notify FDA in writing in an information amendment submitted under §312.31. FDA may withdraw authorization to charge for treatment use drugs if it finds that the requirements of §312.7 are no longer being met [21 CFR 312.7(d)(4)].

Commencing Treatment Use. Treatment use may begin 30 days after FDA receives the application unless the request is denied by FDA [312.35 (a)]. The required contents of a treatment protocol are provided in 21 CFR 312.35. Once approved for treatment use, the investigational drug may be prescribed by physicians who have been specially designated in the application. The physicians must agree to follow the treatment protocol, keep clinical records, and report adverse drug reactions to the FDA.

The Role of the IRB. The primary responsibility of the IRB in reviewing a Treatment IND is the same as in reviewing any proposed investigation involving human subjects: to determine whether the proposed use exposes the subjects to unreasonable or unnecessary risk, to review the informed consent forms and process, and to monitor the progress of the Treatment IND.

Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications, which have not been proven either safe or effective, in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risk involved. IRBs must ensure that potential subjects are fully aware of the risks involved in participation.

IRBs should also pay particular attention to Treatment INDs in which the subjects will be charged for the cost of the drugs. The question here

is one of equitable selection and the involvement in research of vulnerable populations, particularly economically disadvantaged persons [21 CFR 56.111(a)(3)]. If subjects will be charged for use of the test article, economically disadvantaged persons will likely be excluded from participation. The stated purpose of the Treatment IND exemption is to facilitate the availability of promising new drugs to desperately ill patients while obtaining additional data on the drug's safety and effectiveness. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. IRBs will need to balance this interest against the possibility that unless the sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA approval [See also Guidebook Chapter 3, Section C, "Selection of Subjects," and Chapter 3, Section G, "Incentives for Participation."]

Both the research and ethics communities have expressed concern about the effect of the Treatment IND on the ability of investigators to attract subjects to clinical trials for Phase 3 testing. As one scientist put it, "Why would patients who are sophisticated, demanding, and willing to participate in experiments take a chance on receiving a placebo when they want the active compound?" IRBs should be concerned with the effect that the availability of an investigational drug product outside of a clinical trial will have on the ability of the investigator to recruit study subjects. As already mentioned, the cost of the drugs that sponsors can pass on to subjects under the Treatment IND, but not under a regular IND, will likely have an effect on subject recruitment, particularly since third-party payers usually will not reimburse the cost of investigational drugs. As mentioned above, this disparity raises ethical concerns about the equitable selection of subjects.

In response to these concerns, the FDA has recently revised the "clinical hold" provisions of the Treatment IND regulations to allow FDA to place such investigations on clinical hold if it finds that there is reasonable evidence that the investigation 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" [*Federal Register* 57 (April 15, 1992): 13249, adding paragraph b(4)(i)-(vii) to 21 CFR 312.42]. Also addressing these concerns, the revised regulations allow the FDA to place a Treatment IND on clinical hold if insufficient quantities of the investigational drug exist adequately to conduct both the controlled trial and the Treatment IND, if one or more "adequate and well-controlled investigations" strongly suggest lack of effectiveness, and if another drug (either under investigation or approved) for the same indication and available to the same patient population has demonstrated a better potential risk/benefit balance [21 CFR 312.42(b)(4)(iii-v)].

For Additional Information. The FDA's *Clinical Investigator Information Sheets* provide further useful information, and also describe the differences between a "single patient use" situation (see description, below) and a Treatment IND, and between an "emergency use" situation and a Treatment IND. [See pp. 29-35.]

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Single Patient Use. Another mechanism through which practitioners may obtain investigational drugs for treatment use outside of a controlled clinical trial is what is called a "single patient use." Usually, the patient is in a desperate situation and unresponsive to other therapies, or in a situation where no approved or generally recognized treatment is available. Further, there is usually little evidence that the proposed therapy is useful, but may be plausible on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor under a treatment protocol, or through the FDA, by first obtaining the drug from the sponsor and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment use [21 CFR 312.35]. [See also the FDA's *Clinical Investigator Information Sheet* entitled, "Treatment Use of Investigational Drugs" for more detail.]

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Parallel Track. The FDA has devised another mechanism to make available promising investigational agents as quickly as possible to persons with AIDS and other HIV-related diseases while generating data on the safety and effectiveness of the drug [*Federal Register* 57 (April 15, 1992): 13250-13259]. Under the FDA policy, persons with AIDS and HIV-related diseases who are not able to take standard therapy or for whom standard therapy is no longer effective, and who are not able to participate in ongoing controlled clinical trials, would have access to promising investigational drugs. Recipients of the new drugs would be participants in studies without concurrent control groups to monitor drug safety that are conducted in parallel with the principal controlled investigations. This mechanism of expanded availability is therefore called "Parallel Track."

Parallel Track protocols are accomplished under the Treatment IND mechanism, which is described above, and should be thought of as a subset of the Treatment IND. They are distinguished from Treatment INDs by the amount of evidence of effectiveness required. Treatment INDs may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks, but before marketing approval has been granted. According to the FDA, Parallel Track protocols "might be approved for promising investigational drugs when the evidence for effectiveness is less than that generally required for a Treatment IND" [*Federal Register* 57 (April 15, 1992): 13256]. In other words, Treatment INDs have represented an attempt to move drugs from late Phase 2 into Phase 3, and Parallel Track represents an attempt to move drugs from late Phase 1 into Phase 2, both with the intended purpose of making promising new agents available to persons with life-threatening diseases who cannot participate in controlled clinical trials and for whom there are no satisfactory alternative therapies. In addition, the Parallel Track mechanism is available only for AIDS and other HIV-related diseases, while the Treatment IND is available for a number of serious or life-threatening conditions.

Applications for consideration of experimental therapies for Parallel Track expanded availability must be submitted to the FDA as amendments to existing INDs.

The Role of the IRB. FDA human subjects protections regulations (21 CFR 50 and 56), which apply to all investigational drug studies, and DHHS human subjects protections regulations (45 CFR 46), which pertain to all institutions that receive DHHS support for research involving

human subjects, apply fully to Parallel Track protocols. The Parallel Track policy, however, recognizes the difficulty that would be involved in meeting DHHS's requirements for local IRB review and the negotiation of written Assurances from each organization or individual practitioner involved in the research and not affiliated with an assured institution. While local IRBs retain the option of reviewing the expanded availability side of a Parallel Track protocol, to deal with these difficulties, the Secretary, HHS, will consider, on a protocol-by-protocol basis, waiving the provisions of 45 CFR 46 where adequate protections are provided through other mechanisms. The mechanism established by the FDA to meet this need is a national human subject protections review panel that will provide for patient protection, including approval of consent procedures and documentation, and will also provide for continuing ethical oversight of each Parallel Track protocol.

The FDA regulations also allow for waiver of its IRB requirements, where the FDA determines that waiver is in the best interests of the subjects, and that the national human subjects panel would provide an adequate mechanism for protecting patients. The Commissioner of Food and Drugs will consider requests by sponsors of Parallel Track protocols for waivers of the provisions of 21 CFR 56 dealing with local IRB review. Again, individual institutions retain the option of requiring that their IRBs review Parallel Track protocols when a study is conducted by the institution or its affiliated investigators.

In keeping with FDA and DHHS regulations, local IRBs will continue to review protocols on the controlled clinical trial side of the "parallel track" [*Federal Register* 57 (April 15, 1992): 13259].

One of the primary concerns of IRBs that do review the "noncontrolled" side of a Parallel Track study is the informed consent process. It is vital that participating physicians fully appreciate the importance of obtaining adequate informed consent, that subjects be informed of the of the potential risks and benefits of the investigational drug and of other treatment options in appropriate language to enable the individual patient to make an informed decision, and that the consent document be kept up-to-date with new information regarding toxicity and adverse reactions. The eligibility criteria, both for subjects and physicians, are intended to provide additional protection for individuals against the uncertainties presented by using drugs that are still in the early stages of development. For example, physicians must be familiar with potential adverse effects, willing to instruct patients in the early recognition of these effects, and willing to monitor their patients closely.

Charging for Parallel Track Drugs. Charging for investigational drugs is addressed in the section on Treatment INDs, above.

For further information on the FDA's Parallel Track policy, contact:

Mr. Donald Pohl
Office of AIDS Coordination (HF-12)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel: (301) 443-0104

APPLICABLE LAWS AND REGULATIONS

Waiver of IRB Review

21 CFR 50.23 [Informed consent: Exception from general requirements]

21 CFR 56.104 [Exemptions from IRB requirement]

21 CFR 56.105 [Waiver of IRB requirement]

Emergency Use

21 CFR 50.23 [Informed consent: Exception from general requirements]

21 CFR 104 [Exemptions from IRB requirement]

Treatment INDs

21 CFR Part 50 [Informed consent]

21 CFR Part 56 [Institutional Review Boards]

21 CFR 56.111 [Criteria for IRB approval of research]

21 CFR 312.7(d) [Charging for and commercialization of investigational drugs]

21 CFR 312.34 [Treatment use of an investigational new drug]

21 CFR 312.35 [Submissions for treatment use]

21 CFR 312.42 [Clinical holds and requests for modification]

Federal Register 57 (April 15, 1992): 13249, adding paragraph b(4)(i)-(vii) to 21 CFR 312.42

Single Patient Use

21 CFR 312.35 [Submissions for treatment use]

Parallel Track

Federal Register 57 (April 15, 1992): 13250-13259

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SUGGESTIONS FOR FURTHER READING

A. The Federal Policy

- **Porter, Joan P.** "The Federal Policy for the Protection of Human Subjects." *IRB* 13 (No. 5, September/October 1991): 8-9.
- **U.S. Department of Health and Human Services.** Public Health Service. National Institutes of Health. [Dear Colleague Letter.] *OPRR Reports*, July 16, 1991. Memorandum enclosing the final common rule and summarizing the changes from the 1981 DHHS regulations.

B. Food and Drug Administration Regulations and Policies

- **American Society of Hospital Pharmacists.** "ASHP Guidelines for the Use of Investigational Drugs in Institutions." *American Journal of Hospital Pharmacy* 40 (No. 3, March 1983): 449-451.
- **Annas, George J.** "FDA's Compassion for Desperate Drug Companies." *Hastings Center Report* 20 (No. 1, January/February 1990): 35-37.
- **Edgar, Harold, and Rothman, David J.** "New Rules for New Drugs: The Challenge of AIDS to the Regulatory Process." *The Milbank Quarterly* 68 (Supp. 1, 1990): 111-142.
- **Kessler, David A.** "The Regulation of Investigational Drugs." *New England Journal of Medicine* 320 (No. 5, February 2, 1989): 281-288.
- **Levine, Robert J.** "FDA's New Rule on Treatment Use and Sale of Investigational Drugs." *IRB* 9 (No. 4, July/August 1987): 1-4.
- **Levine, Robert J.** "Institutional Review Boards and Collaborations Between Academia and Industry: Some Counterproductive Policies and Practices." *Circulation* 72 (Supp. I(2), August 1985): 148-150.
- **Mariner, Wendy K.** "New FDA Drug Approval Policies and HIV Vaccine Development." *American Journal of Public Health* 80 (No. 3, March 1990): 336-341.
- **Merigan, Thomas C.** "You Can Teach an Old Dog New Tricks: How AIDS Trials are Pioneering New Strategies." *New England Journal of Medicine* 323 (No. 19, November 8, 1990): 1341-1343.
- **Merz, Beverly.** "Treatment INDs: Promising, Problematic." *Journal of the American Medical Association* 259 (No. 11, March 18, 1988): 1607-1608.
- **Monaco, Grace Powers, and Gottlieb, M. Gail.** "Treatment INDs: Research for Hire?" *Journal of the American Medical Association* 258 (No. 22, December 11, 1987): 3296-3297.
- **Nicklas, Richard A.** "The Investigative Process for New Drugs." *Annals of Allergy* 63 (Part III, December 1989): 598-600.
- **Poikonen, J.; McCart, G.M.; and Veatch, R.M.** "Waivers for Military Use of Investigational Agents." *American Journal of Hospital Pharmacy* 48 (No. 7, July 1991): 1525. Discussion, 1525-1529.
- **Richman, Douglas D.** "Public Access to Experimental Drug Therapy: AIDs Raises Yet Another Conflict between Freedom of the Individual and Welfare of the Individual and Public." *Journal of Infectious Diseases* 159 (No. 3, March 1989): 412-415.
- **Rothman, David J., and Edgar, Harold.** "AIDS, Activism and Ethics." *Hospital Practice*, 15 July, 1991, pp. 135-142.
- **Ryan, Mary Kay; Gold, Lawrence; and Kay, Bruce.** "Research on Investigational New Drugs." In *Human Subjects*

Research: A Handbook for Institutional Review Boards, edited by Robert A. Greenwald, Mary Kay Ryan, and James E. Mulvihill, pp. 91-106. New York: Plenum Press, 1982.

- **Tueting, Patricia.** "Investigational Drugs and Research." *Psychiatric Medicine* 9 (No. 2, 1991): 333-347.
- **Veatch, Robert M.** "Drug Research in Humans: The Ethics of Nonrandomized Access." *Clinical Pharmacy* 8 (No. 5, May 1989): 366-370.
- **Young, Frank E.** "The AIDS Epidemic and Clinical Trials." *Academic Medicine* (November 1989): 660-661.
- **Young, Frank E. et al.** "The FDA's New Procedures for the Use of Investigational Drugs in Treatment." *Journal of the American Medical Association* 259 (No. 15, April 15, 1988): 2267-2270.
- **U.S. Department of Health and Human Services.** Public Health Service. Food and Drug Administration. *Clinical Investigator Information Sheets*, May 1989.
- **U.S. Department of Health and Human Services.** Public Health Service. Food and Drug Administration. *IRB Information Sheets*, February 1989.
- **U.S. Department of Health, Education and Welfare.** Food and Drug Administration. *General Considerations for the Clinical Evaluation of Drugs*. Washington, D.C.: U.S. Government Printing Office, 1977. HEW Publication No. (FDA) 77-3040.

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Chapter II: Regulations and Policies

Institutional Review Board Guidebook

* CHAPTER III * *BASIC IRB REVIEW*

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| <p><u>A. Risk/Benefit Analysis</u></p> <p><u>B. Informed Consent</u></p> <p><u>C. Selection of Subjects</u></p> <p><u>D. Privacy and Confidentiality</u></p> | <p><u>E. Monitoring and Observation</u></p> <p><u>F. Additional Safeguards</u></p> <p><u>G. Incentives for Participation</u></p> <p><u>H. Continuing Review</u></p> |
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Suggestions for Further Reading

A. RISK/BENEFIT ANALYSIS

INTRODUCTION

Risks to research subjects posed by participation in research should be justified by the anticipated benefits to the subjects or society. This requirement is clearly stated in all codes of research ethics, and is central to the federal regulations. One of the major responsibilities of the IRB, therefore, is to assess the risks and benefits of proposed research.

DEFINITIONS

Benefit: A valued or desired outcome; an advantage.

Minimal Risk: A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [Federal Policy § __.102(i)]. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

The definition of minimal risk for research involving prisoners differs somewhat from that given for noninstitutionalized adults. [See 45 CFR 303(d) and Guidebook Chapter 6, Section E, "Prisoners."]

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

OVERVIEW

There are two sources of confusion in the assessment of risks and benefits. One arises from the language employed in the discussion: "Risk" is a word expressing probabilities; "benefits" is a word expressing a fact or state of affairs. It is more accurate to speak as if both were in the realm of probability: *i.e.*, risks and expected or anticipated benefits. Another confusion may arise because "risks" can refer to two quite different things: (1) those chances that specific individuals are willing to undertake for some desired goal; or (2) the conditions that make a situation dangerous *per se*. The IRB is responsible for evaluating risk only in the second sense. It must then judge whether the anticipated benefit, either of new knowledge or of improved health for the research subjects, justifies inviting any person to undertake the risks. The IRB should disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits. [See *also* Guidebook Chapter 5, Section A, "Overview: Social Policy Experimentation."]

IRB CONSIDERATIONS

The IRB's assessment of risks and anticipated benefits involves a series of steps. The IRB must: (1) identify the risks associated with the

research, as distinguished from the risks of therapies the subjects would receive even if not participating in research; (2) determine that the risks will be minimized to the extent possible [see Guidebook Chapter 3, Section A, "Risk/Benefit Analysis," and Chapter 3, Section E, "Monitoring and Observation"]; (3) identify the probable benefits to be derived from the research; (4) determine that the risks are reasonable in relation to the benefits to subjects, if any, and the importance of the knowledge to be gained; (5) assure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits [see Guidebook Chapter 3, Section B, "Informed Consent"]; and (6) determine intervals of periodic review, and, where appropriate, determine that adequate provisions are in place for monitoring the data collected [see Guidebook Chapter 3, Section E, "Monitoring and Observation," and Chapter 3, Section H, "Continuing Review"]. In addition, IRBs should determine the adequacy of the provisions to protect the **privacy** of subjects and to maintain the **confidentiality** of the data [see Guidebook Chapter 3, Section D, "Privacy and Confidentiality"], and, where the subjects are likely to be members of a vulnerable population (e.g., mentally disabled), determine that appropriate additional safeguards are in place to protect the rights and welfare of these subjects. [See Guidebook Chapter 6, "Special Classes of Subjects."] Research to which DHHS regulations apply that involves fetuses or pregnant women, prisoners, or children is governed by special provisions [45 CFR 46 Subpart B, 45 CFR 46 Subpart C, and 45 CFR 46 Subpart D, respectively]. [See also, Guidebook Chapter 6, "Special Classes of Subjects."]

Identification and Assessment of Risks. In the process of determining what constitutes a risk, only those risks that may result from the research, as distinguished from those associated with **therapies** subjects would undergo even if not participating in research, should be considered. For example, if the research is designed to measure the behavioral results of physical interventions performed for therapeutic reasons (e.g., effects on memory of brain surgery performed for the relief of epilepsy), then only the risks presented by the memory tests should be considered when the IRB performs its risk/benefit analysis. It is possible for the risks of the research to be minimal even when the therapeutic procedure presents more than minimal risk. IRBs should recognize, however, that distinguishing therapeutic from research activities can sometimes require very fine line drawing. Before eliminating an activity from consideration in its risk/benefit analysis, the IRB should be certain that the activity truly constitutes therapy and not research.

It is important to recognize that the potential risks faced by research subjects may be posed by design features employed to assure valid results as well as by the particular interventions or maneuvers that may be performed in the course of the research. Subjects participating in a study whose research design involves **random assignment** to treatment groups face the chance that they may not receive the treatment that turns out to be more efficacious. Subjects participating in a **double-masked** study take the risk that the information necessary for individual treatment might not be available to the proper persons when needed. In behavioral, social, and some biomedical research, the methods for gathering information may pose the added risk of invasion of **privacy** and possible violations of **confidentiality**. Many risks of research are the risks inherent in the methodologies of gathering and analyzing data, although the more obvious risks may be those posed by particular interventions and procedures performed during the course of research.

A final potential risk to subjects is the possible long-range effect of applying the knowledge gained through research. For example, information gained about associative memory may enable advertising companies to develop new techniques for encouraging arguably harmful consumer behaviors; associations between race or gender and intelligence may have profound effects on public policy. The regulations specifically provide, however, that IRBs should not consider such effects "as among those research risks that fall within the purview of its responsibility" [Federal Policy § __.111].

The risks to which research subjects may be exposed have been classified as physical, psychological, social, and economic [Levine (1986), p. 42].

Physical Harms. Medical research often involves exposure to minor pain, discomfort, or injury from invasive medical procedures, or harm from possible side effects of drugs. All of these should be considered "risks" for purposes of IRB review. Some of the adverse effects that result from medical procedures or drugs can be permanent, but most are transient. Procedures commonly used in medical research usually result in no more than minor discomfort (e.g., temporary dizziness, the pain associated with venipuncture). Some medical research is designed only to measure more carefully the effects of therapeutic or diagnostic procedures applied in the course of caring for an illness. Such research may not entail any significant risks beyond those presented by medically indicated interventions. On the other hand, research designed to evaluate new drugs or procedures may present more than minimal risk, and, on occasion, can cause serious or disabling injuries.

Psychological Harms. Participation in research may result in undesired changes in thought processes and emotion (e.g., episodes of depression, confusion, or hallucination resulting from drugs, feelings of stress, guilt, and loss of self-esteem). These changes may be either transitory, recurrent, or permanent. Most psychological risks are minimal or transitory, but IRBs should be aware that some research has the potential for causing serious psychological harm.

Stress and feelings of guilt or embarrassment may arise simply from thinking or talking about one's own behavior or attitudes on sensitive topics such as drug use, sexual preferences, selfishness, and violence. These feelings may be aroused when the subject is being interviewed or filling out a questionnaire. Stress may also be induced when the researchers manipulate the subjects' environment - as when "emergencies" or fake "assaults" are staged to observe how passersby respond. More frequently, however, IRBs will confront the possibility of psychological harm when reviewing behavioral research that involves an element of deception, particularly if the deception includes false feedback to the subjects about their own performance. Some examples from the American Psychological Association's guidebook, *Ethical Principles in the Conduct of Research with Human Subjects* (1973), illustrate the kinds of research - and the types of psychological risks - IRBs may encounter:

A social psychologist attached a psycho-galvanometer to subjects (male college students). The participants were

told that the needle would be deflected if they were aroused, and that if the needle deflected when they viewed photographs of nude males, it would indicate latent homosexuality. Then false feedback was given so that the subjects were led to believe incorrectly that they were latent homosexuals. After the experiment, the ruse was explained.

Students in a school of education were told by the experimenter that questionnaires revealed that they were unsuited for the teaching profession, although this was untrue. The expectation was that students with such evaluations would do poorly in their course work because these negative appraisals would lower their self-esteem. Many of the students were upset with the "results" of the questionnaire and considered abandoning the teaching profession.

The work which seems to me to raise ethical questions of the most serious type occurred in a military setting. It involved taking untrained soldiers, disorienting them, placing them in an isolated situation, giving them false instructions, and leading them, as individuals, to believe that they had caused artillery to fire on their own troops and that heavy casualties had occurred. The subjects ran, cried, and behaved in what they could only consider an unsoldierly way, and no amount of debriefing could remove the knowledge that they had done so.

Invasion of privacy is a risk of a somewhat different character. In the research context, it usually involves either covert observation or "participant" observation of behavior that the subjects consider private. [See Guidebook Chapter 3, Section D, "Privacy and Confidentiality."] The IRB must make two determinations: (1) is the invasion of privacy involved acceptable in light of the subjects' reasonable expectations of privacy in the situation under study; and (2) is the research question of sufficient importance to justify the intrusion? The IRB should also consider whether the research design could be modified so that the study can be conducted without invading the privacy of the subjects.

Breach of confidentiality is sometimes confused with invasion of privacy, but it is really a different problem. Invasion of privacy concerns access to a person's body or behavior without consent; confidentiality of data concerns safeguarding information that has been given voluntarily by one person to another. [See Guidebook Chapter 3, Section D, "Privacy and Confidentiality."]

Some research requires the use of a subject's hospital, school, or employment records. Access to such records for legitimate research purposes is generally acceptable, as long as the researcher protects the confidentiality of that information. The IRB must be aware, however, that a breach of confidentiality may result in psychological harm to individuals (in the form of embarrassment, guilt, stress, and so forth) or in social harm (see below).

Social and Economic Harms. Some invasions of privacy and breaches of confidentiality may result in embarrassment within one's business or social group, loss of employment, or criminal prosecution. Areas of particular sensitivity are information regarding alcohol or drug abuse, mental illness, illegal activities, and sexual behavior. Some social and behavioral research may yield information about individuals that could "label" or "stigmatize" the subjects. (e.g., as actual or potential delinquents or schizophrenics). Confidentiality safeguards must be strong in these instances. The fact that a person has participated in HIV-related drug trials or has been hospitalized for treatment of mental illness could adversely affect present or future employment, eligibility for insurance, political campaigns, and standing in the community. A researcher's plans to contact such individuals for follow-up studies should be reviewed with care.

Participation in research may result in additional actual costs to individuals. Any anticipated costs to research participants should be described to prospective subjects during the consent process.

Minimal Risk vs. Greater Than Minimal Risk. Once the risks have been identified, the IRB must assess whether the research presents greater than minimal risk. The regulations allow IRBs to provide **expedited review** of proposals if certain conditions exist (the research must present no more than minimal risk, and the involvement of human subjects must fall into one or more categories approved by DHHS) [Federal Policy § __.110]. Alternatively, when the proposed research presents no more than minimal risk, waiver or modification of consent requirements may be available (if certain other conditions are met) [Federal Policy § __.116(d); note, however: FDA does not provide for waiver of consent requirements].

In research presenting more than minimal risk, potential subjects must be informed of the availability of medical treatment and compensation in the case of research-related injury, including who will pay for the treatment and the availability of other financial **compensation** [Federal Policy § __.116(a)(6); 21 CFR 50.25(a)(6)]. Although institutions are not required to provide care or payment for research injuries, many have procedures for reducing the cost of research-related injuries by providing hospitalization and necessary medical care, at least in emergency situations. A few institutions have formal insurance programs to cover lost income, as well as the direct costs of hospitalization and medical care.

Minimal Risk and Especially Vulnerable Populations. DHHS regulations on research involving fetuses and pregnant women [45 CFR 46 Subpart B], research involving prisoners [45 CFR 46 Subpart C], and research involving children [45 CFR 46 Subpart D] strictly limit research presenting more than minimal risk. **The National Commission for the Protection of Human Subjects** recommended special limitations on research presenting more than minimal risk to persons institutionalized as mentally disabled. For such subjects, the Commission recommended that minimal risk be defined in terms of the risks normally encountered in the daily lives or the routine medical and psychological examination of healthy subjects. IRBs should therefore determine whether the proposed subject population would be more sensitive or vulnerable to the

risks posed by the research as a result of their general condition or disabilities. If so, the procedures would constitute more than minimal risk for those subjects.

These concerns are equally applicable to other subjects. Taking a blood sample or pulling a tooth may represent significant risk to a hemophiliac; outdoor exercises might be dangerous to persons with asthma if the air is polluted or saturated with allergens; modest changes in diet might be dangerous to diabetics; and over-the-counter drugs, normally taken for minor ailments, might pose more than minimal risk to pregnant women. Deciding whether or not research procedures will present more than minimal risk to the proposed subject population is a matter requiring careful consideration and case-by-case review. [See also Guidebook Chapter 6, "Special Classes of Subjects."]

Determination That Risks Are Minimized. Risks, even when unavoidable, can be reduced or managed. Precautions, safeguards, and alternatives can be incorporated into the research activity to reduce the probability of harm or limit its severity or duration. IRBs are responsible for assuring that risks are minimized to the extent possible.

In reviewing any protocol, IRBs should obtain complete information regarding experimental design and the scientific rationale (including the results of previous animal and human studies) underlying the proposed research, and the statistical basis for the structure of the investigation. IRBs should analyze the beneficial and harmful effects anticipated in the research, as well as the effects of any treatments that might be administered in ordinary practice, and those associated with receiving no treatment at all. In addition, they should consider whether potentially harmful effects can be adequately detected, prevented, or treated. The risks and complications of any underlying disease that may be present must also be assessed.

IRBs should determine whether the investigators are competent in the area being studied, and whether they serve dual roles (*e.g.*, treating physician, teacher, or employer in addition to researcher) that might complicate their interactions with subjects. For example, an investigator's eagerness for a subject to continue in a research project (to obtain as much data as possible) may conflict with the responsibility, as a treating physician, to discontinue a therapy that is not helpful or that results in significant adverse effects without countervailing benefit. Likewise, teachers or supervisors who conduct research could (wittingly or unwittingly) coerce student- or employee-subjects into participating. Thus any potential conflicts of interest must be identified and resolved before IRB approval is granted.

Another way for IRBs to meet this responsibility is to assess whether the research design will yield useful data. When the sample size is too small to yield valid conclusions or an hypothesis is imprecisely formulated, subjects may be exposed to risk without sufficient justification. While good research design may not itself reduce or eradicate risks to subjects, poor or faulty research design means that the risks are not likely to be reasonable in relation to the benefits. To help assess the research design, some IRBs include a biostatistician as a member; others consult with statisticians when the need arises. Not all procedures designed to increase the statistical validity of a study may be justified. Procedures, even those included for purposes of good research design, that add disproportionate risks to subjects may be unacceptable. [See Guidebook Chapter 4, "Considerations of Research Design."]

A useful method of minimizing risk is to assure that adequate safeguards are incorporated into the research design. Frequent monitoring, the presence of trained personnel who can respond to emergencies, or coding of data to protect confidentiality are examples. It may be necessary to exclude individuals or classes of subjects (*e.g.*, pregnant women, diabetics, people with high blood pressure) whose vulnerability to a drug or procedure may increase with the risks to them. In certain types of clinical trials, special provisions need to be made for monitoring the data as they accumulate to assure the safety of patients, or to assure that no group or subgroup in a trial is compromised by a less effective treatment. Data monitoring should also be used to ensure that the trial does not continue after reliable results have been obtained. In large-scale drug trials, this often requires establishing a specialized **data and safety monitoring board** or committee to review the incoming data at stated intervals. [See Guidebook Chapter 3, Section E, "Monitoring and Observation," Chapter 4, "Considerations of Research Design," and Chapter 5, Section B, "Drug Trials."]

A subject's symptoms or condition may worsen during the course of a study, and medical problems caused by an adverse reaction to experimental therapy or an unrelated illness may arise. If the study design is such that the investigators do not know which treatment individual subjects are receiving, there should be a mechanism permitting someone else to break the code so that appropriate treatment can be provided to a subject experiencing such difficulty. In a medical emergency, individuals in **single- or double-masked** studies may require treatment by physicians unfamiliar with the research. In such cases, providing the subject with a card or bracelet identifying someone who can provide the necessary information is a wise precaution.

The investigator can often obtain research data from the procedures performed for diagnosis or treatment of a patient's condition, thus avoiding unnecessary risks to the subjects. Research should always be designed to avoid exposing participants to unnecessary risks, particularly if invasive or risky procedures (*e.g.*, spinal tap, cardiac catheterization) are involved.

In behavioral research involving deception or incomplete disclosure, especially if the research may induce psychological stress, guilt, or embarrassment, it is often suggested that subjects be "**debriefed**" after their participation. Debriefing gives the investigator an opportunity to explain any deception involved and to help the subjects deal with any distress occasioned by the research. In rare instances, such debriefing may not be helpful or it may even be harmful. Some subjects may not benefit from being told that the research found them to be willing to inflict serious harm on others, have homosexual tendencies, or possess a borderline personality. Again, the IRB must be sensitive to possible harms, and use good judgment, evaluating the potential risks on a case-by-case basis. [See Guidebook Chapter 3, Section B, "Informed Consent."]

Assessment of Anticipated Benefits. The benefits of research fall into two major categories: benefits to subjects and benefits to society.

Frequently, the research subjects are undergoing treatment, diagnosis, or examination for an illness or abnormal condition. This kind of research often involves evaluation of a procedure that may benefit the subjects by ameliorating their conditions or providing a better understanding of their disorders. Patients and healthy individuals may also agree to participate in research that is either not related to any illnesses they might have or that is related to their conditions but not designed to provide any diagnostic or **therapeutic** benefit. Such research is designed principally to increase our understanding and store of knowledge about human physiology and behavior. Research that has no immediate therapeutic intent may, nonetheless, benefit society as a whole. These benefits take the form of increased knowledge, improved safety, technological advances, and better health. The IRB should assure that the anticipated benefits to research subjects and the knowledge researchers expect to gain are clearly identified.

Direct payments or other forms of **remuneration** offered to potential subjects as an incentive or reward for participation should not be considered a "benefit" to be gained from research. [See Guidebook Chapter 3, Section G, "Incentives for Participation."] Although participation in research may be a personally rewarding activity or a humanitarian contribution, these subjective benefits should not enter into the IRB's analysis of benefits and risks.

Determination That the Risks Are Reasonable in Relation to Anticipated Benefits. Evaluation of the risk/benefit ratio is the major ethical judgment that IRBs must make in reviewing research proposals. The risk/benefit assessment is not a technical one valid under all circumstances; rather, it is a judgment that often depends upon prevailing community standards and subjective determinations of risk and benefit. Consequently, different IRBs may arrive at different assessments of a particular risk/benefit ratio.

Determining whether the risks are reasonable in relation to the benefits depends on a number of factors, and each case must be reviewed individually. An IRB's decision depends not only on currently available information about the risks and benefits of the interventions involved in the research, but also on the degree of confidence about this knowledge. Although information drawn from animal research may be highly suggestive of the risks and benefits to be expected for humans, it is not conclusive (because human responses may differ from those of animals). Similarly, absence of data concerning risks does not necessarily mean that no risks exist.

An IRB's assessment of risks and benefits must also take into account the proposed subjects of the research (*e.g.*, children, pregnant women, terminally ill). [See Guidebook Chapter 3, Section C, "Selection of Subjects."] In addition, IRBs should be sensitive to the different feelings individuals may have about risks and benefits. Some subjects may view surgery (and thus avoiding chronic illness or prolonged medication) as a benefit while others would consider it a significant risk (and instead view chronic medication as a benefit because they can avoid the need for surgery). An elderly person might consider hair loss or a small scar an insignificant risk, whereas a teenager could well be concerned about it. IRB members should remember that their appraisals of risks and benefits are also subjective. Finally, risk/benefit assessments will depend on whether the research: (1) involves the use of interventions that have the intent and reasonable probability of providing benefit for the individual subjects; or (2) only involves procedures performed for research purposes.

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

In research where no direct benefits to the subject are anticipated, the IRB must evaluate whether the risks presented by procedures performed solely to obtain generalizable knowledge are ethically acceptable. There should be a limit to the risks society (through the government and research institutions) asks individuals to accept for the benefit of others, but IRBs should not be overprotective. While the IRB must consider the importance of the knowledge that may result from the research, the IRB's appreciation of that importance may, at times, be limited. If only minimal risks are involved IRBs do not need to protect competent adult subjects from participating in research considered unlikely to yield any benefit.

Disclosure of Risks and Benefits. See Guidebook Chapter 3, Section B, "Informed Consent."

Continuing Review and Monitoring of Data. The Federal Policy requires that IRBs continue to reevaluate research projects at intervals appropriate to the degree of risk but not less than once a year [Federal Policy § __. 108(e)]. Periodic review of the research activity is necessary to determine whether the risk/benefit ratio has shifted, whether there are unanticipated findings involving risks to subjects, and whether any new information regarding the risks and benefits should be provided to subjects. It is important to note that the risk/benefit ratio may change over time. At the time of initial review, the IRB should determine whether an independent **data and safety monitoring board** or committee is required, and should also set a date for reevaluating the research project. The issue of continuing review by the IRB is addressed more fully in Guidebook Chapter 3, Section H, "Continuing Review."

During the course of a study, unexpected side effects may occur or knowledge resulting from another research project may become available. The IRB may then need to reassess the balance of risks to benefits. In light of the reassessment, the IRB may require that the research be modified or halted altogether. Alternatively, special precautions or criteria for inclusion may be relaxed. Between IRB reviews, it is largely the researchers' responsibility to keep the IRB informed of significant findings that affect the risk/benefit ratio. In larger studies or clinical trials, a data and safety monitoring committee may be responsible for keeping the IRB up-to-date. Even isolated incidents of unanticipated adverse reactions must be reported to the IRB. The IRB must then decide whether the research should be modified. In addition, a report from one research activity may sometimes be relevant to the evaluation of another.

Federal policy also requires that investigators inform subjects of any important new information that might affect their willingness to continue participating in the research [Federal Policy § __. 116]. [See Guidebook Chapter 3, Section B, "Informed Consent."]

POINTS TO CONSIDER

1. Are both risks and anticipated benefits accurately identified, evaluated, and described?
2. Are the risks greater than minimal risk? Has the IRB taken into account any special vulnerabilities among prospective subjects that might be relevant to evaluating the risk of participation?
3. If the research involves the evaluation of a therapeutic procedure, have the risks and benefits of the research interventions been evaluated separately from those of the therapeutic interventions?
4. Has due care been used to minimize risks and maximize the likelihood of benefits?
5. Are there adequate provisions for a continuing reassessment of the balance between risks and benefits? Should there be a data and safety monitoring committee?

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B. INFORMED CONSENT

INTRODUCTION

Informed consent is one of the primary ethical requirements underpinning research with human subjects; it reflects the basic principle of **respect for persons**. It is too often forgotten that informed consent is an ongoing process, not a piece of paper or a discrete moment in time. Informed consent assures that prospective human subjects will understand the nature of the research and can knowledgeably and **voluntarily** decide whether or not to participate. This assurance protects all parties C both the subject, whose **autonomy** is respected, and the investigator, who otherwise faces legal hazards. The "proxy consent" of someone other than the subject is not the same as the subject's own consent, although it may be an acceptable substitute when a subject is unable to give informed consent. [See Guidebook Chapter 6, "Special Classes of Subjects."] Federal Policy consent requirements are provided in §§ __.116 and __.117; FDA consent requirements are provided in 21 CFR 50.20-27 and 21 CFR 56.109.

OVERVIEW

The **Nuremberg Code**, developed by the International Military Tribunal that tried Nazi physicians for the "experiments" they performed on unconsenting inmates of concentration camps, was the first widely recognized document to deal explicitly with the issue of informed consent and experimentation on human subjects. The first principle of the code states:

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.

All subsequent codes and regulations, insofar as they pertain to competent, adult subjects, follow these principles closely.

Although the elements of informed consent (*i.e.*, full disclosure, adequate comprehension, voluntary choice) are easy to enumerate, recent empirical studies suggest they are not so easy to achieve. Even the best intentions do not ensure against failures of communication C information may be poorly conveyed or subjects may forget (if indeed they ever understood) that they are involved in a research project. Enhancing the likelihood that informed consent will take place is a challenge to which IRBs should respond with imagination and good judgment. When the proposed research will involve vulnerable subjects or the research design involves incomplete disclosure or deception, the challenges to the IRB are even greater. Certain populations (*e.g.*, children or mentally retarded individuals) may not be able to understand the required information, whereas other populations (*e.g.*, prisoners or institutionalized individuals) are so situated that the voluntariness of their consent may be in doubt. Hospitalized patients, particularly those who are seriously ill or undergoing emergency treatment, may also need special protection. Problems raised by the involvement of some vulnerable populations are discussed in other sections of this Guidebook. [See Chapter 6, "Special Classes of Subjects."]

IRB CONSIDERATIONS

The issues discussed in this section are general IRB considerations regarding informed consent, and they apply generally to the review of research that involves human subjects. Problems surrounding the use of deception or incomplete disclosure are discussed near the end of this section under the headings "Exceptions," "Deception and Incomplete Disclosure," and "Placebos, Randomization, and Double-Masked Clinical

The Regulations. The federal regulations require that certain information must be provided to each subject [Federal Policy § ____.116(a)]:

- (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.

The regulations further provide that the following additional information be provided to subjects, where appropriate [Federal Policy § ____.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.

Investigators may seek consent only under circumstances that provide the prospective subject or his or her representative sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. Furthermore, the information must be written in language that is understandable to the subject or representative. The consent process may not involve the use of exculpatory language through which the subject or representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, sponsor, institution, or agents from liability for negligence [Federal Policy § ____.116].

Adequacy of the Content. One of the IRB's most important activities is evaluating the information to be provided to potential subjects in light of the risks and benefits of the proposed research procedures. Each IRB member brings a different perspective to this review. Certain expert members may be able to correct the technical information or identify omissions in the consent documents provided by the investigators. Other members may add their reactions to the way information is provided or question the adequacy of the information. Whether or not the information is deemed "adequate" depends partly on the impression being conveyed (*e.g.*, whether it is clear that a procedure is to be done for research purposes).

In making a judgment concerning what information should be disclosed in the informed consent process, the IRB should attempt to view the matter from the subject's perspective by asking what facts the subjects might want to know before deciding whether or not to participate in the research. Information could be deemed "material" if it might influence the decision of any reasonable person. For example, the risk of death

from cardiac catheterization might be statistically small, and, therefore, seem unimportant to an investigator, but the risk may loom large for people invited to undergo the procedure for the benefit of others. Research in sensitive areas such as child abuse, illegal activities such as drug or alcohol abuse, or reportable communicable diseases such as HIV, also may pose risks to subjects about which they should be informed. Where the potential for the need to report such information to authorities exists, subjects should be so informed before agreeing to participate in the study. Depending on the circumstances, potential subjects may also feel it is "material" to be informed about additional costs that might arise during the course of the research, the identity of the research sponsor, any circumstances that would make it difficult or dangerous to withdraw from the research, or the amount or kind of inconvenience involved.

Expression. IRBs must ensure that information will be presented to prospective subjects in language they can understand. How well subjects understand that information will vary according to the population from which subjects will be drawn. For example, if all the subjects will be registered nurses, they will probably understand most medical terms, but if the population consists of college students, an intermediate level of understanding can be anticipated. If English is not the subject population's primary language, the explanations and the forms should be translated into the subjects' native language.

The medical terms and complex sentences in oral presentations and consent forms often need to be presented in simpler terms even for the educated layperson. If the prospective subjects include children, persons whose primary language is not English, or populations with the average of a sixth grade education, the IRB should take special care to ensure that both oral presentations and consent forms are comprehensible to all subjects. In these cases, ordinary language should replace technical terms (*e.g.*, upper extremities are better referred to as arms, hematoma as a bruise, venipuncture as taking blood from your arm with a needle, and so forth).

Some IRBs find that their lay members are particularly helpful in suggesting necessary modifications. Others ask members of the proposed subject population (*e.g.*, children, clinic patients) to review consent forms and indicate what parts they do not understand.

In addition, **the informed consent may not contain any exculpatory language:** Subjects may not be asked to waive (or appear to waive) any of their legal rights, nor may they be asked to release the investigator, sponsor, or institution (or its agents) from liability for negligence.

Process. It is essential that IRB members think of informed consent not as a form that must be signed, but as an educational process that takes place between the investigator and the prospective subject. No one can guarantee that another person has understood the information presented; one can only inform prospective subjects as clearly as possible. No one can guarantee that another's choice is voluntary; one can only attempt to remove obvious impediments to free choice by being alert to coercive aspects of the consent procedure. In cases where there is reason for special concern about pressure (*e.g.*, when patients are invited to participate in research conducted by their physician, or when students, military personnel, employees, etc., are asked to participate in research conducted by their supervisors), the IRB may require some form of monitoring (such as the presence of an impartial observer). If the research presents significant risk, or if subjects are likely to have difficulty understanding the information to be provided, the IRB may suggest that investigators employ devices such as audiovisual aids, tests of the information presented, or consent advisors.

Because obtaining informed consent is an educational process, the IRB should do what it can to enhance the prospective subject's comprehension of the information presented. It should consider the nature of the proposed subject population, the type of information to be conveyed, and the circumstances under which the consent process will take place (*e.g.*, manner, timing, place, personnel involved). After answering these questions, the IRB may want to suggest changes in the timing or location of an investigator's first contact with potential subjects, or changes in how others will contact subjects during or following the study. For example, some investigators may plan to release their data to a "data broker" who will in turn make the data available to other researchers. IRBs should review the appropriateness of making the data available in this way, and should ensure that subjects will be informed about who will have access to the data and who might contact them.

Sometimes the information to be imparted to prospective subjects is so complex or possibly disturbing that it may require some time for it to be absorbed and appreciated. In these circumstances, the IRB might suggest that the investigator either present the information and discuss the issues with prospective subjects on more than one occasion, or that a period of time elapse between imparting the information and requesting a signature on the consent form. During this waiting period, prospective subjects might be encouraged to discuss their possible participation with family members, close friends, or trusted advisors. Other approaches to communicating complex information include the use of audio-visual materials and brochures.

Documentation. In most cases the federal regulations require that informed consent be documented [Federal Policy § __.117; FDA regulations 21 CFR 50.27], but they also provide for some important exceptions. Documentation usually involves the use of a written consent form containing all the information to be disclosed and signed by the subject or the subject's legal representative. It should be reiterated, however, that these documents are not substitutes for discussion. The person who signed the consent form must be given a copy as a reference and reminder of the information conveyed. A "short form" may sometimes be used [Federal Policy § __.117(b)(2); FDA regulations 21 CFR 50.27(b)(2)]. The use of a short form means that the information is presented without benefit of a written version of the consent document. Before a short form can be used, the IRB must first review and approve a written summary of what will be presented. Each oral presentation must be witnessed by a third person, who must sign both the consent form and a copy of the written summary of the presentation. A copy of the summary must be provided to those who sign the consent form so that they have the information available for future reference [Federal Policy § __.117(b)(2)].

The IRB may waive the regulatory requirement for written documentation of consent in cases where: (1) the principal risks are those associated with a breach of **confidentiality** concerning the subject's participation in the research (*e.g.*, studies on sensitive topics such as drug abuse or

sexual deviance); and (2) the consent document is the only record linking the subject with the research [Federal Policy § __.117(c)(1)]. Written documentation of consent may also be waived when the research presents no more than **minimal risk** and involves procedures that do not require written consent when they are performed outside of a research setting [Federal Policy § __.117(c)(2); FDA regulations on IRB review, 21 CFR 56.109(c)]. [See Guidebook Chapter 3, Section A, "Risk/Benefit Analysis."]

At institutions that require IRB review of all research involving human subjects (including research exempt from the federal regulations), the IRB may decide to waive consent documentation requirements for research that would be exempt from the federal regulations (*e.g.*, most **survey** and observational research). IRBs taking such an approach should be careful, however, to make sure that the subjects will be provided adequate information about the research. The IRB may decide that, in some cases, subjects should be provided written copies of the information conveyed despite the fact that they are not asked to sign a consent form.

Exceptions. Federal regulations on informed consent specify the information that must be disclosed to prospective subjects [Federal Policy § __.116; FDA regulations on consent, 21 CFR 50.25]. The regulations do permit modifications in the consent procedure, and, under certain circumstances, informed consent may be waived entirely if the research meets certain conditions [Federal Policy § __.116(c)-(d)]. Such modifications and waivers are not allowed under FDA regulations. [*But see* 21 CFR 50.23, which sets out conditions under which the obtaining of informed consent for use of a test article can be deemed infeasible]. Situations in which modification or waiver of consent may be indicated call for careful consideration by the IRB. Decisions to waive informed consent or documentation of informed consent should be clearly documented in the IRB's minutes. [See also Guidebook Chapter 6, Section F, "Traumatized and Comatose Patients."]

The IRB may approve a waiver of some or all of the consent requirements provided that: (1) the research involves no more than **minimal risk** to subjects [see Guidebook Chapter 3, Section A, "Risk/Benefit Analysis"]; (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 they have participated in the study [Federal Policy § __.116(d)]. Most commentators suggest that the IRB also determine whether the knowledge being sought is important enough to justify whatever invasion of privacy may be required either to obtain information about unconsenting (or unaware) subjects or to involve them in research under false pretenses. [See Guidebook Chapter 3, Section D, "Privacy and Confidentiality."]

Under the Federal Policy (but not FDA regulations), if the research is designed to evaluate or demonstrate possible changes in (or alternatives to) provision of benefits or services provided for under federal, state, or local programs, an IRB may approve alteration or waiver of the consent requirements [Federal Policy § __.116(c)]. If the research could not practicably be carried out without the waiver or alteration of the consent requirements, the IRB may approve such a waiver. Both the **National Commission for the Protection of Human Subjects and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research** recommended that such waivers be granted only if subjects will not be denied benefits or services to which they are otherwise legally entitled.

Record Reviews. Sometimes, especially in epidemiological studies, scientists need to review thousands of records to identify appropriate subjects for their study. (Consent is not an issue for record reviews of deceased individuals because federal regulations apply only to research involving living human subjects [Federal Policy § __.102(f)].) It is often difficult, if not impossible, to obtain the permission of everyone whose records are contained in the files. For this preliminary part of the research, IRBs will generally waive the consent requirement if: (1) they are satisfied that the information contained in the files is not particularly sensitive; (2) the investigator has devised procedures to protect the confidentiality of the information to be collected; and (3) the study could not practicably be carried out if consent were required. Some university hospitals notify all incoming patients that their records may be reviewed for research purposes; others provide an opportunity to consent (or refuse to consent) to such use.

Contacting potential subjects to obtain further information is a more sensitive phase of the research. IRBs should consider how the investigator proposes to make the initial contact with potential subjects (*e.g.*, through employer, physician, institution having custody of the records, or directly by the investigator) and what information will be conveyed at that time. [See Guidebook Chapter 3, Section D, "Privacy and Confidentiality," and Chapter 4, Section E, "Epidemiologic Studies."]

In making decisions regarding record reviews and plans for contacting individuals thus identified, IRBs should consider the importance of the research, the extent to which privacy will be invaded, the sensitivity of the information to which the investigators will have access, plans for further contact of the subjects, and the feasibility of obtaining consent from all prospective subjects.

For further discussion of records research, including consent issues, see Guidebook Chapter 4, Section E, "Epidemiologic Studies."

Observation in which Subject's Identity will be Recorded. Behavioral scientists sometimes need to observe the behavior of people who either are not aware that they are being observed or who are unaware that their behavior is being recorded for research purposes. Because subjects might behave differently if they knew they were being observed, researchers may request that the consent requirements be waived (if subjects must be unaware of their involvement, they will not have the opportunity to consent or refuse to participate in the research). Videotaping of the responses of passersby to staged emergencies (*e.g.*, heart attacks or criminal assaults), observing the interaction between patients and staff in mental hospitals, and studying homosexual activities in public rest rooms are three examples of this kind of study.

In the first case, the subjects have no knowledge of (and, therefore, have not consented to) the presence of an observer or recording equipment. When the behavior observed may be embarrassing, or when the staged conditions are stressful, this kind of study poses ethical problems for the investigator and the IRB. In the second example, although the patients and staff of the mental hospital may be aware that someone is observing their behavior, they may not be aware of why they are being observed. In the study, "On Being Sane in Insane Places," social scientists

disguised themselves as mental patients and made important observations of the behavior patterns of both patients and staff in mental hospitals. This kind of research presents ethical problems, because the subjects might not consent to the pseudo-patient's presence if they were aware of the real purpose.

In the "Tea Room Trade" study, a social scientist adopted the role of "watch queen" (*i.e.*, lookout) for homosexuals engaged in sexual acts in public rest rooms. Although his subjects obviously knew of his presence, they did not know (at least until after publication of his results) that they were being studied. The unwitting subjects also did not know that the investigator recorded their license plate numbers and searched motor vehicle registration files for their names and addresses. A year later, he disguised his appearance and interviewed these subjects, purportedly for a different kind of study, thus obtaining information about their family and social life. Commentators have suggested that the subjects would neither have consented to the researcher's presence in the rest room nor responded to his later survey questionnaire had they known his real purpose.

The "Tea Room Trade" study raises many of the same ethical questions as the other two examples, but the problems are compounded because the investigator identified the subjects, and, through further deception, obtained possibly private information about their family and social life. (Identifying the subjects placed them at risk of serious legal, social, and economic harm since the behavior being studied was illegal.)

The last two studies illustrate another sensitive problem IRBs must consider when reviewing research involving covert observation. Although consent requirements can be waived if the IRB determines that the knowledge to be gained is important, this decision can easily be influenced by the extent to which IRB members approve of either the subject matter or what they expect may be the findings of the research. IRB members should guard against the inclination to approve or disapprove research based upon their personal feelings about the possible outcome of a research proposal. Drawing the line between judgments about the social or scientific value of a particular study and personal attitudes towards the subject matter of that study is admittedly difficult. IRB members should try to distinguish between qualms they may have about the subject matter (*e.g.*, homosexuality or drug abuse) and qualms they may have about the research methods (*e.g.*, covert observation, staged events, and so forth).

Deception and Incomplete Disclosure. Sometimes, particularly in behavioral research, investigators plan to withhold information about the real purpose of the research or even to give subjects false information about some aspect of the research. This means that the subject's consent may not be fully informed. For example, to discover whether certain kinds of background music are more distracting than others in a learning situation, an investigator might recruit subjects and explain that certain aspects of learning and memory are being studied. If the research is to be conducted, some of the consent requirements must be waived. Subjects would be told that they would be required to learn sets of words and then be tested on how well they remember those words, but they would be deceived about the purpose of the research and certain elements of the study design.

A contrasting example, much discussed in the literature, is the Milgram study of obedience. Subjects of this study were told that, as part of a learning study, they were to give electric shocks each time a "student" made an error in learning. Although they consented to participate in a study of learning, they were unwittingly involved in a study of their own obedience and willingness to inflict pain. Subjects were told about the true nature and purpose of the research after they had participated. This research has been criticized for the emotional stress it caused and the "inflicted insight" provided to the subjects about their own behavior (neither of which they had consented to). Although Milgram's follow-up studies indicated that few if any subjects reported that they had misgivings about participating in the research, many commentators argue that such deception is wrong *per se*. [See Guidebook Chapter 3, Section D, "Privacy and Confidentiality."]

IRBs reviewing research involving incomplete disclosure or outright deception must apply common sense and sensitivity to the problem. They must first decide whether the information to be withheld would influence the decision of prospective subjects about participating in the research. In the case of the research about the effects of background music on learning and memory, this determination would be relatively easy. IRB members might well disagree among themselves, however, about the Milgram study. (Scholars and commentators have disagreed about it for years.) According to the regulations, research should not be permitted at all if the risk to subjects is more than minimal and the subjects are not being informed of things they would consider material to a decision to participate.

In deciding whether to waive or alter consent requirements, IRBs must consider the risks to which subjects will be exposed. To receive a waiver of consent requirements, the study must present no more than minimal risk. Further, the waiver must not adversely affect the rights and welfare of subjects, and must be essential to the ability to carry out the research.

A final condition for waiving some or all of the elements of informed consent is that, whenever appropriate, subjects will be given additional pertinent information after they have participated in such a study. The IRB must decide if subjects should be **debriefed** either after participating in research unwittingly or after knowingly participating in research that involved some form of deception. It is clear that debriefing is appropriate when it contributes to the subject's welfare (*i.e.*, when it corrects painful or stressful misperceptions, or when it reduces pain, stress, or anxiety concerning the subject's performance). There is greater uncertainty over whether it is appropriate to debrief subjects when such a debriefing could itself produce pain, stress, or anxiety (*i.e.*, IRBs must be concerned with cases where debriefing subjects might harm them but failure to debrief subjects would wrong them).

Further descriptions of risks encountered in research involving deception are included in the discussion of psychological harms in the Guidebook Chapter 3, Section A, "Risk/Benefit Analysis."

Placebos, Randomization, and Double-Masked Clinical Trials. Involving subjects in clinical trials where they may receive a **placebo** instead of the experimental therapy or where they may not be told which of several treatments they will receive could be said to entail an

element of deception. Most commentators now believe that if subjects are told they may receive a placebo, and if the design of the clinical trial is explained to them, no deception is involved.

When the particular therapy a subject receives will be assigned on a scientifically **random** basis, this selection process must be explained to prospective subjects in language they can understand. Merely telling them that the assignment to treatment will be done randomly, mathematically, or by lottery may not be sufficient. Instead, more of an explanation should be given. In a two-arm trial, for example, subjects should be told that there is a 50 percent chance of receiving one of two treatments thought to be beneficial for patients with their particular kind of disease; that one is the standard treatment and the other is the experimental treatment; that the experimental treatment is thought to be at least as good as the standard treatment; and that their physician will not be the person who decides which treatment they receive. If the study involves the use of placebos, subjects should be told the chances of receiving the various possible treatments, including the chance of receiving a placebo.

It is important that prospective subjects understand that a **double-masked** design means that neither they, their physicians, nor the investigators treating and evaluating them will know which treatment they have received. If it is important to the research design that neither the investigators nor the subjects know about developing trends in the data, the fact that such developments will not affect their assignment during the course of the study should be communicated to prospective subjects prior to enrollment. [See Guidebook Chapter 4, "Considerations of Research Design."]

Subjects should understand that although they may withdraw from the study at any time, they will not be given any information about which treatment(s) seem to be better or worse until the study is completed. The significance of developing trends in the data has played an important role in placebo trials involving experimental AIDS drugs. When sufficient data showed the drug AZT to be effective in slowing the progress of the disease, the status of subjects receiving the placebos was revealed, and they were offered the drug. Continued provision of placebos once the experimental drug was shown to be effective was considered unethical. IRBs should consider the relevance of developing trends in the data to continued consent.

In double-masked clinical trials, there should be a mechanism for someone other than the investigator to break the code to discover which treatment a particular subject has been given in case the subject experiences a worsening of his or her condition or an adverse effect that requires medical intervention. This procedural safeguard should also be explained to prospective subjects.

Consent as a Continuing Process. Consent is not a single event; rather, it is a process. Since subjects always retain the right to withdraw from a research project, their continuing consent is important. IRBs should be aware that subjects often seem to forget they are involved in research or have difficulty distinguishing research interventions from diagnostic and therapeutic interventions. When a research proposal is first approved, the IRB should determine whether consent should be renegotiated as a formal matter during the course of the research. If renegotiation is required, the frequency and/or events that will trigger this process should be decided upon and made clear to the investigators.

Federal policy also requires that investigators inform subjects of any important new information that might affect their willingness to continue participating in the research [Federal Policy § __. 116]. For instance, a totally independent study might find an unanticipated adverse effect (e.g., birth defects or carcinogenicity) in a drug or substance being used in research. IRBs should determine whether any new findings or reports of adverse effects (in the present study or other studies) should be communicated to subjects. The IRB should also receive copies of any such information conveyed to the subjects.

When the proposed subjects are seriously ill, or, for some other reason, might not be able to make decisions about continuing in the research (e.g., children or cognitively impaired individuals), the IRB may suggest that family members be closely involved with the research to evaluate its impact on the subject and to request that the subject be withdrawn from the study if conditions warrant.

POINTS TO CONSIDER

1. Do the investigators plan to involve a particularly vulnerable subject population?
2. Do the proposed explanations of the research provide an accurate assessment of its risks and anticipated benefits? Is the possibility (or improbability) of direct benefit to the subjects fairly and clearly described?
3. Is the language and presentation of the information to be conveyed appropriate to the subject population? (Consider the level of complexity and the need for translation into a language other than English.)
4. Are the timing of and setting for the explanation of the research conducive to good decision making? Can anything more be done to enhance the prospective subjects' comprehension of the information and their ability to make a choice?
5. Who will be explaining the research to potential subjects? Should someone in addition to or other than the investigator be present?
6. Should subjects be reeducated and their consent required periodically?
7. Should the IRB monitor incoming data to determine whether new information should be conveyed to participating subjects? How often

should this occur? Who is responsible for bringing new information to the attention of the IRB between scheduled reviews?

8. If a waiver of some or all of the consent requirements is requested, does the importance of the research justify such a waiver? Is more than minimal risk involved? Can the research design be modified to eliminate the need for deception or incomplete disclosure? Will subjects be given more information after completing their participation? Would the information to be withheld be something prospective subjects might reasonably want to know in making their decision about participation?

APPLICABLE LAWS AND REGULATIONS

Federal Policy for the protection of human subjects
Federal Policy § ____.116 [General requirements for informed consent]
Federal Policy § ____.117 [Documentation of informed consent]
21 CFR 50 [FDA: Informed consent]
21 CFR 50.20 [FDA: General requirements for informed consent]
21 CFR 50.23 [FDA: Exception from general requirement]
21 CFR 50.25 [FDA: Elements of informed consent]
21 CFR 50.27 [FDA: Documentation of informed consent]
21 CFR 56 [FDA: IRB review and approval]

Local laws: Federal requirements for informed consent do not necessarily meet all the requirements of local laws. Therefore, IRBs should be aware of any state and local requirements regarding informed consent.

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C. SELECTION OF SUBJECTS

INTRODUCTION

Defining the appropriate group of subjects for a research project involves a variety of factors - requirements of scientific design, susceptibility to risk, likelihood of benefit, practicability, and considerations of fairness. IRBs are required to make a specific determination that the selection of subjects is **equitable** [Federal Policy § ____.111(a)(3)].

OVERVIEW

The requirement for an equitable selection of subjects helps ensure that the burdens and benefits of research will be fairly distributed. When the **National Commission for the Protection of Human Subjects** recommended that IRBs be required to make this determination, they noted that questions of equity have only recently been associated with scientific research. In the 19th and early 20th centuries, the burdens of research fell largely upon poor patients in hospital wards, while the benefits flowed primarily to private patients. This inequity was starkly revealed in the Tuskegee syphilis study, in which disadvantaged blacks in the rural south were recruited for studies of the untreated course of a disease that was by no means confined to that population. Such unjustified overutilization of certain segments of the population led the National Commission to recommend that selection of research subjects be scrutinized to determine "whether some classes (*e.g.*, welfare patients, 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."

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

Prisoners and patients in mental institutions are confined under the strict control of people whom they must please and to whom they must appear cooperative and rational if they are to earn their release. These potential subjects may believe, probably as a result of their dependent situation, that agreeing to participate in research will be viewed positively by their wardens, psychiatrists, or social workers. They are also readily available in large numbers, and, therefore, have historically been involved as subjects of drug research that is totally unrelated to the basis of their confinement. Mental patients and prisoners have accepted the risks of research in disproportionate numbers, while the benefits of the research in which they participated went to all segments of the population. This situation led the National Commission to suggest that investigators be required to justify any proposed involvement of hospital patients, other institutionalized persons, disproportionate numbers of racial or ethnic minorities, or persons at the lower end of the socioeconomic scale.

Patients may also be susceptible to real or imaginary pressure to participate. If an investigator also serves as a patient's primary physician, he or she may feel obliged to participate in the research out of a desire to please, gratitude, or fear that failure to do so will result in hostility or abandonment. Patients who are dependent upon a particular facility for their care (*e.g.*, Veterans Hospitals, Indian Health Service Hospitals, or community health clinics) may feel that they will be treated less well or with less favor if they refuse to participate in research.

With these caveats in mind, investigators and IRBs must be careful not to *overprotect* vulnerable populations so that they are excluded from participating in research in which they wish to participate, particularly where the research involves therapies for conditions with no available treatments (such as HIV). So too, patients with serious or poorly understood disorders may want to participate frequently in research designed to provide a better understanding of their condition. The fact that the subject may be either a patient of the principal investigator or a patient in the clinic or hospital where the investigator conducts the research should not preclude them from the opportunity to choose to participate as often as they wish. [See Guidebook Chapter 6, "Special Classes of Subjects."]

Just as the inclusion of disproportionate numbers of racial or ethnic minorities in research studies might overburden these groups without affording them the benefits that will result from the research, so will underrepresentation of these groups in study populations ensure that they will not benefit from the research. The National Institutes of Health (NIH) requires that its research grantees include minorities and women in study populations "so that the research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study." If a proposed project includes a study population in which women and minorities are not appropriately represented, the investigator must provide "a clear compelling rationale for their exclusion or inadequate representation" [Application for PHS Grants, form PHS 398, pp. 21-22, and NIH Requests for Proposals (RFPs)]. See Guidebook Chapter 6, Section B, "Women," and Chapter 6, Section I, "Minorities," for further discussion of this issue.

IRB CONSIDERATIONS

The **National Commission** recommended that, as a matter of social justice, there should be an order of preference in the selection of classes of subjects: adults before children, competent individuals before incompetent individuals, and noninstitutionalized persons before institutionalized persons. In addition, the Commission believed that those who are already burdened (*e.g.*, by disabilities or institutionalization) should not be asked to accept the burdens of research unless other appropriate subjects cannot be found (*i.e.*, if the research concerns their particular disability or circumstance). IRBs should consider the extent to which a proposed subject population is already burdened by poverty, illness, poor education, or chronic disabilities in deciding whether they are a suitable subject population.

When determining whether the burdens of research are being distributed equitably, it is appropriate for an IRB to consider more than the risks associated with the research procedures. It may be appropriate to consider such things as inconvenience (*i.e.*, the time required, travel involved, restrictions on diet, or other activities), discomfort, and embarrassment as burdens of participating in research.

To encourage a broad cross-section of research subjects, IRBs might consider the manner in which subjects will be recruited. Will notices appear only on the bulletin boards of the psychology department or the medical school? Will investigators personally recruit subjects only in community health clinics? If a new treatment is available only in the research context, and it is a scarce resource (in that only a small proportion of those who could benefit from the therapy can be accepted as research subjects), the IRB should try to devise procedures to ensure that subjects from a variety of locations and circumstances have an equal chance of being selected. This becomes particularly important when the intervention is a life-saving procedure (*e.g.*, organ transplant or germ-free environment).

IRBs should consider means for reducing the pressures on certain classes of subjects to participate in research. Patients should be reassured during the consent process that no benefits to which they are otherwise entitled, and no care or concern on the part of the health care providers, will be jeopardized by a decision not to participate in research. In cases where the principal investigator is the potential subject's physician, the IRB might find it preferable for someone other than the physician-investigator to discuss participation with the potential subject or to solicit the patient's consent. In other cases, the possibility of pressure may be reduced by consulting beforehand with representatives of the proposed subject group.

Some IRBs have guidelines that prohibit professors from soliciting their students as subjects and supervisors from including their employees in research. A scientist's proposal to involve students, technicians, and junior members of the laboratory in his or her research should be examined with care. The line between protecting the vulnerable and being unduly **paternalistic** is difficult to draw. This is one of the IRB's recurrent challenges. But avoiding the use of a group of subjects repeatedly on the grounds of mere convenience must not prevent free and **competent** adults from volunteering to be subjects of research as often as they wish.

Those who accept the risks or burdens of being research subjects should be the ones who share in its benefits whenever possible. One group of subjects should not be asked always to bear the risks of research for the benefit of others. Those who have participated as research subjects should have the first opportunity to receive a therapy that the research has demonstrated to be safe and effective (*e.g.*, subjects of clinical trials who were either in a control group or recipients of a therapy that proved not to be superior should be offered the treatment that the trial demonstrated to be preferable). The study design should provide for the adequate representation of women and minorities in the study population so that the findings will be meaningful for those groups and they can, therefore, share in the benefits of the research. Adequate representation of women and minorities is particularly important in studies of diseases, disorders, and conditions that disproportionately affect them. Note that risk/benefit assessments are relevant to subject selection [see, *e.g.*, Guidebook Chapter 5, Section B, "Women"].

POINTS TO CONSIDER

1. Will the burdens of participating in the research fall on those most likely to benefit from the research?
2. Will the solicitation of subjects avoid placing a disproportionate share of the burdens of research on any single group?

3. Does the nature of the research require or justify using the proposed subject population?
4. Are there any groups of people who might be more susceptible to the risks presented by the study and who therefore ought to be excluded from the research? Are the procedures for identifying such individuals adequate?
5. To the extent that benefits to the subjects are anticipated, are they distributed fairly? Do other groups of potential subjects have a greater need to receive any of the anticipated benefits?
6. To the extent that participation in the study is burdensome, are these burdens distributed fairly? Is the proposed subject population already so burdened that it would be unfair to ask them to accept an extra burden?
7. Will any special physiological, psychological, or social characteristics of the subject group pose special risks for them?
8. Would it be possible to conduct the study with other, less vulnerable subjects? What additional expense or inconvenience would that entail? Does the convenience of the researcher or possible improvement in the quality of the research justify the involvement of subjects who may either be susceptible to pressure or who are already burdened?
9. Has the selection process *overprotected* potential subjects who are considered vulnerable (e.g., children, cognitively impaired, economically or educationally disadvantaged persons, patients of researchers, seriously ill persons) so that they are denied opportunities to participate in research?
10. If the subjects are susceptible to pressures, are there mechanisms that might be used to reduce the pressures or minimize their impact?

APPLICABLE LAWS AND REGULATIONS

Federal Policy § .111(a)(3) [Criteria for IRB approval of research]
21 CFR 56.111(a)(3) [FDA: Criteria for IRB approval of research]

NIH policy concerning inclusion of women and minorities in study populations. *NIH Guide for Grants and Contracts* 20 (No. 32, August 23, 1991): 1-3. The policy also appears in the application packet for PHS Grants, form PHS 398, pp. 21-22, and in NIH Requests for Proposals (RFPs).

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D. PRIVACY AND CONFIDENTIALITY

INTRODUCTION

The possibility that research may invade the privacy of individuals or result in a breach of confidentiality sometimes arises in biomedical and behavioral research. Under certain circumstances, an invasion of privacy or breach of confidentiality may even present a risk of serious harm to subjects (e.g., as when the researcher obtains information about subjects that would, if disclosed by the researcher, jeopardize their jobs or lead to their prosecution for criminal behavior). Under less dramatic circumstances, an invasion of privacy or breach of confidentiality can be a moral wrong, or, at least in theory, provide cause for legal action against a researcher or institution.

Privacy can be defined in terms of having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. Confidentiality pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others in ways that are inconsistent with the understanding of the original disclosure without permission.

Privacy and Research. In the context of research, concerns about privacy pertain primarily to the methods used to obtain information about subjects. Objections to the nature of information being sought in research are sometimes couched in the language of privacy (*i.e.*, that it would be an invasion of a subject's privacy even to inquire about certain matters of a personal nature). IRBs are often reluctant to accept these arguments, which tend to preclude research on such topics. In any event, the issue of whether there may be harm in asking certain questions is less a matter of privacy than one of risks versus benefits, and is, therefore, not discussed in this Section.

Researchers ordinarily use information that subjects have disclosed or provided voluntarily for research purposes (*i.e.*, with their informed consent). Under these circumstances, there is little reason for concern about privacy, other than to assure that appropriate confidentiality of research data is maintained. Where privacy issues do arise is in regard to information obtained for research purposes without the consent of subjects. Although serious privacy questions arise with relatively few protocols reviewed by IRBs, the questions that do arise can involve difficult and subjective judgments about matters of propriety.

Concerns about the privacy interests of research subjects may arise in several different contexts.

Privacy Issues in the Use of Personally Identifiable Records. Identifying suitable subjects often presents no ethical problems. Physicians studying a particular disease may be able to identify subjects from among their own patients, and the sociologist interested in studying people who have recently been married can identify their subjects through public records. Privacy concerns may arise when potential subjects cannot be identified from public records or from sources to which the researcher's work provides access.

To identify suitable subjects, researchers must sometimes approach institutions (*e.g.*, hospitals or schools) seeking information generally regarded as confidential (*e.g.*, the identity of patients treated for a particular condition or students meeting a particular criterion). In some circumstances, the researcher needs information that would make it possible to contact suitable subjects to obtain further data. In other circumstances, no contact with subjects is contemplated because the information to be obtained from the records is sufficient (or will be combined with data from other sources). In these cases, personal identifiers may not need to be recorded by the researchers, or, if recorded, can be destroyed at some stage of the research. All of these factors are relevant to IRB assessments of privacy and confidentiality issues in research.

When patients give information about themselves to a doctor or hospital for the purpose of facilitating diagnosis or treatment of disease, they do so in a relationship of trust. They generally expect that the information will be shared only as necessary for their health care or reimbursement by their insurance company or other third party payer; patients would not expect information that identifies them to be passed on in casual conversations at cocktail parties or made available to journalists or to university students writing papers. Nor do they necessarily intend that the information will be shared with even their closest family members. Health care providers should respect the patient's trust. They should not betray the confidence placed in them. (The same may be said of educators with regard to students, and of employers with regard to employees.) Yet such confidences are not absolute; patient records are commonly used for a variety of purposes other than the care of a particular patient *C* for the management of the organization through quality assurance programs and for utilization review. To say that an organization has an obligation to keep certain patient information confidential does not resolve the question of what uses are appropriate for those records.

Clearly, some important research cannot be conducted unless an investigator gains access to many records (sometimes thousands). In epidemiological studies, scientists may seek to determine, for example, whether certain industrial or environmental contaminants are associated with an increase in birth defects or deaths from cancer. In their search they might wish to review thousands of hospital or employment records to identify infants born with a defect, patients suffering from a particular form of cancer, or workers exposed to a particular substance. Without access to such records, an investigator cannot identify potential subjects or match the relevant records. [*See Guidebook Chapter 4, Section E, "Epidemiologic Studies."*]

It is not possible to specify precisely when an institution should honor a researcher's request to examine records or when an IRB should approve this potential invasion of privacy. In 1977, the Privacy Protection Study Commission concluded that medical records can legitimately be used for biomedical or epidemiological research without the individual's explicit authorization, provided that the medical care provider maintaining the record:

- (i) determines that such use or disclosure does not violate any limitations under which the record or information was collected;
- (ii) ascertains that use or disclosure in individually identifiable form is necessary to accomplish the research or statistical purpose for which use or disclosure is to be made;
- (iii) determines that the importance of the research or statistical purpose for which any use or disclosure is to be made is such as to warrant the risk to the individual from additional exposure of the record or information contained therein;
- (iv) requires that adequate safeguards to protect the record or information from unauthorized disclosure be established and maintained by the user or recipient, including a program for removal or destruction of identifiers; and
- (v) obtains consent in writing before any further use or redisclosure of the record or information in individually identifiable form is permitted.

The **National Commission** endorsed this recommendation, and concluded that in studies of documents, records, or pathological specimens where the subjects are identified, informed consent may be waived if the IRB determines that the subject's interests are adequately protected and the importance of the research justifies the invasion of privacy. Unless otherwise required by the head of the department or agency funding or conducting the research, federal regulations (exc

stated; this is one of many areas in which IRBs must exercise common sense and sound judgment.

Observational Studies. Of all the methods used to locate suitable subjects and obtain data, covert observation and participant observation are especially likely to raise concerns about privacy. Covert observation includes the use of concealed devices to record information for later analysis (e.g., tape recording conversations or videotaping personal interactions) and concealment of the researcher (e.g., behind a one-way mirror) as the behavior of subjects is observed and recorded. In participant observation, the researcher assumes a role in the setting or group being studied. When the purpose of these methods is to gain access to information not ordinarily available to "outsiders," questions of privacy arise. (Similar issues about obtaining information not intended to be disclosed can be raised about many other forms of research that involve deception.)

Several factors may be relevant to an IRB's evaluation of such privacy questions. One is the extent to which the behavior in question is public. Covert observation of public behavior (e.g., observing pedestrians on the street) raises little if any concern about privacy; concealed observation of people in their homes would be quite another matter. Some behavior that occurs in public places may not really be public behavior if the individuals involved have a reasonable expectation of privacy. Research involving covert recording of conversations in public parks or filming of activities in public rest rooms clearly raises invasion of privacy questions. Observational studies in quasi-public places (e.g., hospital emergency rooms or state mental hospital wards) may also raise such concerns.

A question sometimes raised about the use of covert observation in research is whether an ethical issue exists if the subjects never become aware of the invasion of privacy. That is, if subjects are never aware that their behavior has been observed or recorded for research purposes, they can hardly feel embarrassed, guilty, or that their rights have been violated. On the other hand, it can be argued that an invasion of privacy is wrong, whether or not the subjects are ever aware of it. In some cases, subjects may inadvertently learn of their involvement in the research, perhaps when the study is published, and feel that they have been harmed.

Most observational research, except that involving children and minors, is exempt from federal regulations. For studies involving adults, current regulations require IRB review only for the most risky observational investigations—those in which two conditions exist: (1) the observations are recorded in a manner that allows the subjects to be identified, directly or through identifiers linked to them; and (2) the observations recorded, if they became known outside the research, could reasonably place the subject either at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or reputation [Federal Policy § __.101(b)(2)]. Clearly, in such studies one of the IRB's major concerns should be to determine if it is necessary to record information in a way that entails such risk, and, if so, whether the provisions for maintaining confidentiality of the data are adequate. Observational research involving children and minors must be reviewed by the IRB unless the research involves observations of public behavior when the investigator(s) do not participate in the activities being observed; IRB review is also required where the two conditions described above obtain (i.e., identifiers will be recorded and the observations could place the subjects at risk).

Confidentiality of Research Data. A major set of concerns about confidentiality pertains to the methods used to ensure that information obtained by researchers about their subjects is not improperly divulged. Perhaps because the creation and handling of confidential records is routine in medical institutions, discussions of confidentiality as a special ethical responsibility of researchers have been more prominent in the social sciences than in the biomedical sciences. Nevertheless, the need for confidentiality exists in virtually all studies in which data are collected about identified subjects. It is in the interest of researchers and essential to the conduct of research on sensitive topics that researchers be able to offer subjects some assurance of confidentiality. These assurances should be given honestly, which sometimes requires the researcher and the IRB to make explicit provisions for preventing breaches of confidentiality.

In most research, assuring confidentiality is only a matter of following some routine practices: substituting codes for identifiers, removing face sheets (containing such items as names and addresses) from survey instruments containing data, properly disposing of computer sheets and other papers, limiting access to identified data, impressing on the research staff the importance of confidentiality, and storing research records in locked cabinets. Most researchers are familiar with the routine precautions that should be taken to maintain the confidentiality of data. More elaborate procedures may be needed in some studies, either to give subjects the confidence they need to participate and answer questions honestly, or to enable researchers to offer strong, truthful assurances of confidentiality. Such elaborate procedures may be particularly necessary for studies in which data are collected on sensitive matters such as sexual behavior or criminal activities.

In studies where subjects are selected because of a sensitive, stigmatizing, or illegal characteristic (e.g., persons who have sexually abused children, sought treatment in a drug abuse program, or who have tested positive for HIV), keeping the identity of participants confidential may be as or more important than keeping the data obtained about the participants confidential. In such instances, any written record linking subjects to the study can create a threat to confidentiality. Having the subjects of these studies sign consent forms may increase the risk of a breach of confidentiality, because the consent form itself constitutes a record, complete with signature, that identifies particular individuals of the group studied. The Federal Policy allows IRBs to waive the requirement for the investigator to obtain a signed consent form where it will be the only record linking subjects to the research, and where a breach of confidentiality presents the principal risk of harm that might result from the research [Federal Policy § __.117(c)]. FDA regulations allow IRBs to waive the signed consent form requirement only when the research presents no more than minimal risk and involves procedures that do not normally require consent when performed outside the research context [21 CFR 56.109(c)]. If both FDA regulations and the Federal Policy apply to a protocol, the IRB must meet the requirements of both. In this instance, documentation of informed consent can be waived only if the consent form is the sole record linking subjects to the research, the research involves minimal risk, breach of confidentiality is the principal risk of harm and the procedure involved in the research is one that does not normally require consent when performed outside the research context. (Note that the foregoing waiver provisions apply to documentation of informed consent and not waiver of the requirement to obtain informed consent.)

Where data are being collected about sensitive issues (such as illegal behavior, alcohol or drug use, or sexual practices or preferences) protection of confidentiality consists of more than preventing accidental disclosures. There have been instances where the identities of subjects or research data about particular subjects have been sought by law enforcement agencies, sometimes under subpoena, and with the threat of incarceration of the uncooperative researcher. Under federal law (and some state laws), researchers can obtain an advance grant of confidentiality that will provide protection even against a subpoena for research data [Public Health Service Act §301(d)]. Although regulations implementing §301(d) are not in place as of this writing, the PHS has issued an Interim Policy Statement [also called the "Interim Guidance" (May 22, 1989)] that sets forth PHS policy exercising its authority to grant certificates of confidentiality. Section 301(d) extends to "biomedical, behavioral, clinical, or other research" an earlier authority (in '303 of the Public Health Service Act) that was available only for "research on mental health, including research on the use and effect of alcohol and other psychoactive drugs."

To take advantage of §301(d), the investigator must request a grant of confidentiality from the appropriate official. Protection for research on mental disorders or the use and effects of alcohol and other psychoactive drugs can be obtained from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), or the National Institute of Mental Health (NIMH), which, in 1991, became components of NIH. Certificates of confidentiality for biomedical, behavioral, clinical, or other research that does not fall into these categories are issued by the Assistant Secretary for Health. Protection is available for: (1) direct federal activities (*i.e.*, intramural research); (2) federally-funded activities; and (3) research in the United States that has no federal funding. Under the Interim Policy, protection will be granted "sparingly," and only "when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives." The Policy defines "sensitive" research as involving the collection of information falling into any of the following categories:

- (a) Information relating to sexual attitudes, preferences, or practices;
- (b) Information relating to the use of alcohol, drugs, or other addictive products;
- (c) Information pertaining to illegal conduct;
- (d) Information that if released could reasonably be damaging to an individual's financial standing, employability, or reputation within the community;
- (e) Information that would normally be recorded in a patient's medical record, and the disclosure of which could reasonably lead to social stigmatization or discrimination;
- (f) Information pertaining to an individual's psychological well-being or mental health.

Information in other categories, not listed here, might also be considered sensitive because of specific cultural or other factors, and protection can be granted in such cases upon appropriate justification and explanation.

Additional policy considerations apply to research that involves the collection of data that relates to communicable diseases. The Assistant Secretary for Health has, therefore, issued a further PHS policy on the granting of certificates of confidentiality to projects that "intend routinely to determine whether its subjects have communicable diseases and that are required to report them under State law" [Memorandum, James O. Mason, "Certificates of Confidentiality-C Disease Reporting," August 9, 1991]. Certificates will be issued: (1) where the referring treating physicians assure the project that they have complied with reporting requirements; or (2) where there is no referring physician, the investigator has reached an agreement with the health department about how he or she will cooperate with the department to help serve the purposes of the reporting requirements (unless the investigator can show why such cooperation is precluded); and (3) only where disclosures of identifiable information about subjects comply with regulations on subject protection and are explained clearly to subjects prior to their participation.

For further information concerning PHS certificates of confidentiality under '301(d) of the Public Health Service Act and the Interim Guidance, contact:

Ms. Olga Boikess
National Institute of Mental Health
17C-02 Parklawn Building
5600 Fishers Lane
Rockville, MD 20857
Tel: (301) 443-3877

In addition to certificates of confidentiality available under §301(d), the U.S. Attorney General is authorized to grant protection for research concerning drug abuse under the Controlled Substance Act. For more information write to the Drug Enforcement Administration, 14501 I St., N.W., Washington, D.C. 20537.

For studies in which the data to be obtained concern illegal or stigmatizing activities but which are not eligible for these statutory shields against subpoena, careful attention should be given to a series of decisions related to confidentiality: (1) whether the researcher will record subject identifiers at all (including on consent forms); (2) if identifiers are to be collected, whether they will be retained after the data are coded; (3) if identifiers are not destroyed, how are they to be maintained; and (4) what subjects should be told about these matters as part of the informed consent process. Some researchers enlist a third party (sometimes in another country) to act as a custodian of keys to coded identifiers or lists of participants. This approach may provide some protection for the data, but may expose the researcher to legal risks. Where such steps

are contemplated, investigators should seek competent legal advice regarding the advisability of such arrangements.

Clearly, different types of studies entail different confidentiality problems. A variety of methods for protecting confidentiality are available for different situations, including situations in which there is a danger of deductive identification of otherwise anonymous subjects on the basis of separate elements of data (e.g., birthdate, occupation, and zip code). A substantial and highly specialized literature has developed on methods for safeguarding confidentiality. Among the available methods for assuring confidentiality are statistical techniques and physical or computerized methods for maintaining the security of stored data. The more sensitive the data being collected, the more important it is for the researcher and the IRB to be familiar with the state of the art in protecting confidentiality.

IRB CONSIDERATIONS

Privacy. In reviewing some protocols, an IRB may have to consider whether an invasion of privacy is involved. No ready and clear criteria are available for evaluating this question. IRBs must base decisions on their members' sense of propriety and the particular circumstances of the study. Among the relevant factors are: the private nature of the information sought, the likelihood the subjects would regard the release of information as an invasion of privacy, the importance of the research, and the availability of alternative ways to do the study.

Much research in which privacy concerns may be relevant will not necessarily come to the attention of the IRB. Under federal regulations, IRBs need not even review proposed research involving observation unless someone (e.g., the investigator or department head) determines that it falls in the category of research that requires IRB review, as discussed above [Federal Policy §-- __.101(b)(2)]. Some institutions review all observational research, as a matter of policy, to ensure that the IRB sees those few protocols for which review is required. Although the Federal Policy exempts from IRB review most research involving access to existing records, data, and surgical and diagnostic specimens, some institutions require review of the protocols to assure that the information is sought for a legitimate purpose and that research involving a record of individually identifiable information receives regular IRB review.

Investigators sometimes want access to existing records to identify people suitable for inclusion in a study. If the subjects' names will be recorded by the investigator for follow-up (either for further record reviews or for personal contact), this research requires IRB review. In such instances, the IRB must determine whether the consent of subjects should be sought (e.g., by the institution holding the records) before the researcher gains access to the records. Factors to consider in deciding if consent must be sought include the sensitivity of the information to be reviewed, the vulnerability of the subject population, and the purpose for which the investigator wants access to the information. The Buckley Amendment [the General Education Provisions Act (20 USC 1232)] requires parental consent for release of records or identifiable information about children in public schools; instructional materials to be used in connection with any research or experimental program must be open to inspection by the parents or guardians of the children to be involved.

Protection of Confidentiality. When information linked to individuals will be recorded as part of the research design, IRBs should assure that adequate precautions will be taken to safeguard the confidentiality of the information. Sensitive information is sometimes obtained in the course of behavioral research, research with the cognitively impaired, AIDS research, and research dealing with drug and alcohol abuse. Various specialized security methods have been developed to maintain the confidentiality of such information. IRBs that review research in which confidentiality of data is important should have at least one member (or consultant) familiar with the strengths and weaknesses of the different mechanisms available, including the statutory shields against subpoena that are available. IRBs should also be aware of the regulatory provision for waiving documentation of consent when a signed consent form would itself constitute a risk to the subjects [Federal Policy § __.117(c)(1)].

Finally, IRBs should be aware that federal officials have the right to inspect research records, including consent forms and individual medical records, to ensure compliance with the rules and standards of their programs. FDA rules require that information regarding this authority be included on the consent forms for all research regulated by that agency; the Federal Policy, which applies to DHHS, and FDA regulations require that subjects be informed of the extent to which confidentiality of research records can be maintained [Federal Policy § __.116(a)(5); 21 CFR 50.25(a)(5)]. Identifiable information obtained by federal officials during such inspections is protected by the provisions of the Privacy Act of 1974.

POINTS TO CONSIDER

1. Does the research involve observation or intrusion in situations where the subjects have a reasonable expectation of privacy? Would reasonable people be offended by such an intrusion? Can the research be redesigned to avoid the intrusion?
2. If privacy is to be invaded, does the importance of the research objective justify the intrusion? What if anything, will the subject be told later?
3. If the investigators want to review existing records to select subjects for further study, whose permission should be sought for access to those records (the physician, the institution maintaining the records, the subjects)? How should the subjects be approached (through their physician, the medical records department, the institution)?
4. Will the investigator(s) be collecting sensitive information about individuals? If so, have they made adequate provisions for protecting the confidentiality of the data through coding, destruction of identifying information, limiting access to the data, or whatever methods that may be appropriate to the study? If the information obtained about subjects might interest law enforcement or other government agencies to the extent

that they might demand personally identifiable information, can a grant of confidentiality be sought from a federal or state agency to protect the research data and the identity of the subjects from subpoena or other legal process?

5. Are the investigator's disclosures to subjects about confidentiality adequate? Should documentation of consent be waived in order to protect confidentiality?

APPLICABLE LAWS AND REGULATIONS

The Public Health Service Act [§301(d)] permits the Secretary, HHS, to authorize persons conducting biomedical and behavioral research to protect the privacy of subjects, even against subpoena. Persons so authorized may not be compelled to testify in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Regulations that predate §301(d) and that are used for guidance in implementing '301 (d) for research relating to mental health (including alcohol and drug abuse) are published at 42 CFR 2A. The "Interim Policy Statement" on protection of identity of research subjects dated May 22, 1989, sets forth the policy of the PHS in accordance with §301(d).

The Controlled Substance Act (21 USC 872) permits the U.S. Attorney General to authorize persons conducting educational or research programs concerning drug abuse to withhold the names and other identifying characteristics of the subjects of such research. This provision is implemented by FDA regulations published at 21 CFR 1315.21.

The Buckley Amendment to the General Education Provisions Act (20 USC 1232) requires parental permission for access to records or identifiable information of children in public schools.

The Privacy Act of 1974 [5 USC 552(a)] prohibits federal agencies from disclosing records maintained in a system of records to any person, with certain exceptions, or other agency except upon a written request by, or with the prior written consent of, the individual to whom the record pertains.

The Freedom of Information Act (5 USC 552) exempts information such as medical or personnel records the disclosure of which would constitute a clearly unwarranted invasion of personal privacy from mandatory release by federal agencies.

Federal Policy § ____.101(b)(2) [To what does this policy apply?]

Federal Policy § ____.101(b)(4) [To what does this policy apply?]

Federal Policy § ____.115(a)(5) [IRB records]

Federal Policy § ____.116(a)(5) [General requirements for informed consent]

Federal Policy § ____.117 [Documentation of informed consent]

21 CFR 50.25 [FDA: Elements of informed consent]

21 CFR 50.27 [FDA: Documentation of informed consent]

21 CFR 56.109(c) [FDA: IRB review of research]

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E. MONITORING AND OBSERVATION

INTRODUCTION

One of the areas to be reviewed in proposed research is the researcher's plan for collection, storage, and analysis of data. Monitoring of the research by the researcher is important because preliminary data may signal the need to change the research design, change the information presented to subjects, or even to terminate the project before the scheduled end date.

Both the timing and adequacy of the plan for analysis are important. If the data are not analyzed until the project is terminated, the chance to make mid-course corrections is lost. If the data are not properly analyzed, the research itself is not valid, and proper conclusions may not result.

DEFINITIONS

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

Review: The concurrent oversight of research on a periodic basis by an IRB. In addition to the at least annual reviews mandated by the federal regulations, reviews may, if deemed appropriate, also be conducted on a continuous or periodic basis [Federal Policy § ____.108(e)].

IRB CONSIDERATIONS

For an IRB to approve proposed research, the protocol must, when appropriate, include plans for monitoring the data collected to ensure the safety of subjects [Federal Policy § ____.111(a)(6)]. Investigators sometimes misinterpret this requirement as calling for annual reports to the

IRB so that the IRB can monitor the project. In fact, however, § ____.111 requires that, when appropriate, researchers must provide the IRB with a description of their plans for analyzing the data during the collection process. Concurrent collection and analysis enables the researcher to identify flaws in the study design early in the project. At this point, researchers are to reevaluate the risks to human subjects to assure that they are no greater than initially predicted.

Like other considerations, the level of monitoring in the research plan should be related to the degree of risk posed by the research. Furthermore, where the research will be performed at foreign sites, the IRB at the United States institution may want to require different monitoring and/or more frequent reporting than that required by the foreign institution. [See also Guidebook Chapter 3, Section A, "Risk/Benefit Analysis," and Chapter 6, Section K, "International Research."]

IRBs should assure themselves that the progress of clinical trials will be adequately monitored to determine if information generated from them (or other related trials) should be passed on to the subjects, affect recruitment of subjects, change the ratio of risks and benefits, or lead to modification or discontinuation of the treatments being evaluated. Under normal circumstances, it is neither necessary nor desirable for the IRB itself to undertake data monitoring. Because investigators may have strong interests in continuing a clinical trial, however (*e.g.*, to obtain a higher level of statistical significance to ensure publication of the results), it is important that other, independent persons be responsible for monitoring trials and for decisions about modification or discontinuation of trials. It is the IRB's responsibility to ensure that these functions are carried out by an appropriate group. The review group should be required to report its findings to the IRB on an appropriate schedule.

Many trials, especially multicentered or double-masked studies, have independent data monitoring boards that fulfill this function. The primary responsibility of these monitoring boards is to safeguard human subjects by analyzing accumulating data relevant to risks and benefits on a regular basis. Especially in long-term trials, where patient enrollment or follow-up occurs over a long period of time, the boards review data periodically to assess effectiveness and toxicity. They must decide if and when the data are sufficiently favorable to one treatment that the study should be ended, which sometimes occurs sooner than the investigators had planned. Similarly, monitoring boards must decide whether adverse effects are serious enough to warrant termination of the trial [Federal Policy § ____.113]. [See also Guidebook Chapter 3, Section E, "Monitoring and Observation."]

IRBs may want to monitor not only the collection of data but also the informed consent process. The IRB should not delegate the monitoring of the informed consent process to others.

Finally, the regulations also require periodic IRB reviews of research [Federal Policy § ____.109(e)]. Periodic IRB review is discussed in the Guidebook in Chapter 3, Section H, "Continuing Review."

POINTS TO CONSIDER

1. How will the research data be recorded and maintained?
2. Considering the degree of risk, is the plan for monitoring the research adequate in terms of timeliness and thoroughness?
3. If the principal investigator is other than full-time on the project, is the oversight and monitoring time sufficient?
4. Is there a mechanism for providing information to the IRB in the event that unexpected results are discovered? (Unexpected results may raise the possibility of unanticipated risks to subjects.)
5. Does the institution have a data and safety monitoring board? If so, should it be asked to monitor the project under review? If the institution does not have a data and safety monitoring board, should the IRB request or recommend that one be appointed, either by the institution or the sponsor, for this project?

APPLICABLE LAWS AND REGULATIONS

Federal Policy § ____.111(a)(6) [Criteria for IRB approval of research]

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F. ADDITIONAL SAFEGUARDS

INTRODUCTION

The protection of human subjects is the paramount consideration of the IRB. Each project should be reviewed to determine whether some or all of the subjects are likely to be vulnerable to coercion or undue influence to participate. These vulnerabilities may be subtle but may limit the ability of certain subjects to refuse to participate or to continue to participate in the research. The IRB must assure that due consideration of this issue is addressed in the research plan. Additional safeguards may need to be included in the study to protect the rights and welfare of these subjects.

IRB CONSIDERATIONS

The federal regulations provide that additional safeguards to protect subjects' rights and welfare must be included in any study where "some or all of the subjects are likely to be vulnerable to coercion or undue influence" [Federal Policy § __.111(b)]. Examples of such vulnerable subjects are children, prisoners, pregnant women, mentally disabled persons, and persons who are economically or educationally disadvantaged. Provision of additional safeguards for three of these groups (children, prisoners, and pregnant women) is handled differently by DHHS. The DHHS regulations provide distinct rules (which differ from the Federal Policy) for research involving fetuses, pregnant women, and human in vitro fertilization (45 CFR 46 Subpart B), prisoners (Subpart C), and children (Subpart D).

The consent process must be conducted only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate. Research conditions must also minimize the possibility of coercion or undue influence to give consent.

Persons with acute and/or severe physical or mental illness may be overly compliant with requests to participate in research due to the effects of their illness or due to the prospect of relief from suffering. Clinical studies must be specially designed to assure that patients are able to consent freely. Additional safeguards may include such requirements as the co-consent of relatives, parents, or impartial observers. In acute illness, patients may need to be treated before being entered into research protocols as subjects. This may mean that subjects are sometimes lost to the research protocol.

Occasionally, the institutional setting in which the consent is sought will pose the possibility of coercion. Conducting research at institutions that provide services to subjects may be perceived as implying that continued service is dependent upon participation in the research. Students in the educational setting may be concerned that refusal to participate will affect their grades. These institutional pressures should be addressed in the research design. The protocol must adequately preserve the right to refuse participation. There are many other examples of possible sources of undue influence on subjects. It may not be possible to remove all sources of influence, but the IRB must examine each project to assure the elimination of coercion and minimization of other influences.

The requirement to obtain informed consent should be seen as not only a legal obligation, but also as a moral obligation. The research design must adequately address how informed consent will be obtained and what information will be given to prospective subjects. IRBs must look at the coercion issue in each proposal and insist on experimental designs that protect against undue influence to participate. See Guidebook Chapter 3, Section B for a fuller description of informed consent requirements.

POINTS TO CONSIDER

1. Are recruitment procedures designed to assure that informed consent is freely given?
2. What special safeguards are included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence (*e.g.*, children, prisoners, pregnant women, persons with physical or mental illness, and persons who are economically or educationally disadvantaged)?
3. Does the nature of the disease or behavioral issue to be studied permit free consent?
4. Are any incentives offered for participation likely to unduly influence a prospective subject's decision to participate?
5. Is there an adequate procedure for monitoring the consent process, and should the IRB or its representative observe the process?

APPLICABLE LAWS AND REGULATIONS

Federal Policy § __.111(b) [Criteria for IRB approval of research]

Federal Policy § __.116 [General requirements for consent]

Federal Policy § __.117 [Documentation of informed consent]

45 CFR 46.111(b) [DHHS: Criteria for IRB approval of research]

45 CFR 46 Subpart B [DHHS: Additional protections pertaining to research, development, and related activities involving fetuses, pregnant women, and human in vitro fertilization]

45 CFR 46 Subpart C [DHHS: Additional protections pertaining to biomedical and behavioral research involving prisoners as subjects]

45 CFR 46 Subpart D [DHHS: Additional protections for children involved as subjects in research]

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G. INCENTIVES FOR PARTICIPATION

INTRODUCTION

Each year, thousands of individuals are paid for participating in biomedical and behavioral research funded either by federal departments and agencies or private institutions. Although payments are usually monetary, both patients and normal healthy volunteers may be offered other rewards in lieu of or in addition to money. Free medical care, extra vacation time, and academic rewards (in the form of a grade or a letter of recommendation) are examples of alternative rewards. Regardless of the form of remuneration, the issues for IRBs remain the same. IRBs must consider whether paid participants in research are recruited fairly, informed adequately, and paid appropriately. Taking into consideration the subjects' medical, employment, and educational status, and their financial, emotional and community resources, the IRB must determine whether the rewards offered for participation in research constitute undue inducement.

OVERVIEW

Federal regulations governing research with human subjects contain no specific guidance for IRB review of payment practices. One of the primary responsibilities of IRBs, however, is to ensure that a subject's decision to participate in research will be truly voluntary, and that consent will be sought "only under circumstances that provide the prospective subject...sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence" [Federal Policy § __, 116; 21 CFR 50.20]. Incentives for participation in research are discussed in the FDA's Information Sheet, "Payment to Research Subjects" (February 1989).

Clear cases of coercion (*i.e.*, actual threats) are readily identifiable; it is more difficult to recognize undue inducement. An offer one could not refuse is essentially coercive (or "undue"). Undue inducements may be troublesome because: (1) offers that are too attractive may blind prospective subjects to the risks or impair their ability to exercise proper judgment; and (2) they may prompt subjects to lie or conceal information that, if known, would disqualify them from enrolling — or continuing — as participants in a research project.

IRB CONSIDERATIONS

IRBs must attempt to make sure that prospective subjects realize that their participation is voluntary, and that choosing not to participate will not adversely affect their relationship with the institution or its staff in any way. To make this determination, IRBs should know who the subjects will be, what incentives are being offered, and the conditions under which the offer will be made.

Some institutions have adopted policies regarding the recruitment and payment of volunteers. In general, they attempt to minimize the possibility of coercion or undue influence by requesting that subjects be recruited by open, written invitation rather than by personal solicitation. Institutions try to ensure that the consent document contains a detailed account of the terms of payment, including a description of the conditions under which a subject would receive partial or no payment (for example, what will happen if they withdraw part way through the research).

Determining the appropriateness of the incentive is another matter. For research that requires subjects to undergo only minor inconvenience or discomfort, a modest payment will usually be adequate. Reimbursement for travel, babysitting, and so forth may also be provided. In more complex research projects, IRBs tend to base their assessment on the prevailing payment practices within their institution or general locale. Volunteers are often compensated for their participation according to an established fee schedule, based upon the complexity of the study, the type and number of procedures to be performed, the time involved, and the anticipated discomfort or inconvenience. Standard payments may be established for each tissue or fluid sample collected, depending on the type of sample (blood, urine, or saliva) and the time (day or evening) the sample is to be collected. Alternatively, subjects may be paid an hourly rate or a fixed amount, depending on the duration of the study and whether the study requires admission to research ward. Extra payments are usually provided for a variety of additional inconveniences (*e.g.*, the imposition of dietary restrictions). Payments may vary according to a number of factors, and, therefore, IRBs may need to become familiar with the accepted standards within their community as well as the anticipated discomforts and inconveniences involved in a particular study to judge appropriateness of payments. Some institutions have a ceiling on the amount an individual may earn in any one study or during a given length of time (*e.g.*, per year, per semester).

One of the most perplexing problems for IRBs is how to assess the appropriateness of payment offers for experiments that involve the assumption of risk or significant discomfort. On a practical level, it is probably impossible for an IRB to determine what amount of money or type of reward would unduly influence a particular individual to accept a given degree of risk. Although our society generally accepts the premise that those assuming risk deserve reward, the application of this rule in establishing payment for subjects in biomedical and behavioral experiments is still being debated. The appropriateness of proposed payments is a matter each institution must address in formulating its policies.

IRB members tend to approach the problem of assuming risk for pay from one of two positions. One side argues that normal healthy volunteers are able to exercise free choice, and that, since judging the acceptability of risk and weighing the benefits is a personal matter, IRBs should refrain from imposing their own views on potential subjects. On this view, IRB responsibility should be confined to ensuring that consent is properly informed. Other IRB members argue that the IRB should protect potential subjects from inducements that may affect their ability to make an informed, voluntary choice. It should be noted that, in this context, incentives need not be financial to cause problems. Free health care for persons with limited resources and major medical problems may be a significant inducement to participate in research (even if the research activity is nontherapeutic). There is no consensus as to whether this kind of inducement is unacceptable. In assessing this potential problem, IRBs might consider whether only the destitute agree to volunteer or if people who can obtain good medical care on their own agree to participate as well. IRBs may need to monitor subject recruitment to make such determinations.

POINTS TO CONSIDER

1. Are all conditions in keeping with standards for voluntary and informed consent?
2. Are the incentives offered reasonable, based upon the complexities and inconveniences of the study and the particular subject population?
3. Are there special standards that the IRB ought to apply to the review of research in which volunteers are asked to assume significant risk?
4. Should the IRB monitor subject recruitment to determine whether coercion or undue influence is a problem?

APPLICABLE LAWS AND REGULATIONS

Federal Policy § ____.109(e) [IRB review of research]

Federal Policy § ____.111 [Criteria for IRB approval of research]

Federal Policy § ____.116 [General requirements for informed consent]

45 CFR 50.20 [FDA: General requirements for informed consent]

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H. CONTINUING REVIEW

INTRODUCTION

It would be a mistake to see the IRB approval process as a one-time step in the life of a research project. IRB approval is a temporary authority that may be withdrawn at any time if warranted by the conduct of the research. The regulations authorize the IRB to establish procedures for the concurrent monitoring of research activities [Federal Policy § ____.109(e)]. DHHS and FDA rules require reevaluation of approved research at intervals that are appropriate to the degree of risk [Federal Policy § ____.109(e)]. Periodic review of research activities is necessary to determine whether approval should be continued or withdrawn. All research must be reviewed at least annually.

IRB CONSIDERATIONS

The initial IRB review is based on the researcher's best assessment about anticipated results, risk, and procedures. The IRB uses its expertise to judge whether this estimate is reasonable and supportable. At the time of its initial review, the IRB must determine how often it should reevaluate the research project and set a date for its next review.

The responsibility for continued monitoring of approved research is as important as the initial review and approval. It is only after research has begun that the real risks can be evaluated and the preliminary results used to compute the actual risk/benefit ratio; the IRB can then determine the correctness of the initial judgment. Some IRBs have set up a complaint procedure that allows subjects to indicate whether they believe that they were treated unfairly or that they were placed at more risk than was agreed upon at the beginning of the research. A report form available to all researchers and staff may be helpful for informing the IRB of unforeseen problems or accidents. The IRB may find that scheduled progress reports are an effective means of monitoring some research.

The risk/benefit ratio may change over time. Not only unexpected results and effects of the research project itself, but new knowledge resulting from other research may affect the balance. After reassessment, the IRB may require that the research be modified or halted altogether. The IRB may need to impose special precautions or relax special requirements it had previously imposed on the research protocol.

Federal policy requires that investigators inform subjects of any important new information that might affect their willingness to continue participating in the research [Federal Policy § ____.116(b)(5)]. The IRB should make a determination whether any new findings, new knowledge, or adverse effects should be communicated to subjects. The IRB should receive copies of any such information conveyed to subjects. Any necessary changes to the consent document(s) must be reviewed and approved by the IRB. [See also Guidebook Chapter 3, Section B, "Informed Consent."]

The IRB has the authority to observe, or have a third party observe, the consent process and the research itself [Federal Policy § ____.109(e)]. The researcher is obligated to keep the IRB informed of unexpected findings involving risks and to report any occurrence of serious harm to subjects [Federal Policy § ____.103(b)(5)]. Reports of preliminary data analysis may be helpful to the researcher and the IRB in monitoring the need to continue the project. An open and cooperative effort between the researcher and the IRB protects everyone concerned.

IRBs have the 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 [Federal Policy § ____.113]. If the IRB decides to suspend or terminate its approval of a research project, the IRB shall report its decision promptly to the investigator(s),

appropriate institutional officials, and the department or agency head (or designated office, such as OPRR). The IRB's report must include a statement of the reasons for the suspension or termination.

POINTS TO CONSIDER

1. Are the actual risks and benefits as anticipated?
2. Have any subjects been seriously harmed?
3. Has the IRB been informed of any unforeseen problems or accidents that may have occurred?
4. Should the IRB request that the investigator(s) submit scheduled progress reports?
5. Should the investigator(s) submit progress reports more often than annually?
6. Since the last IRB review, have subjects been informed of any important new information that might affect their willingness to continue participating in the research?
7. Have any new findings, knowledge, or adverse effects come to light that should be, but have not been, communicated to subjects?
8. Does the progress of the project together with the results of other new research indicate that the IRB should either impose special precautions or relax special requirements it had previously imposed?
9. Do the consent documents need to be revised?
10. Has due care been used to reduce risks and increase the likelihood of benefit?
11. Are the procedures agreed upon at the beginning of the research still being used?
12. Does the protocol adequately provide for continuing assessment of the balance between risks and benefits?
13. Should IRB approval be continued, or should approval be suspended or terminated?
14. When should the IRB next review the project (taking into account what has been learned about the actual risk to subjects since the project first received IRB approval)?

APPLICABLE LAWS AND REGULATIONS

Federal Policy § __.103(b)(4)-(5) [Assuring compliance with this policy — research conducted or supported by federal departments or agencies]

Federal Policy § __.109(e) [IRB review of research]

Federal Policy § __.110(b) [Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research]

Federal Policy § __.113 [Suspension or termination of IRB approval]

Federal Policy § __.116(b)(5) [General requirements for informed consent]

Federal Policy § __.117 [Documentation of informed consent]

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*** CHAPTER IV * CONSIDERATIONS OF RESEARCH DESIGN**

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A. INTRODUCTION

The value of research depends upon the integrity of study results. One of the ethical justifications for research involving human subjects is the social value of advancing scientific understanding and promoting human welfare by improving health care. But if a research study is so methodologically flawed that little or no reliable information will result, it is unethical to put subjects at risk or even to inconvenience them through participation in such a study. One question that every IRB member asks is "To what degree is it our responsibility to review the underlying science of the proposed research?" Clearly, if it is not good science, it is not ethical. The federal regulations under which IRBs operate, however, do not clearly call for IRB review of the scientific validity of the research design. Nonetheless, they do require that IRBs determine whether "[r]isks to subjects are reasonable in relation to...the importance of the knowledge that may reasonably be expected to result" [Federal Policy § __.111(a)(2)]. If the underlying science is no good, then surely no important knowledge may reasonably be expected to result.

Left without clear direction on this point, most IRBs appear to take the following approach, which has been described approvingly by Robert Levine (1986, p. 21): Where the investigator conducting the research under review is seeking funding from the federal government or other extramural funding agency, rigorous review of the science is left to the agency's peer review process. The IRB provides a less detailed examination to satisfy itself that there are no obvious flaws that would place subjects at unnecessary risk. Where the protocol will not receive such detailed scientific review, IRBs review the research design with much more care, perhaps with the assistance of consultants, if the IRB itself does not possess sufficient expertise to perform such a review. Levine suggests that IRBs should establish their authority to criticize the scientific merits of protocols and to exercise that authority to require that investigators correct design flaws identified by the IRB before receiving IRB approval, but that IRBs should recognize their limits in this regard as well. [See also Commentary by Levine following McLarty (1987), p. 3.] Benjamin Freedman suggests that research must be both valid and of value [Freedman (1987b)]. Although IRB members do not need to be experts in scientific methodology or statistics, they should understand the basic features of experimental design, and they should not hesitate to consult experts when aspects of research design seem to pose a significant problem.

The purpose of this chapter of the Guidebook is to provide some basic background information on scientific research design, some of the research techniques used by scientists, and some ethical considerations raised by these designs and techniques.

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EXEMPTION FROM IRB REVIEW

The federal regulations provide for exemption from review for certain kinds of research described in this chapter (*e.g.*, reviews of records or surveys) if certain conditions are met, unless: (1) information will be recorded by investigators in such a manner that subjects can be identified directly or through identifiers; and (2) disclosure of subjects' responses could reasonably place the subjects at risk of criminal or civil liability, or be damaging to the subjects' financial standing, employability, or reputation). The exemptions appear at Federal Policy § __.101(b). In

fulfilling the provisions of their institution's Assurance, however, individual IRBs may have policies that require the review of all research involving human subjects, whether or not the research is subject to federal regulation, including research that is exempt from review under the regulations. [See Federal Policy § ___.103(b)(1).] Some Sections in this chapter will describe certain kinds of research as "exempt from IRB review." This exemption refers to research subject to the federal regulations. IRBs should follow the written policies established by their institutions. [See Guidebook Chapter 1, Section A, "Jurisdiction of the Institutional Review Board."]

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RESEARCH METHODOLOGY IN SCIENCE

The pursuit of science is an attempt to understand the physical world; that is, to describe the phenomena that characterize physical reality, and, when possible, to define, predict, and even control the conditions under which these phenomena occur. Basic to scientific inquiry is an acceptance of the philosophical perspectives known as empiricism and determinism. Scientists take for granted that knowledge results from experience and is based on observations of physical events. Moreover, these physical events are assumed to follow physical laws in that they depend upon causal factors that can be discovered.

Scientific understanding, then, must be based on objective, systematic observation of physical events and on analytical reasoning, or inference, that is truly logical. The two adjectives used here, objective and systematic, describe critical characteristics of the observations upon which science is based. Objective observations can be experienced directly and are repeatable, making it possible for scientists to verify each others' work. Systematic observations are obtained under clearly specified, and, where possible, controlled conditions that can be measured and evaluated. Research methodology provides the tools needed to produce objective and systematic observations, called empirical data, and to ensure that inferences based on these observations are grounded in logic.

Scientists develop theories to organize their empirical observations. A theory is a set of principles that attempts to explain the causal factors underlying related scientific observations. The usefulness of any theory depends upon its internal consistency, its ability to account for existing data, and its precision in prediction. Scientists use hypotheses to generate predictions that can be tested empirically. It is important to understand that scientific theories and hypotheses can never be "proven true" but can only be supported (confirmed) or not supported (disconfirmed) by currently available data.

Biomedical investigations can be broadly categorized into two types: experimental studies and descriptive studies. A true experimental study is one in which subjects are randomly assigned to groups that experience carefully controlled treatments manipulated by the experimenter according to a strict logic allowing causal inference about the effects of the treatments under investigation. Descriptive studies, although objective and systematic, lack the rigid control achieved through random assignment of subjects and precise manipulation of treatment conditions. As a result, causal inferences cannot logically be derived from descriptive studies.

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DEFINITIONS

- **Adverse Effect:** An undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention (*e.g.*, headache following spinal tap or intestinal bleeding associated with aspirin therapy). IRBs should establish policies and procedures for monitoring such effects in approved studies.
- **Case-Control Study:** A study comparing persons with a given condition or disease (the cases) and persons without the condition or disease (the controls) with respect to antecedent factors. (*See: Retrospective Studies.*)
- **Clinical Trial:** A controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or devices or of behavioral interventions.
- **Cohort:** A group of subjects initially identified as having one or more characteristics in common who are followed over time. In social science research, this term may refer to any group of persons who are born at about the same time and share common historical or cultural experiences.
- **Control(s):** Subject(s) used for comparison who are not given a treatment under study or do not have a given condition, background, or risk factor that is the object of study. Control conditions may be concurrent (occurring more or less simultaneously with the condition under study) or historical (preceding the condition under study). When the present condition of subjects is compared with their own condition on a prior regimen or treatment the study is considered historically controlled.
- **Correlation Coefficient:** A statistical index of the degree of relationship between two variables. Values of correlation coefficients range from -1.00 through zero to +1.00. A correlation coefficient of 0.00 indicates no relationship between the variables. Correlations approaching -1.00 or +1.00 indicate strong relationships between the variables. However, causal inferences about the relationship between two variables can never be made on the basis of correlation coefficients, no matter how strong a relationship is indicated.
- **Cross-Over Design:** A type of clinical trial in which each subject experiences, at different times, both the experimental and control therapy. For example, half of the subjects might be randomly assigned first to the control group and then to the experimental intervention, while the other half would have the sequence reversed.
- **Data and Safety Monitoring Board:** A committee of scientists, physicians, statisticians, and others that collects and analyzes accumulating data during the course of a clinical trial to monitor for adverse effects and other trends (such as an indication that one treatment is significantly better than another, particularly when one arm of the trial involves a placebo control) that would warrant modification or termination of the trial, or notification of subjects about new information that might affect their willingness to continue

in the trial.

- **Dependent Variables:** The outcomes that are measured in an experiment. Dependent variables are expected to change as a result of an experimental manipulation of the independent variable(s).
- **Descriptive Study:** Any study that is not truly experimental (*e.g.*, quasi-experimental studies, correlational studies, record reviews, case histories, and observational studies).
- **Double-Masked Design:** A study design in which neither the investigators nor the subjects know the treatment group assignments of individual subjects. Sometimes referred to as "double-blind."
- **Ethnographic Research:** Ethnography is the study of people and their culture. Ethnographic research, also called fieldwork, involves observation of and interaction with the persons or group being studied in the group's own environment, often for long periods of time. (*See also: Fieldwork.*)
- **Experimental Study:** A true experimental study is one in which subjects are randomly assigned to groups that experience carefully controlled interventions manipulated by the experimenter according to a strict logic allowing causal inference about the effects of the interventions under investigation. (*See also: Quasi-Experimental Study.*)
- **Fieldwork:** Behavioral, social, or anthropological research involving the study of persons or groups in their own environment and without manipulation for research purposes (distinguished from laboratory or controlled settings). (*See also: Ethnographic Research.*)
- **Historical Controls:** Control subjects (followed at some time in the past or for whom data are available through records) who are used for comparison with subjects being treated concurrently. The study is considered historically controlled when the present condition of subjects is compared with their own condition on a prior regimen or treatment.
- **Human Subjects:** Individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project. Under the federal regulations, human subjects are defined as: living individual(s) about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information [Federal Policy §__.102(f)].
- **Independent Variables:** The conditions of an experiment that are systematically manipulated by the investigator.
- **Longitudinal Study:** A study designed to follow subjects forward through time.
- **Masked Study Designs:** Study designs comparing two or more interventions in which either the investigators, the subjects, or some combination thereof do not know the treatment group assignments of individual subjects. Sometimes called "blind" study designs. (*See also: Double-Masked Design; Single-Masked Design.*)
- **Null Hypothesis:** The proposition, to be tested statistically, that the experimental intervention has "no effect," meaning that the treatment and control groups will not differ as a result of the intervention. Investigators usually hope that the data will demonstrate some effect from the intervention, thereby allowing the investigator to reject the null hypothesis.
- **Open Design:** An experimental design in which both the investigator(s) and the subjects know the treatment group(s) to which subjects are assigned.
- **Placebo:** A chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side effects may reflect imagination or anticipation rather than actual power of a drug.
- **Prospective Studies:** Studies designed to observe outcomes or events that occur subsequent to the identification of the group of subjects to be studied. Prospective studies need not involve manipulation or intervention but may be purely observational or involve only the collection of data. IRBs should note that prospective studies do *not* qualify for exemption under Federal Policy §__.101(b)(4) because the data or specimens in prospective studies are not extant at the time the study begins.
- **Protocol:** The formal design or plan of an experiment or research activity; specifically, the plan submitted to an IRB for review and to an agency for research support. The protocol includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen(s), and the proposed methods of analysis that will be performed on the collected data.
- **Quasi-Experimental Study:** A study that is similar to a true experimental study except that it lacks random assignment of subjects to treatment groups. (*See also: Experimental Study.*)
- **Random, Random Assignment, Randomization, Randomized Conditions, Randomized Trials:** Assignment of subjects to different treatments, interventions, or conditions according to chance rather than systematically (*e.g.*, as dictated by the standard or usual response to their condition, history, or prognosis, or according to demographic characteristics). Random assignment of subjects to conditions is an essential element of experimental research because it makes more likely the probability that differences observed between subject groups are the result of the experimental intervention.
- **Research:** A systematic investigation (*i.e.*, the gathering and analysis of information) designed to develop or contribute to generalizable knowledge [Federal Policy §__.102(d)].
- **Retrospective Studies:** Research conducted by reviewing records from the past (*e.g.*, birth and death certificates, medical records, school records, or employment records) or by obtaining information about past events elicited through interviews or surveys. Case control studies are an example of this type of research.
- **Single-Masked Design:** Typically, a study design in which the investigator, but not the subject, knows the identity of the treatment assignment. Occasionally the subject, but not the investigator, knows the assignment. Sometimes called "single-blind design."
- **Statistical Significance:** A determination of the probability of obtaining the particular distribution of the data on the assumption that the null hypothesis is true. Or, more simply put, the probability of coming to a false positive conclusion. [*See McLarty (1987), p. 2.*] If the probability is less than or equal to a predetermined value (*e.g.*, 0.05 or 0.01), then the null hypothesis is rejected at that significance level (0.05 or 0.01).

B. OBSERVATION

Some behavioral research involves only observation of people in public places (*e.g.*, observing shopping or eating habits). Where the subjects are adults, research of this type is exempt from IRB review unless the information obtained is recorded in such a manner that the subjects can be identified, and the information obtained could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation [Federal Policy § __.101(b)(2)]. For research to which the DHHS regulations are applicable, observational research involving the public behavior of children is also exempt, as long as, in addition to the above criteria, the investigator does not participate in the activities being observed [Federal Policy § __.101(b)(2); 45 CFR 401(b)].

Observational studies that involve intervention in or manipulation of the subjects' environment do require IRB review. For example, an investigator studying reactions to emergencies may want to modify the environment and then observe people's reactions in public places. Some researchers studying this phenomenon have contrived "emergencies" with the help of confederates who pretend to have a heart attack on the subway or to be victims of an assault in a public park. Responses of passersby are recorded. Because there is a risk of inducing a real medical emergency or causing psychological distress in a bystander, such research must be reviewed by an IRB. Similarly, if people are to be observed in places or circumstances in which they have a reasonable expectation of privacy, the research must be reviewed by an IRB.

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C. RECORD REVIEWS AND HISTORICAL STUDIES

Sometimes a study involves only the use of existing public or privately held records. In such a case, an IRB could exempt the study from review, give it expedited review, or subject it to full board review, depending on the nature of the study and the policy of the institution's IRB [Federal Policy §§ __.101(b)(4), __.110, and __.111]. For example, if a researcher wanted to know whether the conviction rates for various violent crimes vary from one part of the country to another he or she could examine public records (*e.g.*, court or police records) in different parts of the country. Variations related to sex, race, age, and so forth could also be studied. Such research, utilizing only information available in public documents, would be exempt from IRB review [Federal Policy § __.101(b)(4)].

On other hand, if a researcher wanted to learn about risk factors (*e.g.*, smoking habits, industrial employment, or family history) related to cancer, he or she might start with medical records. This research would be exempt from review under the federal regulations if the records preexist the start of the research project and if the investigator records the information in such a manner that subjects cannot be identified directly or through identifiers [Federal Policy § __.101(b)(4)]. If, however, such identifiers are to be recorded, the research would require IRB review to ensure that, among other things, procedures for protecting privacy and confidentiality are adequate. Furthermore, the investigator studying cancer risk factors may propose to go on to contact the subjects (if still living) or family members (if the subject is deceased) to gather additional information, which may or may not be subject to the federal regulations. Note, however, that some IRBs review all research involving human subjects, even where the research is exempt under the federal regulations, and that records research that is conducted without the prior consent of the subjects raises **privacy** concerns, which are discussed in the Section on epidemiologic studies, below. [See Chapter 4, Section D, "Surveys, Questionnaires and Interviews," and Chapter 4, Section E, "Epidemiologic Studies."]

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D. SURVEYS, QUESTIONNAIRES, AND INTERVIEWS

Surveys, questionnaires, and interviews are commonly used in social science disciplines such as anthropology, economics, political science, psychology, and sociology. Statistical procedures are used to ensure that the sample interviewed or questioned properly represents the subject population and to estimate measurement and sampling error so that valid and reliable inferences may be drawn about the population surveyed.

Some surveys use interview methods to obtain information directly from individuals. Unlike informal interviews often used in clinical settings or informal surveys, in standardized interviews those interviewed respond to a predetermined set of questions asked by a trained interviewer. The interview instrument (questionnaire) is systematically developed and pretested on a small number of people drawn from the subject population so that any ambiguities or biases in the way the questions are stated can be identified and corrected.

Research involving survey or interview procedures with adult subjects is exempt from the federal regulations unless the information obtained is recorded in such a manner that the subjects can be identified, and the information obtained could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation [Federal Policy § __.101(b)(2)]. Survey and interview research involving children is *not* exempt, but rather requires full IRB review [Federal Policy § __.101(b)(2); 45 CFR 401(b)]. Furthermore, some IRBs review all research involving human subjects, even where the research is exempt under the federal regulations. [See Guidebook Chapter 4, Section E, "Epidemiologic Studies."]

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E. EPIDEMIOLOGIC STUDIES

INTRODUCTION

Epidemiologic studies present several unique problems because they often use sensitive private documents, such as medical records, and link them with other data, such as employment, insurance, or police records. They also often combine historical research with survey and interview techniques. There is some debate in the literature on the question of whether epidemiologic research is exempt from IRB review. [See Guidebook Chapter 1, Section A, "Jurisdiction of the Institutional Review Board."] Nevertheless, epidemiologic studies do present significant problems regarding **privacy** and **confidentiality**, issues that IRBs that do review such research must address. A set of ethical guidelines for epidemiologists has been developed, which IRBs may wish to consult. [See Beauchamp, *et al.* (1991).]

In epidemiologic studies, the investigator is attempting to identify risk factors for particular diseases, conditions, or behaviors, or risks that result from particular causes, such as environmental or industrial agents. The research techniques usually employed involve record reviews to identify potential subjects, followed by telephone or in-person surveys or interviews, or mailed questionnaires. Epidemiologic studies may also be limited to reviews of records from various sources (*e.g.*, medical, employment, and police records), which the investigator links together. The validity of epidemiologic studies requires a very high degree of participation (as much as 90 percent) by potential subjects. The behavioral component of the factors often studied in epidemiologic research means that significant rates of nonparticipation are likely to produce biased findings. IRBs need to balance the need for high participation rates against the ethical concerns raised by epidemiologic research.

The role usually played by IRBs reviewing epidemiologic research is to ensure that epidemiologists:

take adequate steps to preserve the confidentiality of the data they collect, requiring that they specify who will have access to the data, how and at what point in the research personal information will be separated from other data, and whether the data will be retained at the conclusion of the study. IRB reviewers also require a thorough description of interview instruments and questionnaires, and they make sure that the informed consent of subjects will be obtained before interviews are conducted [Wallace (1982), p. 287].

They should also, as they do with other research protocols, require epidemiologists "to justify particular projects according to their anticipated risks and benefits" [*id.*]. With respect to data retention, IRBs should note that other institutional or regulatory policies (*e.g.*, those concerning scientific integrity) may require that data be retained for some period of years.

IRB CONSIDERATIONS

The primary ethical concerns presented by epidemiologic studies are protection of subjects' privacy (*i.e.*, the right "to determine what will be known about oneself") and the confidentiality of data (*i.e.*, the determination that information will not be disclosed without permission) [Wallace (1982), pp. 277, 278]. Privacy concerns in turn raise questions about the role of informed consent. Even where subjects are not at risk of *harm* from epidemiologic research, access to records for which individuals have not consented clearly constitutes an invasion of privacy, a moral *wrong* [Capron (1991)]. The multitude of records that are now kept as a routine part of our daily lives (*e.g.*, medical, employment, insurance, and school records) constitutes a wealth of information, but information in which we have an expectation of privacy. In particular, we expect that the privacy of those records will be maintained, and their contents will be kept confidential. Access to those records without prior consent of the subject raises concerns about the violation of the ethical principle of **respect for persons** (sometimes referred to as **autonomy**).

When a study involves reviews of records without any contact with individuals, it can be argued that the subjects of the research are at no risk of harm, beyond the "wrong" of invasion of privacy, unless their identity is or can be linked to the research records. Such linkage is often used in epidemiological research, in which case IRBs must ensure that subjects' privacy interests will be adequately protected. Some commentators have suggested that those interests should be balanced against the importance of the research; others argue that the right of privacy cannot or should not be overridden by the value of the research. However, the obtaining of prior consent as a means of eliminating the problem of invasion of privacy may, as a practical matter, be impossible. The issue of consent is discussed below and in Chapter 4, Section I, "Identification and Recruitment of Subjects."

Where the investigator will have personal contact with subjects, however, a potential for harm does exist. Since they are identified as potential subjects because they either have or are at risk of developing a disease or condition, simple contact with subjects may present a risk of harm, either because of sensitivity to discussing a disease or condition they know they have, or because they may not be aware of their condition. Where the person with the disease or condition is deceased, investigators may want to contact relatives who may not have been aware of the deceased's condition. The potential for harm is greatest in the early stages of the research, when the investigator is identifying appropriate subjects for study. Once potential subjects are identified, the investigator can obtain their consent to participation in the study.

Consider the case of epidemiologic research into risk factors for HIV infection [human immunodeficiency virus (HIV) is the virus that causes acquired immune deficiency syndrome (AIDS)]. Potential subjects are, by definition, under investigation because of an anticipated relationship to HIV (except for control subjects, who may or may not know which group they are in). Members of known risk groups (*e.g.*, injecting drug users, homosexual males, individuals with hemophilia) may face considerable emotional disturbance by being contacted for an HIV study. In cancer studies as well, potential subjects (or their relatives) may be disturbed by the prospect of discussing their medical condition or experience.

With respect to confidentiality, disclosure of information such as that usually collected in epidemiologic studies also presents an ethical concern that IRBs should address. All information collected as part of a study is confidential: Data must be stored in a secure manner and must not be shared inappropriately. The threat of disclosure of data that can be linked to individuals represents another risk of harm to individuals. In properly designed studies, this risk is insignificant. To maintain this confidentiality, researchers must be prepared to resist subpoenas seeking to

obtain research data. [See Guidebook Chapter 3, Section D, "Privacy and Confidentiality." The section on confidentiality of research data discusses §301(d) of the Public Health Service Act, which provides for protection of research data.] Using HIV as an example again, subjects included in an HIV-related study would be understandably concerned about the confidentiality of the data, since breaches in confidentiality could have severe adverse consequences such as loss of employment or insurance coverage, or criminal charges. OPRR guidance on HIV studies states that:

where identifiers are not required by the design of the study, they are not to be recorded. If identifiers are recorded, they should be separated, if possible, from data and stored securely, with linkage restored only when necessary to conduct the research. No lists should be retained identifying those who elected not to participate. Participants must be given a fair, clear explanation of how information about them will be handled.

As a general principle, information is not to be disclosed without the subject's consent. The protocol must clearly state who is entitled to see records with identifiers, both within and outside the project. This statement must take account of the possibility of review of records by the funding agency.... [OPRR (1984).]

[See also Guidebook Chapter 5, Section F, "AIDS/HIV-Related Research."]

Another question is whether and at what point subjects must consent to epidemiologic research: prior to selection but after first contact, before the first contact, or before gaining access to records (through the custodian of the records). In general, wherever possible, potentially eligible subjects should be contacted either by the person to whom they originally gave the information, by a person with whom they have a trust relationship [McCarthy and Porter (1991), p. 239]. Guidebook Chapter 4, Section I, "Identification and Recruitment of Subjects," describes the various approaches commonly used for obtaining consent at the subject identification stage.

Where identifiers that can be linked to individuals will be used, each subject must provide informed consent prior to participation, except in certain limited circumstances. The federal regulations allow for waiver or alteration of consent requirements under the following conditions: (1) the research involves no more than minimal risk; (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 [Federal Policy § ___.116]. Further, when the study involves the collection of information of a sensitive nature (e.g., sexual or criminal activity), an investigator may request that the requirement to obtain written consent be waived. IRBs 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; 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 [Federal Policy § ___.117].

Commentators on the subject of consent in epidemiologic studies agree that some relaxation of the usual informed consent requirements may be necessary. [See, e.g., Beauchamp, *et al.* (1991), pp. 159s-161s; McCarthy and Porter (1991), pp. 238-39]. Where prior consent to participation in a survey or record review is precluded by the research design, the investigator might use a veto approach, in which the subject can elect not to have his or her data included in the study. [See Capron (1991), p. 86s] It has also been suggested that epidemiologic research conducted without consent should meet four requirements: "(1) the invasion of privacy involved must be necessary to the conduct of the research; (2) the invasion of privacy must involve only a minimal intrusion; (3) the research must additionally present only insignificant risk of specifiable harms to the interests of subjects; and (4) the results of the research must be likely to bring social benefits of a significant nature" [Wallace (1982), p. 280 and ff].

In those cases where informed consent will be obtained, the specific information that the investigator will give a potential subject, both at the time of first contact and in the consent negotiations, should be considered by the IRB. McCarthy and Porter (1991) provide some useful guidance on the information that should be communicated to subjects. They suggest that the information provided to prospective subjects should include descriptions of: the kind of data that will be collected, the identity of the persons who will have access to the data, the safeguards that will be used to protect the data from inappropriate disclosure, and the risks that could result from disclosure of the data. If identifiers will be collected and retained, subjects should be so informed, and should also be told whether they will be contacted again in the future. The investigator should also provide subjects with a written assurance that any publications that result from the research will present the data only in aggregate form, and in such a manner that individuals cannot be identified. Investigators should inform subjects of what information gained from the study will be passed along to them (e.g., the presence of diseases or conditions they may not have known about) [McCarthy and Porter (1991), p. 239].

When epidemiologic research involves particularly vulnerable populations, an IRB should consider seeking the advice of persons sensitive to their concerns [Federal Policy §107(a)]. Such consultation may help the IRB identify and resolve sensitive ethical concerns.

Various writers have also suggested that consent to epidemiological research should be sought from the communities in which the research will be conducted. [See, e.g., McCarthy and Porter (1991), p. 239.] Further, "the size, composition, mixture, and origin of the study population should be chosen with great care to avoid or minimize community or group harms" [p. 240]. [See also Council for International Organizations of Medical Sciences (1991).]

F. CASE-CONTROL STUDIES

One popular type of descriptive study is the case-control study, in which persons with a specific condition (the cases) and persons without the condition (the controls) are selected to participate in the study. The proportions of cases and controls with certain characteristics (*e.g.*, exposure to a particular drug) are then compared.

In the usual case-control study, there is no risk of physical injury since no interventions are performed. Such studies may, however, entail legal risks, where, for instance, a study may reveal illegal drug use; or psychological risks, where the investigation reviews traumatic experiences, such as the loss of a child. IRBs should make certain that the investigator has made adequate provisions to protect **privacy**, assure **confidentiality** of data, and respect the subject's rights (including refusal to participate). Each case-control study should be considered individually by the IRB, since different levels of protection are needed for different studies.

Most case-control studies require investigators to review medical records and interview subjects, or, when subjects are deceased, their next-of-kin. This type of study may require review by the full IRB, which should assure that adequate **informed consent** will be obtained and that the investigator will use a suitable system for contacting subjects. Case-control studies that are limited solely to the review of existing records may be appropriate for **expedited review** or for exemption from review, depending on the nature of the study. [See Federal Policy §§ ___.101(b)(4) and ___.110; see also Guidebook Chapter 4, Section D, "Surveys, Questionnaires and Interviews," and Chapter 4, Section I, "Identification and Recruitment of Subjects."]

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G. PROSPECTIVE STUDIES

A prospective study is designed to observe events (*e.g.*, diseases, behavioral or physiological responses) that may occur after the subjects have been identified. All concurrently controlled clinical trials are prospective.

Longitudinal studies follow one or more subject **cohorts** over an extended period of time. The duration of the study may or may not be specified at the outset of the investigation. For example, several large-scale longitudinal studies whose original purpose was to study children eventually followed their subjects into adulthood, and, later, into old age.

Cohorts in longitudinal studies are sometimes divided into those who have and those who have not been exposed to some risk factor prior to the initiation of the investigation [*e.g.*, a study that follows the occurrence of diseases in workers in a particular industry compared to a group of persons not in that industry (the controls) but matched for age, sex, smoking and drinking habits, and other relevant factors]. The well-known Framingham Study, begun in the 1950s, was designed to monitor the incidence of coronary artery disease in over 5,000 residents who were examined every two years for a period of twenty years. This study has yielded important data demonstrating the relationship between various factors (smoking, obesity, diet, and high blood pressure) and the development of heart disease.

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H. CLINICAL TRIALS

The clinical trial is an important research design used to assess the safety and efficacy of new drugs, devices, treatments, or preventive measures in humans by comparing two or more interventions or regimens. Clinical trials are frequently "multicentered," that is, a number of research institutions may cooperate in a common study **protocol**.

Clinical trials can be used to evaluate most treatments or preventive measures for almost any condition or disease. Clinical trials (sometimes called "randomized clinical trials," or RCTs) are controlled (one subject group receives the treatment under investigation while a control subject group receives either another treatment or no treatment), with participants being randomly assigned to either the subject or control group. They are also either single- or double-masked, so that either the investigator, the subjects or both do not know who is in the treatment or control group until the conclusion of the study.

Randomized clinical trials present numerous ethical issues, some of which are discussed in other Sections of this Guidebook as well as in this Section (*e.g.*, Chapter 4, Section J, "Assignment of Subjects to Experimental and Control Groups.")

A primary ethical concern is one of fairness: If the trial therapy is known to be superior to currently available alternative therapies (*i.e.*, prior research indicates that it is superior), it is unethical to assign subjects to the inferior treatment. Furthermore, it would not be ethical to perform a clinical trial comparing two treatments when there is a third therapy that is known to be superior to either or both, unless there is some reason why that therapy is not useful for the study population. Researchers must therefore honestly be able to state a null hypothesis (also called "theoretical equipoise": the assumption that subjects treated with therapy A - the trial therapy - will not differ in outcome from subjects treated with therapy B - the control therapy) before beginning a randomized clinical trial [Freedman (1987)]. According to a somewhat broader concept called "clinical equipoise," a randomized controlled design may be justified where there is a "current or likely dispute among expert members of the clinical community as to which of two or more therapies is superior in all relevant respects" [Levine, Dubler, and Levine (1991), p. 3, restating Freedman (1987)]. Furthermore, the trial must be designed such that its "successful completion will show which [of the

therapies] is superior" [Freedman (1990), p. 5]. The "results of a successful clinical trial should be convincing enough to resolve the dispute among physicians" [Freedman (1987), p. 144]. The control treatment must be the best standard therapy currently available for the condition being treated [Freedman (1990); Levine (1986), (1985)].

Placebos. Placebos may be used in clinical trials where there is no known or available (*i.e.*, FDA-approved) alternative therapy that can be tolerated by subjects. IRBs should scrutinize studies that propose to use placebos to ensure that subjects are not deceived into believing that they have received an active agent.

Where the disease is lethal or seriously debilitating, however (as in the case of HIV), the use of a placebo control in place of an active control may be, and indeed has been, questioned. The onslaught of HIV has led to considerable discussion of clinical trial design and the need to maximize benefits in every arm of the trial. [See, *e.g.*, Levine, Dubler, and Levine (1991) and Freedman (1990).] A design involving a placebo control should not be used where there is a standard treatment that has been shown to be superior to placebo by convincing evidence [Freedman (1990)]. It has been argued that placebo controls must be used, however, when the experimental treatment is of "dubious efficacy" or when there are known serious side effects [Freedman (1990); Levine (1985), 1986]. The use of placebos in controlled clinical trials must be justified by a positive risk-benefit analysis, and subjects must be fully informed of the risks involved in assignment to the placebo group. There is a consensus that continued assignment of subjects to placebo is unethical once there is good evidence to support the efficacy of the trial therapy. Clinical trials should be stopped or their protocols modified when there is sufficient evidence of either a beneficial therapeutic effect or unacceptable side effects. Monitoring for such information during the course of the trial is discussed in Guidebook Chapter 3, Section E, "Monitoring and Observation."

Some drug trials involve a period during which all subjects receive only a placebo prior to the initiation of the study. This period is called a "placebo washout." The purposes of a washout period include: (1) terminating the effects of any drug the subject may have been taking before entering the clinical trial, so that the effects of the trial drug - and only the trial drug - may be observed; (2) learning whether subjects cooperate with instructions to take drugs ("compliance"); and (3) learning which subjects are "placebo responders," in that they experience a high degree of placebo effect. In some protocols, the investigators plan to exclude those subjects they find either poorly compliant or highly responsive to the placebo. The risks entailed in withdrawing subjects from therapy during a placebo washout period should be carefully evaluated by the IRB; great care must be taken to exclude subjects who are vulnerable to injury if they are withdrawn from effective therapy. In studies involving a placebo washout, subjects should be told that at some point during the study all subjects will receive placebo treatment; investigators but not subjects will know when subjects are receiving placebos for washout purposes, so that during the washout, the study is single-masked.

See also Chapter 4, Section J, "Assignment of Subjects to Experimental and Control Groups."

Informed consent. Informed consent is of particular importance in randomized clinical trials as in all **prospective studies**. The IRB should assure that initial, and, where necessary, continuing consent is obtained from the subjects at critical intervals (*e.g.*, at points where the study protocol is materially altered, new procedures are introduced, new information - about risks or benefits, for instance - becomes available, or toxicity becomes manifest). In such instances, blanket consent at the beginning of the study does not suffice. Because subjects may forget crucial aspects of the trial, it may also be advisable periodically to ascertain continuing consent in long-term studies.

Despite the fact that subjects may be kept unaware of their treatment assignments in "masked" studies and research involving placebos, the information provided to prospective subjects should clearly communicate the nature of the study design, method of treatment assignment (including the probability of assignment to the various groups), possible interventions, and the implications of the possible interventions. Ethical considerations demand that subjects be informed when their assignment will be **random**, and that one of the possible consequences of participation is that the group to which they are assigned will turn out to have received the less effective intervention.

Subjects must be fully informed of the likelihood of receiving the experimental treatment. For example, if there are two subject groups, experimental and control, and the assignment of subjects to groups is random, subjects must be informed that they have a 50 percent chance of receiving the experimental therapy and a 50 percent chance of receiving the alternative treatment. **If the alternative "treatment" is placebo, subjects must be so informed.** Informing subjects that the study involves the use of placebos and the probability of their being assigned to the placebo group eliminates the ethically objectionable element of deception from the study. Further, subjects should be told who will know whether they are receiving the placebo or the active agent. In a double-masked trial, for example, subjects should be told that neither they nor the investigator will know whether they are receiving the placebo or the experimental therapy.

Since assignment to one or another of the interventions should take place after informed consent has been given, the subject must be made aware of all the possible alternative interventions and what is known about the efficacy and safety of each. Prospective subjects should also be told whether participation in the study precludes participation in other programs or therapeutic regimens that may be beneficial to them and the extent to which this restriction presents a risk.

A more fundamental consent question centers on communicating the uncertainties and risks involved in clinical trials to prospective subjects. Particularly in Phase 1 trials, where the safety of therapies in humans is first being tested, IRBs must assure themselves that those risks and uncertainties will be clearly communicated to prospective subjects, and that the process of communication with subjects will continue throughout the study.

A related issue is the selection of subjects. Subjects who are particularly vulnerable, such as persons who are desperately ill, are, perhaps, more likely than others to be willing to accept great risks in the hope that they will benefit from an experimental treatment. IRBs need to ensure that

their welfare is protected by requiring full and open disclosure of risks and benefits, while at the same time avoiding paternalism. Vulnerable subjects should not be precluded from studies solely on the basis of their vulnerability. To do so would preclude them from the opportunity to benefit from the availability of investigational therapies through research studies. [See also Guidebook Chapter 3, Section A, "Risk/Benefit Analysis," Chapter 3, Section C, "Selection of Subjects," Chapter 5, "Biomedical and Behavioral Research," and Chapter 6, "Special Classes of Subjects."]

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I. IDENTIFICATION AND RECRUITMENT OF SUBJECTS

This Section deals specifically with practical aspects of how investigators go about identifying and recruiting individual subjects, and IRB considerations related to these activities. These considerations are especially important in **epidemiologic** research.

See also Guidebook Chapter 3, Section C, "Selection of Subjects," and Chapter 3, Section G, "Incentives for Participation." "Selection of Subjects" deals with the question of equitable selection of subjects in terms of defining the appropriate group of subjects for a research project. "Incentives for Participation" deals in greater depth than the present Section with incentives offered to encourage participation and the ethical concerns of coercion and undue influence.

IRB CONSIDERATIONS

Using Records to Identify Subjects. IRBs are responsible for ensuring the equitable selection of research subjects [Federal Policy § ____ .111(a)(3)]. In fulfilling this responsibility, IRBs should review the methods that investigators use to recruit subjects.

Subjects with specific diseases or conditions are often identified as potential subjects through some type of record (*e.g.*, registries for cancer cases, surgical or X-ray log books, employment or school records). **Controls** may come from the same population as the subjects (which is always the case in a randomized clinical trial), be persons with unrelated conditions or be volunteers from the general population. Potential subjects may be identified through records maintained at hospitals or physicians' private offices. If potential subjects are identified through medical records, log books, physicians' records, or other records that are not public documents, the IRB should make certain that the following conditions have been met: (1) the investigator is allowed access to such records by the institution or the physician; and (2) responsibility for **confidentiality** and protection of **privacy** is clearly accepted by the investigator.

Sometimes, as in epidemiologic research, it is necessary for an investigator to review thousands of medical records to identify a very small number of subjects who are suitable for a study. At present, there is no agreement among commentators as to whether the investigator needs **consent** from all patients whose records will be searched, or only from the few who are selected for the study. An alternative in some circumstances may be the use of a "data broker," that is, an intermediary who already has access to the data. The broker can review records to identify appropriate subjects, whose consent to participate in the study can then be sought. With automated record keeping systems, it may be easier to identify appropriate subjects without reviewing all the records. Where the records are not computerized, however, IRBs will have to decide under what conditions a scientist may scan thousands of medical or other private records while searching for a small number of appropriate subjects. One factor to consider would be the sensitivity of the information likely to be contained in the records. For example, did the patients have broken ankles or abortions? Were they treated for strep throat or venereal disease? Another factor to consider is the type of information the investigator wishes to obtain from those who are selected as suitable subjects for the study.

Some institutions notify patients at the time of admission or initial treatment that: (1) their records may be used for research purposes; and (2) precautions will be taken to ensure that if the records are used, the researchers will respect and protect the confidentiality of the records. Some institutions go further and provide an opportunity for patients to consent or refuse consent to such use of their records at the time of admission.

In the event that names are sought from physicians' private offices, the patient's physician should request permission from the patient to release his or her name.

For a hospital-based study, most IRBs require that a potential subject's physician give approval before the subject is contacted, particularly when there may be medical or emotional contraindications to participation. If the subject is in the hospital, someone on the hospital staff may inform the patient that he or she is going to be invited to participate in a study, or, more often, an interviewer may approach the subject directly after consultation with his or her physician.

If the subject has left the hospital, various options may be considered. (For each option, most IRBs require that the potential subject's physician give approval before the subject is contacted.) For instance, the investigator may send a letter describing the purpose of the study and requesting that the subject return a postcard indicating whether he or she would like to participate. The effectiveness of this method depends on how many of the postcards are returned.

A second option is to invite participation by letter, and for the subject to send back a postcard (or to telephone) only if he or she does not wish to participate. If no postcard is returned, the subject may then be contacted by an interviewer. This method is less preferable, as it requires that potential subjects take positive action to avoid being made part of a study rather than the other way around. Subjects may become unwitting participants if, for example, they never receive the letter, don't read English, or are simply confused by the instructions. This approach also raises **privacy** concerns for certain types of research (*e.g.*, research involving sexually transmitted diseases or psychiatric illness, or drug or

alcohol abuse).

A third approach that is often used is for the patient's physician to send a letter informing the subject about the study and inviting the patient to participate. This method may work well if the study is being undertaken by a relatively small number of physicians who are willing to cooperate with the investigator. Response rates are likely to be high, since the subject often considers it significant that the letter has come from his or her own physician. IRBs should consider whether use of this method will subject potential participants to coercion or undue influence. Finally, the investigator can send a letter to the potential subject explaining the purpose of the study, and then an interviewer can call to invite the potential subject to participate. By permitting interchange between the subject and interviewer, this method allows the subject to make an informed decision about participation. Although there is the risk of coercion by the interviewer, in general this method helps the subject better understand what the purposes of the research are, why his or her participation is important, what procedures are used to protect confidentiality, and what would be asked of him or her as a participant. This approach usually secures the highest response rate; however, people may be offended, especially in research on sensitive topics, by the investigator's having direct access to their name, address, and phone number. IRBs should be sensitive to this concern.

Advertising for Subjects. One method of recruiting subjects is through advertisements (*e.g.*, posted notices and newspaper or magazine ads). Advertising for research subjects is not, in and of itself, an objectionable practice. When advertising is to be used, however, the FDA requests that IRBs review the information contained in the advertisement, as well as the mode of its communication, to determine whether the procedure for recruiting subjects affords adequate protection. IRB review is necessary to ensure that the information is not misleading to subjects, especially when a study will involve persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged.

The FDA believes that any advertisement to recruit subjects should be limited to: (1) the name and address of the clinical investigator; (2) the purpose of the research, and, in summary form, the eligibility criteria that will be used to admit subjects into the study; (3) a straightforward and truthful description of the incentives to the subject for participation in the study (*e.g.*, payments or free treatment); and (4) the location of the research and the person to contact for further information [*FDA IRB Information Sheet: "Advertising For Study Subjects"* (1989)].

If a study involves investigational drugs or devices, no claims should be made, either explicitly or implicitly, that the drug or device is safe or effective for the purposes under investigation, or that the drug or device is in any way equivalent or superior to any other drug or device. Such representation would not only be misleading to subjects, but would also violate FDA regulations concerning the promotion of investigational drugs [21 CFR 312.7(a)] and investigational devices [21 CFR 812.7(d)].

Paying Subjects to Participate. Another method of recruiting research subjects is to pay them for their participation. It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug or device development. In such cases, the IRB should review both the amount of payment and the proposed method of disbursement to assure that neither entails problems of coercion or undue influence. Such problems might occur, for example, if the entire payment were to be contingent upon completion of the study or if the payment were unusually large. Payments should reflect the degree of risk, inconvenience, or discomfort associated with participation. *See* Guidebook Chapter 3, Section G, "Incentives for Participation."

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J. ASSIGNMENT OF SUBJECTS TO EXPERIMENTAL AND CONTROL GROUPS

INTRODUCTION

The choice of study design depends largely upon the nature and goals of the research. Good methodology requires that studies be designed to minimize bias both in assignment to treatment groups (*e.g.*, by randomizing) and in assessment of outcome. Bias may enter into a study in several ways. The investigator may have strong beliefs or hopes regarding the success of a particular intervention or the truth of a particular hypothesis; these expectations may unconsciously influence his or her evaluation of the outcome of the research. To avoid this possibility, it is now accepted and preferred practice to conduct controlled investigations by dividing subjects into at least two groups: those who receive the experimental intervention (the experimental or treatment group) and those who do not (the control group).

See also Guidebook Chapter 4, Section H, "Clinical Trials," for additional discussion of the issues raised by random assignment of subjects to treatment groups and the use of placebos.

IRB CONSIDERATIONS

Random Assignment. To minimize the possibility that investigators may consciously or unconsciously select one sort of subject (*e.g.*, the most intelligent or the least sick) for the experimental group, it has become accepted and preferred practice to devise methods of randomly assigning subjects to experimental and control groups, unless there are important scientific or ethical reasons to do otherwise. The justifying pre-condition for ethical use of randomization is that a **null hypothesis** (*i.e.*, the stated experimental hypothesis that the experimental and control conditions have equally beneficial effects) can be reasonably entertained.

Sometimes experimental subjects and control subjects are assigned to groups upon admission to the study and remain in those groups for the duration of the study. This design is called "parallel control." On the other hand, it is sometimes advisable to let each subject be his or her own

control by having the subject be on both regimens - first the experimental treatment and then the control, or vice versa. This "**cross-over design**" can be useful because it reduces variability (since every subject receives both the experimental intervention and the control treatment) and it requires fewer subjects.

Several conditions are required for the cross-over design to be appropriate. First, the condition or disease must be stable, and, if relieved, not permanently cured by either the intervention or control. Second, there must be no "carry-over" effect from the first to the second treatment assignment (e.g., in a drug study, sufficient time must elapse between treatments to ensure that all traces of the first treatment have been eliminated). Unfortunately, it is often difficult to demonstrate that these conditions exist.

Regardless of the type of design, random assignment of subjects to treatment groups is generally the preferred method in most controlled studies. Random assignment is preferred because other techniques hold the opportunity for bias in the selection of subjects for particular treatments. Assigning every other consenting subject to a given treatment or assigning subjects to a treatment group based on the day of hospital admission are not truly random methods of assignment.

In situations where the course of the disease (under currently available standard treatment) is so clear or well-known that randomization is not ethically possible (see Guidebook Chapter 4, Section H, "Clinical Trials"), a *historical control* design may be an alternative design choice. In historically controlled studies, the condition of subjects is compared with their own past condition on a prior regimen or treatment. For example, if a disease is known to be fatal in 80 percent of the cases and no conventional therapy exists, an experimental treatment with a good chance of success (e.g., based on the results of animal studies) might be offered to all eligible subjects identified by the investigators. It may not be ethically acceptable to ask subjects to accept the possibility of assignment to a control (untreated) group if the null hypothesis cannot reasonably be entertained.

In some circumstances, however, the use of historical controls can yield erroneous conclusions. Because changing standards of hygiene, lifestyle patterns, and medical care can markedly alter the course of a disease, the use of historical controls to demonstrate the effectiveness of a new treatment could be misleading. Small effects are particularly difficult to detect with such designs.

Placebos. To minimize the possibility that the investigators' beliefs or hopes regarding the outcome of the research will bias their evaluation of the subjects' responses, investigators may be kept unaware of the identity of subjects who are assigned to each treatment group. Similarly, the subjects' hopes for a "cure" for a disease or their fears of side effects may cause them to experience improvement or adverse effects unrelated to the experimental treatment. Furthermore, it is generally agreed that a substantial number of patients will experience improvement in their symptoms regardless of treatment. To reduce the possibility that subjects' responses will result from their expectations rather than the interventions under study, it has become accepted and preferred practice to have subjects be unaware whether the "treatment" they are given is the experimental intervention. In **clinical trials**, control subjects may be given either a conventional treatment, or, if none is available or appropriate, a **placebo** - an inert substance prepared to resemble an experimental drug in size, shape, color, taste, etc. The use of placebos is generally unacceptable if there is an effective therapy that the subjects could be receiving for relief of severe symptoms or amelioration of a serious condition. [See also Guidebook Chapter 3, Section B, "Informed Consent," and Chapter 4, Section H, "Clinical Trials."]

Some drug trials involve a period during which all subjects receive only a placebo prior to the initiation of the study. This period is called a "placebo washout." The purposes of a washout period include: (1) terminating the effects of any drug the subject may have been taking before entering the clinical trial, so that the effects of the trial drug - and only the trial drug - may be observed; (2) learning whether subjects cooperate with instructions to take drugs ("compliance"); and (3) learning which subjects are "placebo responders," in that they experience a high degree of placebo effect. In some protocols, the investigators plan to exclude those subjects they find either poorly compliant or highly responsive to the placebo. The risks entailed in withdrawing subjects from therapy during a placebo washout period should be carefully evaluated by the IRB; great care must be taken to exclude subjects who are vulnerable to injury if they are withdrawn from effective therapy. In studies involving a placebo washout, subjects should be told that at some point during the study all subjects will receive placebo treatment; investigators but not subjects will know when subjects are receiving placebos for washout purposes, so that during the washout, the study is single-masked (see below).

When both the investigator and the subjects are unaware of the treatment assignments, the design is called "**double-masked**;" when one or the other (but not both) know, it is called "**single-masked**." Whenever the investigator remains unaware of the treatment that subjects are receiving, it is important that someone be able to find out, in case it becomes necessary to protect the health and well-being of a subject (i.e., in case of serious adverse effect or deterioration of a patient's condition). Therefore, investigators usually arrange for an independent person to have access to a code indicating the identity of subjects assigned to each treatment. This independent person is given the authority to break the code for individual subjects in case of emergency. This arrangement permits treatment to be provided, as necessary, to a particular subject without breaking the "masked" aspect of the experimental design. The protocol should describe how these arrangements will be made. [See also Guidebook Chapter 4, Section H, "Clinical Trials."]

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POINTS TO CONSIDER

1. Does the study involve reviews of records, observation, surveys, or interviews? If so, does it qualify for exemption or expedited review under the federal regulations and institutional policy?

2. Is the scientific design adequate to answer the questions posed? Is the sample size (number of subjects) adequate? Is the method proposed for selecting and assigning subjects to treatment groups unbiased?
3. Does the investigator serve a dual role that may pose a conflict of interest?
4. Is any of the information to be collected sensitive (*e.g.*, related to sexual practices, substance abuse, or illegal behavior)?
5. Are there adequate plans to protect participants from the risks of breach of confidentiality and invasion of privacy?
6. Are there plans for approaching subjects in a way that will respect their privacy and their right to refuse? If the protocol involves an epidemiologic study, will subjects or their relatives be protected from learning inappropriate information?
7. Does the recruitment process protect subjects from being coerced or unduly influenced to participate? Are any payments to subjects reasonable in relation to the risks, discomfort, or inconvenience to which subjects will be exposed?
8. Are there adequate plans to exclude subjects who are vulnerable to injury during the period of withdrawal of active and effective therapy, if that is part of the research design?
9. Have the rights and interests of vulnerable subjects (*e.g.*, desperately ill persons) been adequately considered?
10. Are all appropriate elements of informed consent clearly provided for [Federal Policy § __.116], including:
 - a. Do the consent documents describe the study design (including plans for randomization, use of placebos, and the probability that the subject will receive a given treatment) and conditions for breaking the code (if the study is masked)?
 - b. Do the consent documents describe the risks and benefits of each of the proposed interventions and of alternative courses or actions available to the participants?
 - c. Do the consent documents clearly describe the extent to which participation in the study precludes other therapeutic interventions?
 - d. Are provisions made for supplying new information to subjects during the course of the study and for obtaining continuing consent, where appropriate?
 - e. Must investigators obtain consent before reviewing records?
11. Will the consent process take place under conditions most likely to provide potential subjects an opportunity to make a decision about participation without undue pressure?
12. If the study is a clinical trial, how will the trial be monitored? What will be done with preliminary data? Should an independent data and safety monitoring board be established? How will decisions about stopping the trial be made? By whom? On what basis?
13. At what interval should the IRB perform continuing review of this project?

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APPLICABLE LAWS AND REGULATIONS

Federal Policy § __.101 [To what does this policy apply?]

Federal Policy § __.101(b)(2) [Exemption for surveys, interviews, and observation of public behavior]

Federal Policy § __.101(b)(4) [Exemption for existing data, documents, records, pathological specimens, or diagnostic specimens]

Federal Policy § __.102 [Definitions]

Federal Policy § __.116(d) [General requirements for informed consent: Alteration or waiver of consent requirements]

Federal Policy § __.116(e) [General requirements for informed consent: No preemption of applicable state and local laws]

Federal Policy § __.117 [Documentation of informed consent]

45 CFR 46.401(b) [DHHS: Protection of human research subjects subpart D - additional protections for children involved as subjects in research]

21 CFR 312.7(a) [FDA: Promotion of investigational drugs]

21 CFR 314.111 [FDA: Statement concerning adequate and well-controlled clinical investigations]

21 CFR 812.7(d) [FDA: Promotion of investigational devices]

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