Institutional Review Board Guidebook

* CHAPTER III *
BASIC IRB REVIEW

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 be 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 C 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 to 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?