

G-5: Guidance for Assessing Risk Level Using Magnitude of Harm

Risk Level	Potential Harm Health/Physical	Potential Harm Privacy/Social/Legal	Potential Harm Psychological	Potential Harm Financial
No More Than Minimal Risk	<p>The probability and magnitude of harm or discomfort anticipated in the research is not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [45 CFR 46.102(i)].</p> <p>For children, minimal risk is further defined as the level of risk that a normal, average, healthy child may be exposed to in the course of that child’s everyday life, or those risks encountered by normal, average, healthy children living in safe environments in daily life or during the performance or routine physical or psychological examinations or tests*</p> <p>For prisoners, minimal risk is further defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental or psychological examination of healthy persons [45 CFR 46.303.</p>			
Minor Increase Over Minimal Risk	<p>This risk category may be used to classify research involving adult participants, it must be considered in the evaluation of risk in research involving children as defined in 45 CFR 46 section 404 – 407**. Risks are more severe than those defined above (NMMR) and less severe than those defined below (Moderate Risk).</p>			
Moderate Risk	<p>Temporary (lasting more than 24 hours) but reversible or moderate discomfort, dysfunction, bodily harm, or pain.</p>	<p>Temporary or moderate harm to social reputation in any of the other 3 domains, e.g., release of research data results in embarrassment.</p>	<p>Subjectively upsetting, unwanted emotional or behavioral responses that are non-impairing and transient (up to a few days), e.g., feeling sad, nervous, sleep disruption, altered relationship dynamics. Nb: Informed consent procedures may reduce risk to minimal</p>	<p>Temporary or moderate financial costs or loss, e.g., short absence from work resulting in lost wages. Possibly significant wasted time if research lacks scientific merit.</p>
High Risk & Life-Threatening Risk	<p>Death, severe pain and/or permanent dysfunction or harm to body organ or structure.</p>	<p>Severe or long-term harm to social reputation or any of the other three domains, e.g., release of research data resulting in loss of employment, insurability, social stigma or criminal penalties.</p>	<p>Pronounced distress during the research activity, or negative outcomes that impair or persist for more than a few days, e.g. depressive symptoms, impulsive behavior, major alteration in relationship dynamics or social reputation</p>	<p>Severe and/or permanent financial harm, e.g., permanent disability resulting in job loss or loss of assets.</p>

Research classified as greater than minimal risk must be reviewed by the full board at a convened meeting.

* SACHRPP research involving children subcommittee. Kornetsky et al, October 4-5, 2005, OHRP Subcommittee on Research Involving Children Report Issues 4th Report for SACHRPP Consideration Clarifying 45 CFR 46 Subpart D Definitions, slide 14.

** The assessment of risk to a participant is not made at the same time that benefit assessment is made except under the conditions of 45 CFR 46 sections 404-407.

Background:

1. Per DHHS and FDA regulations (45 CFR 46.111 and 21 CFR 56.111) two of the required criteria for granting IRB approval of the research are:
 - a. Risks to subjects are *minimized* by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
 - b. Risks to subjects are *reasonable* in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB Committee will consider only those risks and benefits that may result from the research, as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research.

Definitions:

1. **Benefit:** A valued or desired outcome; an advantage.
2. **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."
3. **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 lives of the general population** or during the performance of routine physical or psychological examinations or tests.
4. **Minimal Risk for Research Involving Prisoners:** The definition of minimal risk for research involving prisoners differs somewhat from that given for non-institutionalized adults. Minimal risk is in this case is defined as, "the probability and magnitude of physical or psychological harm that is normally encountered in the **daily lives**, or in the routine medical, dental or psychological examinations of **healthy persons**."

Overview of Risks and Benefits:

1. There are two sources of confusion in the assessment of risks and benefits. One arises from the language employed in the discussion:
 - a. "Risk" is a word expressing probabilities;
 - b. "Benefits" is a word expressing a fact or state of affairs.
2. It is more accurate to speak as if both were in the **realm of probability**: i.e., risks and expected or anticipated benefits.
3. Confusion also may arise because "risks" can refer to two quite different things:
 - a. Those chances that specific individuals are willing to undertake for some desired goal; or
 - b. the conditions that make a situation harmful to a subject.

Researchers should provide detailed information in the IRB application about potential risks and benefits associated with the research, and provide information about the probability, magnitude and potential harms associated with each risk.

Risk/Benefit Assessment:

1. The IRB is responsible for evaluating the potential risks and weighing the probability of the risk occurring and the magnitude of harm that may result. 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 cannot approve research in which the risks are judged unreasonable in relation to the anticipated benefits. The IRB must:
 - a. Identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research;
 - b. Determine that the risks will be minimized to the extent possible [see below];
 - c. Identify the probable benefits to be derived from the research;
 - d. Determine that the risks are reasonable in relation to be benefits to subjects, if any, and the importance of the knowledge to be gained; and
 - e. Assure that potential subjects will be provided with an accurate and fair description (during consent) of the risks or discomforts and the anticipated benefits.

Types of Risk to Research Subjects:

1. The risks to which research subjects may be exposed have been classified as physical, psychological, social, and economic.

- a. **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.

- b. **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 transitory, recurrent, or permanent. Most psychological risks are minimal or transitory, but 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, is the possibility of psychological harm when behavioral research involves an element of deception.

- c. **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.

i. 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?

ii. The IRB must also consider whether the research design could be modified so that the study can be conducted without invading the privacy of the subjects.

- d. **Breach of confidentiality** is sometimes confused with invasion of privacy, but it is really a different risk. 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.

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. However, it is important to recognize 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).

- e. **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.

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.

Ways to Minimize Risk:

1. Provide complete information in the protocol regarding the experimental design and the scientific rationale underlying the proposed research, including the results of previous animal and human studies.
2. Assemble a research team with sufficient expertise and experience to conduct the research.
3. Ensure that the projected sample size is sufficient to yield useful results.
4. Collect data from standard-of-care procedures to avoid unnecessary risk, particularly for invasive or risky procedures (e.g., spinal taps, cardiac catheterization).
5. Incorporate adequate safeguards into the research design such as an appropriate data safety monitoring plan, the presence of trained personnel who can respond to emergencies, and procedures to protect the confidentiality of the data (e.g., encryption, codes, and passwords).

See also OHRP Guidance on Research involving vulnerable populations (Column #4) at: <http://www.hhs.gov/ohrp/policy/index/index.html>