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# Guidance on Assessing and Minimizing Risk in Human Research

The purpose of this guidance is to provide information on how to assess the risk of harm to participants in human research and what procedures to implement in order to minimize risk.

## Risk in Human Subjects Research

Risk is the probability of harm or injury (physical, psychological, social, legal or economic) occurring because of participation in a research study. Both the probability and magnitude (severity) of a possible harm may vary from minimal to significant. The magnitude of potential harm is the summative measure of its severity, duration and reversibility. Thus, a research protocol with a low probability of harm occurring, but a high severity of harm if it occurs, may be determined to be greater than minimal risk (e.g. a severe allergic reaction to a new medication, or stigmatization from unintentionally releasing HIV status of participants). Alternatively, a protocol with a high probability of harm occurring, but a low severity of harm, may be assigned minimal risk for participants (e.g. itchiness after electrode tape removal, or distress related to answering sensitive, personal questions).

Federal regulations define only "minimal risk". Minimal risk is where 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" (45CFR46.102 and 21CRF56.102). The IRB will consider a wide range of categories or types of risks including physical, psychological, social, economic, legal or unknown risks. In most cases these risks apply to individuals, however, risks can also apply to groups of individuals (e.g. research on alcoholism in a specific community may be perceived as denoting a negative stereotype). A research procedure or intervention may be minimal risk to certain individuals or groups, but greater than minimal risk to others. For example, the effect on "vulnerable" populations and the specific circumstances of a protocol may change the risk/benefit ratio making the study greater than minimal risk. Many risks in social, behavioral, and educational research are often subjective from the perspective of the participant and the researcher should consider this when evaluating risks. The overall study risk is determined by the risk to the most vulnerable known members of the group.

## Types of Risk to Research Subjects

**Physical Harms**: This would consist of pain, discomfort or injury from a procedure or side effect from a drug. The physical harm could be permanent but most are transient in nature, e.g. nausea, dizziness, headaches, muscle soreness, numbness, tingling.

**Psychological Harms**: Research may result in undesired changes in thought processes and emotion (e.g. episodes of depression, confusion, feelings of stress, guilt, loss of self-esteem, embarrassment, distress). The possibility of psychological harm may be more prevalent when the research involves an element of deception.

**Invasion of Privacy**: Participant's perception/observation of behavior that is considered private. When developing your research, consider if the invasion of privacy involved is acceptable in light of the participants' reasonable expectations of privacy in the situation and whether the research question is of sufficient importance to justify the intrusion. Invasion of privacy can be intrusion of one's solitude or into one's private affairs, public disclosure of embarrassing private information, publicity that puts the individual in a false light to the public, or appropriation of one's name or picture for personal/commercial advantage.

**Loss of Confidentiality**: Unlike physical risks related to direct interaction and data collection from the participants, the risk of breach of confidentiality concerns safeguarding information given voluntarily by one person to another. Some research requires the use of medical, school or employment records. Access to such records for legitimate research purposes is generally acceptable, as long as the researcher protects

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the confidentiality of that information. It is important to recognize that a loss of confidentiality may result in psychological harm to individuals (in the form of embarrassment, guilt, stress, etc.) or in social harm. Social 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 and 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 participants (e.g. as actual or potential delinquents or people with schizophrenia). Confidentiality safeguards must be strong in these instances.

**Economic Harms**: Participation in research may result in additional costs to individuals. Any anticipated costs to research participants should be described to prospective participants during the consent process. Legal Harms: Many researchers find themselves in ethical and legal quandaries when presented with a subpoena, which is a legal document requesting an appearance in court. While a subpoena is not likely for most research studies, if a study is examining things like sexual abuse, drug use or criminal activity, then it may cause the participants legal harm (consequences). Legal harm can be defined as causing an interaction between the participant and the court system.

**Vulnerable populations: Special considerations for risk assessment**

**Pregnant Women, Fetuses, and Neonates**: Research related risks to this population are those that are directly or indirectly connected to the medical condition of being pregnant. Taking a survey about personal career interests is a minimal risk activity for anyone, including pregnant women. However, something like taking a new medication for acne may be minimal risk for non-pregnant adults but is greater than minimal risk for pregnant women because it is unknown what effects the medication may have on the fetus. Therefore, the only time pregnant women are considered a vulnerable population is when the intervention has the potential to influence the safety of the fetus. Surveys, questionnaires, interviews, focus groups, and various cognitive tasks are considered minimal risk to pregnant women (45CFR46 Subpart B).

**Prisoners**: Assessing research related risks to incarcerated research participants is especially challenging due to the difficulty in assuring uncoerced, voluntary participation. Federal regulations specify that research involving prisoners has additional required protections and restrictions on permitted goals and intent of the study (www.hhs.gov/ohrp/policy/prisoner.html) (45CFR46 Subpart C).

**Minors**: Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under applicable law of the jurisdiction in which the research will be conducted. Generally, the law considers any person under 18 years old to be a child. When assessing the risks and potential benefits, consider the circumstances of the children to be enrolled in the study - for example their health status, age, and ability to understand what is involved in the research - as well as potential benefits to participants, other children with the same condition or situation, or society as a whole (www.hhs.gov/ohrp/policy/populations/children.html) (45CFR46 Subpart D).

**Significantly Disadvantaged Persons**: Persons significantly disadvantaged due to mental, social, economic, or educational circumstances including the sensory and mobility challenged, cognitively impaired, the poor and the illiterate may require additional protections of their interest and welfare before allowing them to enroll in research studies. Researchers planning or anticipating enrolling significantly disadvantaged persons in their research should describe planned procedures for minimizing risks to these individuals.

**Risks/Benefit Ratio Assessment**
Risk to participants must be reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result. The benefits of a study do not alter the risk classification. The risk/benefit assessment only refers to the acceptability of the risk, not the level of the risk.

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A study deemed greater than minimal risk cannot be classified as minimal risk just because the potential benefits are great, but the research could be approved for this reason. However, the same study may not be approvable if the risks are greater than minimal, but anticipated benefits are minimal or lacking. In evaluating risks and benefits, the IRB will consider only those risks and benefits that are directly related to participation in the research, as distinguished from risks and benefits of procedures/interventions individuals would receive even if not participating in the research. IRB reviewers identify any anticipated risks involved with the study and classify those risks as minimal or as greater than minimal risk. Reviewers then determine whether the anticipated risks to participants are reasonable in relation to the anticipated benefits to participants, if any, and the importance of the knowledge that may reasonably be expected to result (45CFR46.111(a)(2)).

**Risks and Benefits to include in protocol**
Researchers should provide detailed information in the IRB protocol about potential risks and benefits associated with the research and provide information about the probability, magnitude and potential harms associated with each risk. Please keep in mind that these risks are to be directly related to participation in the research components themselves and be immediate or reasonably foreseeable risks. They should not be risks or benefits of procedures or interventions individuals would receive even if not participating in the study and they should not be long-range effects of applying knowledge gained in the research.

**Minimizing Risk**
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. An important aspect of risk assessment is the nature and type of planned protections to minimize the probability and/or severity of potential harm to participants. A greater than minimal risk may be reduced to minimal risk if protections for research participants are judged to be adequate. For example, a breach of confidentiality of sensitive information poses a risk of serious harm, but protections such as restricted access (encrypted data storage, locked files, Certificates of Confidentiality) reduce the absolute risk significantly and may thereby render a minimal overall risk to participants. To minimize risk to study participants, consider the following:

- Provide complete information in the protocol regarding the experimental design and the scientific rationale underlying the proposed research, including the results of previous research.
- Use procedures which are consistent with sound research design and which do not unnecessarily expose participants to risk.
- Assemble a research team with sufficient expertise and experience to conduct the research.
- Ensure that the projected sample size is sufficient to yield useful results.
- Develop inclusion/exclusion criteria that will enroll only the desired population of interest.
- Collect data from standard-of-care or methodologically appropriate procedures to avoid unnecessary risk, particularly for invasive or risky procedures.
- For studies involving an element of deception, provide a thorough debriefing following completion of the study.
- Provide up to date resources for additional help/support for participants (counselors, rehab centers, etc.).
- Incorporate adequate safeguards into the research design such as an appropriate data and safety monitoring plan and the presence of trained personnel who can respond to emergencies.
- Store data in such a way that it is impossible to connect research data directly to the individuals from whom or about the data pertain; limit access to key codes and store separately from the data.
- Incorporate procedures to protect confidentiality of data (e.g. encryption, codes, passwords).
- Obtain a Certificate of Confidentiality (CoC). This legal document provides protection against compelled (legal demand) disclosure of identifying information about individuals enrolled in sensitive biomedical, behavioral, clinical or other research. CoCs are issued by the National Institutes of Health (https://humansubjects.nih.gov/coc/index).

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- Obtain HIPAA Authorization or a waiver. Depending on the construct of your research, you may request access to one's personal medical records through a HIPAA Authorization form or you may request a waiver of HIPAA under very specific circumstances (see SOP 505 HIPAA in Research).
- Obtain FERPA Permission or an exception. Depending on the construct of your research, you may request access to one's education records through signed permission or you may request an exception to FERPA under very specific circumstances (see Guidance on FERPA for further details on obtaining permission or exception).
- Obtain signature from the Legally Authorized Representative (LAR) for potential adult participants with diminished decision-making capacity (e.g. result of trauma, mental retardation, forms of mental illness, or dementia). The LAR is an individual, 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 (45CFR46.102(i)