

University of Kentucky

Assessing the Research Risk

Determining the proper risk classification of a research protocol is an important aspect of the review by an Institutional Review Board (IRB). The risk classification may influence the mode of review (expedited vs. full board), whether or not a protocol can be approved by the IRB (if children or prisoners are involved, whether or not it must be sent to the DHHS Secretary), the need for a Certificate of Confidentiality, the frequency of review, consent requirements (waiver, third party, etc.), and several other factors.

1. Definitions

Minimal Risk:

- a) *Minimal Risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. [45 CFR 46.102]

- b) *Minimal risk* is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. [45 CFR 46.303] (This definition only applies to research involving prisoners.)

The definition of minimal risk provided by the Federal Regulations invites interpretation which may lead to inconsistencies among IRB and reviewers. This document will provide guidance with your IRB review.

2. Identifying and Evaluating the Research-Related Risks

- a) IRB reviewers should be diligent to focus only on the risks associated with the protocol that are **directly related to the research**. Risks associated with the standard of care procedures that may provide the framework for the research should not factor into the risk classification.
In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research) [45 CFR 46.111 (a)(2)]

- b) The IRB should concentrate on the **immediate or reasonably foreseeable risks of the research** rather than the risks associated with the long-term outcome or consequences of applying the knowledge gained from the research.
The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility. [45 CFR 46.111(a)(2)]

- c) In identifying risks, the IRB should consider a wide range of categories regarding types of risks. For example, risks can be physical, psychological, social, economic, legal or unknown.

- d) In identifying risks, the IRB should consider that risks can apply to individuals. However, risks can also apply to groups of individuals (e.g., research on alcoholism in Native Americans).

3. Interpretation of Minimal Risk as Defined in 45 CFR 46

Classifying the risk category is not an easy task. One of the most recent advisory reports (released in 2001) is that of the National Bioethics Advisory Commission (NBAC) formed by President Clinton in 1995. The NBAC report recommends using a minimal risk standard related to the **risks of daily life that are familiar to the general population**. Studies involving a level of risk no greater than that encountered in the daily lives of those in the general population (i.e. healthy subjects) should be considered minimal risk. The DHHS Secretary's Advisory Committee on Human Research Protection (SACHRP) recommended in 2005 that DHHS use a "healthy" person standard when applying 45 CFR 46 Subpart D. University of Kentucky IRB policy also recommends that the IRB use a general population (i.e. healthy person standard) when applying the federal definition of "minimal risk".

4. Minimal vs. Greater Than Minimal

Once the risks associated with the research have been identified, the process of categorizing the risks as *minimal* or *greater than minimal* may begin. Two characteristics influence the nature of the risk: 1) the probability of harm; 2) the magnitude of harm. The magnitude of harm can be related to the severity, duration and reversibility of a potential harm. The IRB reviewer should consider both the likelihood and magnitude of harm and whether they are greater than the ordinary daily life of a healthy person.

5. Minimizing the Risks : Impact on Minimal Risk Assessment

An aspect of risk assessment that is often overlooked is what protections are in place to minimize the harm. An IRB may diminish the risks to subjects by minimizing the probability and/or magnitude of harm to subjects. A greater than minimal risk may be reduced to minimal risk if protections are adequate to protect subjects. For example, a breach of confidentiality is a serious risk, but protections such as restricted access (locked files, stand-alone computers, and Certificates of Confidentiality) reduce the absolute risk significantly and may thereby make the overall risk to the subject minimal.

6. Minor Increment Over Minimal Risk (for research involving children):

For suggestions for determining what constitutes a "minor increase over minimal risk":

- a). Procedure(s) does not meet minimal risk criteria.
- b). The increase in the probability and magnitude of harm is only slightly more than minimal risk.
- c). The IRB's criterion to approve a study as slightly more than minimal risk is a subjective decision and the IRB should review each study on a case by case basis. The IRB may use the following criteria to help determine whether a risk is slightly more than minimal:
 - 1. Any harms associated with the procedures if they occur will be transient (restricted to time of procedure or short post-experimental period) and reversible (requiring no more than a short post-experimental clinical intervention); and

2. There is no or an extremely small probability that the potential pain, discomfort, stress or harm associated with the procedure(s) which the subject might experience will be severe.
3. The investigator has presented sufficient evidence to the IRB that criteria 6a and 6b are met in consideration of the specific subject population and the qualification of the research personnel.

7. Risk/Benefit Ratio Assessment

An IRB reviewer identifies any risks involved with the study and classifies those risks as minimal or as greater than minimal risk, weighing the benefits of the study against those risks. The IRB reviewer then assesses whether the risk 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.

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. A study deemed greater than minimal risk cannot be classified as minimal risk because the potential benefits are great, but it could be approved for this reason. Whereas, the same greater than minimal risk study may not be approvable if the benefits are lacking. An IRB reviewer should disapprove research in which the risks are judged to be unreasonable in relation to the anticipated benefits (IRB Guidebook, '93).

In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied: (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. [45 CFR 46.111: (a)]

- ## 8. Clarification from Office of Human Research Protections (OHRP) regarding MRI studies.
- A Magnetic Resonance Imaging (MRI) study should be reviewed carefully since a MRI may be greater than minimal risk to certain individuals. For example, the use of "vulnerable" populations and the specific circumstances of a protocol may change the risk/benefit ratio making the study greater than minimal risk. OHRP has ruled that a MRI for children, depending on the age and circumstances, would or could be greater than minimal risk if sedation was required.

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