Department: UAMS Institutional Review Board
Policy Number: 7.11
Section: Procedures for Study Review
Effective Date: July 31, 2002
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SUBJECT: Risk/Benefit Analysis

POLICY

The IRB, in its review of research, shall consider whether study-related risks to participants are reasonable to anticipated benefits, if any, to subjects, and the importance of the knowledge expected to result from the research. The IRB may approve research only if risks to subjects are minimized and proportional to anticipated benefits.

When assessing risks and benefits, the IRB must evaluate the proposed research's scientific validity. This responsibility does not require the IRB undertake a peer review function or compare the proposed research to other research studies. However, it does require the IRB, either through its own expertise or outside consultants, to understand the background, aims, and research methods enough to address two specific regulatory requirements:

Risks to participants are minimized by using procedures which are consistent with sound research design; and

Risks to participants are reasonable in relation to the anticipated benefits, if any, to the participants and to society and the importance of the knowledge that may reasonably be expected from the study.

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.

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."

Pediatric Category 1: Minimal Risk

Pediatric Category 2: Greater than minimal risk, but presenting the prospect of direct benefit to individual participants

Pediatric Category 3: Greater than minimal risk and no prospect of direct benefit to individual participants but likely to yield important generalizable knowledge about the participant's disorder or condition.

Pediatric Category 4: Not otherwise approvable, but presents an opportunity to understand serious health or welfare problems of children

PROCEDURE

A. The IRB must be cognizant of some language details when considering risks and benefits. "Risk" expresses probabilities; "benefits" expresses a fact or state of affairs. It is more accurate to consider both as probabilities, *i.e.*, risks and expected or anticipated benefits. Another point of 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 participants, justifies inviting any person to accept the risks.

B. The IRB may not approve research in which the risks are judged unreasonable in relation to the anticipated benefits.

C. In assessing risks and benefits, the IRB must:
   1. Identify the risks associated with the research, as distinguished from the risks of therapies the participants would receive even if not participating in research
      a. Example: In research examining the behavioral effects of physical interventions performed for therapeutic reasons, only the risks of the tests of the behavioral effects are research related. The risks associated with the physical intervention the subject would undergo regardless of research participation are not research-related risks.
      b. Research-related risks may be minimal even when the therapeutic procedure poses greater than minimal risks.
      c. The IRB must remain cognizant that it can be difficult to distinguish between therapeutic and research-only activities. Before eliminating a procedure from consideration in the risk/benefit analysis, the IRB should be certain the activity is indeed therapeutic and not part of the research.
   2. Determine that the risks will be minimized to the extent possible
   3. Identify the probable benefits to be derived from the research
   4. Determine that the risks are reasonable in relation to the benefits for participants, if any, and the importance of the knowledge to be gained
   5. Assure that potential participants will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits.
   6. Determine intervals of periodic review, and, where appropriate, determine that adequate provisions are in place for monitoring the data collected.
   7. determine the adequacy of the provisions to protect the privacy of participants and to maintain the confidentiality of the data
   8. When the participants are likely to be members of a vulnerable population (*e.g.*, impaired decision-making capacity, prisoners), determine that appropriate additional safeguards are in place to protect the rights and welfare of these participants, as described in IRB Policy Section 17.

D. The IRB must recognize potential risks may stem from design features employed to assure valid results as well as by the particular interventions or maneuvers that may be performed for the research. Participants in a study whose research design involves random assignment to treatment groups face the chance that they may not receive the more efficacious treatment. Participants in a double-blind study take the risk that the information necessary for individual treatment might not be immediately available 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.

E. An additional potential risk 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 the IRB should not consider such effects "as among those research risks that fall within the purview of its responsibility.

F. **Classification of Risk**. The risks to which research participants may be exposed have been classified as physical, psychological, social, and economic

   Physical Harms. Examples include pain, discomfort, or injury from invasive medical procedures, or harm from possible side effects of drugs. These harms can be permanent or transient.

   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.

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 participants (*e.g.*, as actual or potential delinquents or schizophrenics). Confidentiality safeguards must be strong in these instances, and plans to contact subjects in the future should be carefully considered.

Participation in research may result in additional actual costs to individuals. Any anticipated costs to research participants should be described to prospective participants during the consent process.

G. **Minimal Risk and Especially Vulnerable Populations**. DHHS regulations on research involving fetuses and pregnant women [45 CFR46 (Subpart B)], research involving prisoners [45CFR46(Subpart C)], and research involving children [45 CFR 46 (Subpart D)] strictly limit research presenting more than minimal risk. For more information about "Special Populations", see IRB policy section 17 “Special Populations”.

H. The IRB must assess whether research-related risks, if unavoidable, can be appropriately reduced or managed, as the IRB is responsible for assuring risks are minimized to the extent possible.
   1. If precautions, safeguards, and/or alternatives can be incorporated into the research activity to reduce the probability of harm or limit its severity or duration, the IRB should require these changes before approving the study.

I. Information helpful to the IRB’s assessment of risks, appropriate risk mitigation, and benefits includes, but is not limited to:
   1. 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.
   2. A completion description of 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.
   3. Whether potentially harmful effects can be adequately detected, prevented, or treated, and if so, the proposed measures to do so.
   4. The risks and complications of any underlying disease or condition that may be present in the study population.
   5. The investigators’ qualifications in the area being studied.
   6. Whether the study team serves dual roles that may unduly influence research-related treatment decisions or the decision whether or not to join a study. Examples:
      a. An investigator who is also the treating physician may be influenced by eagerness for a participant to continue in a project in making treatment decisions.
      b. An instructor or employer of prospective subjects may unduly influence a decision about participating.
   7. Whether the proposed research design adequately addresses the research question, taking into consideration factors such as relevance of the proposed data; appropriate study sample size; and whether the data can be appropriately evaluated. While sound research design may not in and of itself reduce or eliminate research-related risks, poor or faulty research design means risks are not likely to be reasonable in relation to benefits to participants or society.
   8. Adequacy of resources available to mitigate risk.

J. Examples of risk mitigation measures include, but are not limited to:
   1. Appropriate study monitoring, either by study staff or by an outside observer.
   2. Presence of trained personnel and other resources to address any emergencies.
   3. Data handling methods designed to enhance confidentiality.
   4. Exclusion of certain populations that may be unusually susceptible to the risks of a particular test article or intervention.

K. Assessing anticipated benefits
    1. The UAMS IRB does not allow compensation offered to participants or the provision of medical care at no charge or that the subject would not otherwise receive to be described as a benefit.
    2. The two most common types of research-related benefits are:
        a. Benefits to participants, stemming from treatment, diagnosis or examination for an illness or abnormal condition. Such research may offer the benefit of ameliorating their condition or providing a better understanding of their disorder.
        b. Benefits to society, stemming from increased knowledge about a particular disorder or behavior.

L. The IRB must assure benefits are accurately described in the submission, including in the informed consent materials or other items that will be seen by subjects.
    1. Because research, by definition, is designed to answer a question about whether something is effective, care should be taken to ensure there are no promises of benefits that cannot be guaranteed.
    2. The research should make clear that there may be no possibility of direct benefit, when appropriate. For example, the placebo arm in a clinical trial, or an untried, experimental intervention, may not yield direct benefit, and this possibility must be described and adequately explained to potential subjects.

REFERENCES

45 CFR 46
21 CFR 56
AAHRPP Elements II.3.A; III.1.C; III.1.D
Levine, Robert J. *Ethics and Regulation of Clinical Research*, 2d ed. Baltimore: Urban and Schwarzenberg, 1986, p.42].

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