Department: **UAMS Institutional Review Board**
Policy Number: **16.1**
Section: **Risk/Benefit Analysis-Guidance For Reviewers**
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Subject: Risk/Benefit Analysis

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 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.

Adult 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 [38CFR16.102(i)].

Adult 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 subjects

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

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

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.**

The IRB's assessment of risks and anticipated benefits involves a series of steps. The IRB must:

1. Include the fact that the risk of death or induced illness resulting from the treatment be considered.
2. Assure that the informed consent document completely discusses any known potential risks, including death or induced illness and benefits if they are known to exist.
3. Identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research.
4. Determine that the risks will be minimized to the extent possible.
5. Identify the probable benefits to be derived from the research.
6. Determine that the risks are reasonable in relation to be benefits to subjects, if any, and the importance of the knowledge to be gained.
7. Assure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits and.
8. Determine intervals of periodic review, and, where appropriate, determine that adequate provisions are in place for monitoring the data collected.

In addition, the IRB should determine the adequacy of the provisions to protect the privacy of subjects and to maintain the confidentiality of the data 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 IRB policy 17.1-17.9).

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. The IRB 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 the IRB should not consider such effects "as among those research risks that fall within the purview of its responsibility(45 CFR 46.111)

Classification of Risk. The risks to which research subjects may be exposed have been classified as physical, psychological, social, and economic [**Levine**, Robert J. *Ethics and Regulation of Clinical Research*, 2d ed. Baltimore: Urban and Schwarzenberg, 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.
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> **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 the IRB should be aware that some research has the potential for causing serious psychological harm.
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> **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 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”.

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. The IRB is responsible for assuring that risks are minimized to the extent possible.

In reviewing any protocol, the IRB 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. The IRB 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.

The IRB should determine whether the investigators are qualified 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 the IRB 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.

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.

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. 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.