NOTE: This document is for IRB reviewers and investigators.

The IRB is obligated to evaluate the scientific value of a study: whether a research study is designed to minimize risks to participants and to determine that the potential benefits to the participants from the research justify the potential risks. This obligation is set forth in Department of Health and Human Services and the corresponding FDA regulations and supported by accepted ethical codes such as the Declaration of Helsinki of 2000 (Sections 11, 18, and 29) and the Nuremberg Code of 1949 (point 3).

Federal research regulations [45 CFR 46.111 (a) and 21 CFR 56.111 (a) include as criteria for IRB approval:

1. Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.

The IRB should not approve a research protocol if:

1. The study objectives can be accomplished through procedures that pose less risk to participants;

2. The study involves risks to participants and is not designed to ask a question that is important or it asks a question that has already been answered by prior research.

3. The study design will likely yield results of no discernible value or cannot answer the question. (See “The Role of IRB Judgment in Scientific Review of Minimal Risk Studies” below for exceptions related to protocols involving little or no risk to participants.)

Scientific Review

Evaluation of the scientific aspects of a research study (e.g., design, statistical validity, significance of the study) requires both general and specific scientific expertise. The
IRB makes every effort to obtain IRB members whose expertise represents the kinds of research conducted at the University of Alabama and to assign applications to reviewers who have the appropriate expertise to evaluate study design. If this expertise is not available or sufficient to address a particular application, the IRB may rely, in part, on prior scientific review (e.g., NIH peer review, review by another IRB/performance site) or it may seek consultation from an expert in the field. Principal investigators are welcome to be present at IRB meetings to address IRB questions about their work.

*The IRB cannot overemphasize how important it is for investigators to help IRB by fully explaining and justifying their work. Familiarity with the FORM: IRB Checklist for Reviewers and Investigators and adherence to the GUIDANCE: IRB Application Guide when preparing the application will help assure that the IRB will appreciate the significance of the work and the design.*

It is not the charge of the IRB to comment on the scientific value/merit of proposals where "scientific merit" refers to the value of the research proposal relative to other research proposals. However, proposals with many or major scientific weaknesses, no apparent benefits to participants or science, or doubts about the answerability of the question may raise the ethical issue of whether persons should be asked to invest their time in the study. Again, adequate explanation of the study is very helpful to the IRB.

**Minimization of Risks in Studies**

Investigator should describe how risks will be minimized and justify why the risks are necessary and acceptable in relation to the study significance. There are many strategies for minimizing risks in studies. They include:

1. Exposing participants to the lowest dose/burden for the shortest possible period of time.
2. Ensuring that pre-clinical work in the laboratory or on animal models has been done before research on human participants.
3. Ensuring that prior studies have been done on healthy persons before using sick persons or that mildly ill persons have been studied before seriously ill persons.
4. Conducting pilot studies of instruments and procedures for recruitment or data collection.
5. Selecting established instruments and instruments imposing the least burden on participants.
6. Evaluating the appropriateness, health, or decision-making capacity of prospective participants and participants in ongoing multi-session studies.
7. Evaluating psychological, economic, and social risks as well as physical risks. Consider such things as whether questions are sensitive, whether participants would be stigmatized if their participation or condition became known, and whether employers or faculty would know of their participation or their responses. Provisions for privacy and confidentiality address many such risks.
8. Establishing procedures by which the investigator may remove a participant from a study.
9. Justifying the use of vulnerable populations and providing benefits relevant to their vulnerable status whenever possible.
10. Assessing prospective participants' comprehension of the study and risks to them.

Investigators are urged to cite references for their appraisals of risk and risk-minimization strategies whenever possible.

**Placebo-controlled Studies.** A study that involves removing participants from a standard medication or treatment for their disease or condition and randomizing them to receive either an investigational agent or a placebo raises questions about participant safety. If participants will receive no potentially beneficial drug or treatment for all or a significant portion of the study, the principal investigator should specify in the protocol and consent form the nature and severity of the associated risk to those participants.

Depending on the degree of risk, the principal investigator should consider modifying the study design to minimize the risk. For example, one might define a benchmark for unacceptable worsening of the participant’s condition, together with a monitoring plan for identifying participants who reach that benchmark and a “rescue mechanism” for ameliorating the participant’s condition once the benchmark is reach. Or, the investigator might consider a cross-over design in which all participants will receive both the placebo and the experimental treatment.

Other design options include restricting study eligibility to individuals who refuse, or have been show to be unresponsive to, the standard medication/treatment or who have only a mild form of the disease or condition. In cases where the standard treatment is known to be well-tolerated and to prevent serious harm such as death or irreversible morbidity in the participant population, the IRB may determine that a placebo design is not acceptable.

**Active Control Studies.** Designs in which some participants receive the investigational agent or treatment but are removed from standard therapy for serious conditions may raise questions about participant safety because the investigational treatment may turn out to be ineffective. Unless there is strong reason to expect that the investigational treatment will be at least as effective as the standard treatment, the principal investigator should consider one of the design modifications described above or carefully justify chosen design.

**Deliberate Induction of Undesirable States.** Special measures should be in place to minimize risk in research that deliberately induces an undesirable state or condition in participants (e.g., pain, panic attack, allergic attack, airway narrowing in medical studies; psychological stress, emotional conflict, fear, humiliation in sociobehavioral studies). The IRB will scrutinize such studies thoroughly to ensure that adequate measures have been instituted to minimize participant risk.
The Role of IRB Judgment in Scientific Review of Minimal Risk Studies

Judgment and common sense also have a role in determining whether to approve a research protocol. The IRB reviews many studies that pose little or no risk to participants and research applications from investigators who vary widely in research experience—from high school students taking part in special opportunities to acquaint them with research to heavily funded faculty. Therefore, the IRB makes every effort to consider the investigator’s experience, the presence or absence of funding, and the state of knowledge about the studied topic in its decisions. Student research is not expected to be as "solid" as that of a seasoned investigator or to answer as large a question. It is recognized that unfunded research and preliminary studies may not allow or require a statistically powerful sample and that the knowledge base for an exploratory study of a new topic may not provide a basis for identifying all variables of interest or possible risks. Perfect studies are rare and no ethical guidelines require the IRB to disapprove flawed research.

Sometimes IRB members with expertise on a topic will offer recommendations to improve the study design. The feedback to the investigator will make clear whether the recommendations are only suggestions or are requirements.

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