Guidance -
Evaluating Sound Study Design

The IRB is obligated to evaluate 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 those potential risks. This obligation is set forth in Department of Health and Human Services and 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:

- The study objectives can be achieved through procedures that pose less risks to participants;
- The study involves risks to participants and is not designed to ask a question that is important or asks a question that has already been answered by prior research; or
- The study design will likely yield results of no discernible value (see 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., statistical validity, prospect of study value) may require specific expertise. The IRB will assign protocols to reviewers who have the appropriate expertise to evaluate study design; however, depending on IRB membership background, and availability, this expertise may not be available or sufficient to address the complexities of a particular protocol. The IRB may rely, in part, on prior scientific review (e.g., NIH peer review, internal scientific committee reviews) as described in the HRPP Handbook, Section 1. An expert may be asked to provide opinion as addressed in Section 6.

Minimization of Risks in Clinical Studies

Whenever possible, studies should utilize procedures that are already being performed on the participants for diagnostic or treatment purposes. Where this is not the case and the research procedure carries a high level of risk with no potential benefit to participants, the

Principal Investigator (PI) should be prepared to justify why the procedure is necessary to achieve the research objectives, or why enrollment should not be limited to those already scheduled for the procedure for non-research purposes. Certain types of clinical protocols may require special attention from the PI to minimize risks. Several examples are described below:

Placebo-Controlled Studies

A protocol that involves removing participants from the standard medication for their disease or condition, and randomizing them to receive either an investigational agent or a placebo, may raise issues of participant safety. If some participants will receive no potentially beneficial drug for all or a significant portion of the trial, the PI should specify in the protocol and consent form the nature and severity of the associated risk to those participants. Depending upon the degree of risk, the PI should consider modification of study design to minimize the risk.

The study design might be modified to define a benchmark for unacceptable worsening of the participant's disease or condition, together with a monitoring plan for timely detection of participants who reach the benchmark and a "rescue mechanism" for ameliorating the participant's condition once the benchmark is reached. Alternatively, the PI might consider modifying the research design to include a cross-over design (from placebo to investigational drug and vice versa).

Other design options include restricting eligibility to individuals who refuse, or have been shown not to respond to, the standard medication, or who have only a mild form of the disease or condition. In situations where the standard treatment is tolerated by and known 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

Study designs in which some participants receive the investigational agent but are removed from standard therapy for serious conditions may raise similar issues, as the investigational treatment may turn out to be ineffective. Unless there is strong reason to expect that the investigational drug will be at least as good as the standard therapy, consideration should be given to one of the design modifications discussed above.

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, a condition of airway narrowing) in order to learn more about the undesirable state or condition. The IRB, with expert advice as needed, will scrutinize thoroughly the design aspects of such research to ensure that adequate measures have been instituted to minimize participant risks.

Protocols Involving Little or No Risk to Participants

Judgment and common sense also have a place in determining whether to approve a research protocol. The IRB reviews a large volume of retrospective record review or prospective survey research. Many of these protocols pose little or no risk to the participants (e.g., surveys that ask the participant non-sensitive questions). If the study design is flawed (e.g., not likely to render the information necessary to answer the research question), the IRB may make recommendations to improve study design, but must review the risk/benefit ratio careful before a decision is made to not approve such research.