Introduction:
Note: The factors that influence the choice of control group and related issues in a clinical trial are discussed in detail in an FDA/ICH guidance document (see weblink on page 2). The following information from that document is basic to our discussion about placebo control groups and is not found in the IRB Handbook.

The two main characteristics of a control group are:
- The type of treatment received.
  - Active control – the control group is treated with a therapy that is known to have specific activity in the study setting
  - Placebo
  - No treatment
- The relationship of the control group to the present study population.
  - Control group chosen from the current study population (called concomitant or concurrent control)
  - Control group chosen from an external database

Types of control groups:
- Concurrent control groups are usually selected by randomization with blinding of the subject and/or researchers to the treatment group.
- External control groups are usually chosen from previously conducted trials of the study medication in circumstances similar to those of the current study. A control group that is chosen from studies that were completed in the past is called a historical control group.

The Use of Placebo in Place of Standard Therapy
1. Is placebo being used instead of standard therapy?
   - When an available therapy is considered to be beneficial, the use of a placebo instead of accepted therapy may be unethical.
   - When a placebo is being used in addition to standard therapy, there is no ethical problem.
2. Is standard treatment considered to be effective?
   - If standard therapy does not meaningfully improve length or quality of life, it is ethical to enroll informed subjects in research that uses a placebo in place of standard treatment.

The Toxicity of Standard Treatment:
3. Is the toxicity of standard therapy is such that patients routinely refuse treatment or local physicians do not recommend the therapy?
   - If so, it is ethical to conduct research that treats informed subjects with placebo in place of standard therapy, even when standard therapy is proven to have activity for their condition.

Temporary Discomfort versus Irreversible Harm
4. Could the use of a placebo instead of standard treatment cause irreversible health problems or extreme suffering?
If the risk is minor and/or causes temporary discomfort, standard informed consent procedures are adequate and the use of a placebo is ethical.

- If the risk is high, additional protections are required that recognize the fact that informed consent is often suboptimal, which has a major effect on the ethics of the research.
- If the use of a placebo carries a risk of irreversible and serious harm, the ethics of research will hinge on the ability of alternate study designs to provide valuable information on the study questions with less risk to subjects.

**Considering Alternative Study Designs**

**Discussion:**
- A fundamental ethical standard is that research should be designed so the risks to subjects are minimized and reasonable in relation to anticipated benefits.
- As a society, we want to design clinical trials that minimize the chance of false-positive results.
- The scientific quality of a clinical trial refers to the aspects of the study that influence the credibility and the persuasiveness of research results.
- The main issue is the value of a positive result in a trial with placebo versus active control.
- This is a complex and controversial topic, the explanation of which is beyond the scope of the IRB handbook, but a more complete discussion can be found in the FDA/ICH E10 guidance document.

The IRB should consider the following question:

5. Is it possible to predict the placebo response rate in the research study with a degree of accuracy?
   - If so, alternative study designs are likely to produce meaningful results with less risk to subjects; however, a study with concurrent placebo control is not ethical.
   - If not, the credibility of altruism may be considered.

**Evaluating the Credibility of Altruism Using the Reasonable-Person Standard**

6. Could this trial benefit future patients to the point that a reasonable person with an average degree of altruism and risk-aversiveness would consent to being randomized in this trial?
   - Major guidelines related to research ethics stress the importance of not sacrificing the individual for the sake of society.
   - Each person who is asked to be a research subject should be permitted to decide what is acceptable and unacceptable based on personal values.
   - To accept the altruism argument, one must assume full and voluntary informed consent will be obtained; however, in this type of situation, it is difficult for a subject to comprehend and give the level of informed consent that is a requirement for ethical research.

**SUMMARY OF TAKE-AWAYS FOR BOARD MEMBERS**

To evaluate the ethics of a placebo-controlled clinical trial, IRB members should ask the following basic questions, taken from an algorithm on p. 169 of the IRB Handbook:

1. Is placebo being used instead of standard therapy?
2. Is standard treatment considered to be effective?
3. Is the toxicity of standard therapy is such that patients routinely refuse treatment or local physicians do not recommend the therapy?
4. Could the use of a placebo instead of standard treatment cause irreversible health problems or extreme suffering?
5. Is it possible to predict the placebo response rate in the research study with a degree of accuracy?
6. Could this trial benefit future patients to the point that a reasonable person with an average degree of altruism and risk-aversiveness would consent to being randomized in this trial?

FOR YOUR REFERENCE AS DESIRED

FDA/ICH: Guidance for Industry E10 – Choice of Control Group and Related Issues in Clinical Trials