

## ***AMA Code of Medical Ethics***

### ***7.3.1 Ethical Use of Placebo Controls in Research***

A fundamental requirement of biomedical and health research is that it must provide scientifically valid data. In some research, this can best be achieved by comparing an intervention against a control to identify the effects of the intervention. Used appropriately, a placebo control can provide valuable data, particularly when there is no accepted therapy for the condition under study.

The existence of an accepted therapy does not necessarily preclude use of placebo controls, but because use of a placebo deprives participants in the control arm of access to accepted therapy for some period of time, it requires thoughtful ethical justification. In general, the use of a placebo control will more easily be justified as the severity and number of negative side effects of standard therapy increase.

To ensure that the interests of human participants are protected, physician-researchers and those who serve on oversight bodies should give careful attention to issues of methodological rigor, informed consent, characteristics of the medical condition under study, and safety and monitoring, in keeping with the following guidelines:

- (a) Evaluate each study protocol to determine whether a placebo control is scientifically necessary or an alternative study design using a different type of control would be sufficient for the purposes of the research. Placebo controls are ethically justifiable when no other research design will yield the requisite data.
- (b) Assess the use of placebo controls in relation to the characteristics of the condition under study in keeping with the following considerations:
  - (i) Studies that involve conditions likely to cause death or irreversible damage cannot ethically employ placebo controls if an alternative therapy would prevent or slow the progression of illness;
  - (ii) Studies that involve illnesses characterized by severe or painful symptoms require a thorough exploration of alternatives to the use of a placebo control;
  - (iii) In general, the more severe the consequences or symptoms of the illness under study, the more difficult it will be to justify the use of a placebo control when alternative therapy exists. Consequently, there will almost certainly be conditions for which placebo controls cannot ethically be justified.
- (c) Design studies to minimize the amount of time participants are on placebo without compromising the scientific integrity of the study or the value of study data.
- (d) Pay particular attention to the informed consent process when enrolling participants in research that uses a placebo control. In addition to general guidelines for informed consent in research, physician-researchers (or other health care professionals) who obtain informed consent from prospective subjects should:
  - (i) describe the differences among the research arms, emphasizing the essential intervention(s) that will or will not be performed in each;

- (ii) be sensitive to the possible need for additional safeguards in the consent process, such as having a neutral third party obtain consent or using a consent monitor to oversee the consent process.
- (e) Ensure that interim data analysis and monitoring are in place to allow researchers to terminate a study because of either positive or negative results, thus protecting participants from remaining on placebo longer than needed to ensure the scientific integrity of the study.
- (f) Avoid using surgical placebo controls—i.e., a control arm in which participants undergo surgical procedures that have the appearance of therapeutic interventions but during which the essential therapeutic maneuver is not performed—when there is a standard treatment that is efficacious and acceptable to the patient and forgoing standard treatment would result in significant injury. In these situations, physician-researchers must offer standard treatment as part of the study design. Use of surgical placebo controls may be justified when:
  - (i) an existing, accepted surgical procedure is being tested for efficacy. Use of a placebo control is not justified to test the effectiveness of an innovative surgical technique that represents only a minor modification of an existing, accepted surgical procedure;
  - (ii) a new surgical procedure is developed with the prospect of treating a condition for which there is no known surgical therapy. In such cases, the use of placebo must be evaluated in light of whether the current standard of care includes a nonsurgical treatment and the risks, benefits, and side effects of that treatment;
  - (iii) the standard (nonsurgical) treatment is not efficacious or not acceptable to the patient;
  - (iv) Additional safeguards are in place in the informed consent process.

*AMA Principles of Medical Ethics: I,V*