The Ethics of Placebo-Controlled Trials

Robert M. Kaplan
University of California, San Diego
Declaration of Helsinki

• “In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method”
Arguments Against Placebo-Controlled Trials

- Providers should always act in the best interest of the patient.
- There is no circumstance in which an effective treatment should be withheld.
- Placebo-controlled trials are unnecessary—they test only significant differences from placebo, not improvement over baseline.

(Rothman & Michels, NEJM, 1994,331,394-398)
Ethical Principles

• Respect for patient autonomy
  – Patient must be informed and choose without coercion

• Beneficence
  – Provider should look out for the best interest of the patient
  – The potential benefit to the patient supercedes investigators scientific interests
Why Placebo Controlled Trials are Ethical

• Informed consent
  – Participants must be informed about the rationale for the trial and must understand that they may be assigned to a placebo condition
  – Participants must be informed of any risks of the interventions and the risks associated with delaying treatment if assigned to a placebo condition
Alternative Designs

• Active-Control Equivalence Trials (Noninferiority Trials) (ACET)

• Patients assigned to new treatment or to another treatment believed to be effective

• A null result suggests that the new treatment works because it is not inferior to a known intervention.
Problems with ACET Designs

• Sample size requirements-- violates the principle that trials should be as small as possible
• The meaning of a retained null hypothesis
• No incentive to run a clean trial
  – The poorer the trial, the more error variance and the higher the probability of a null result
How Do You Know If Comparison is Effective?

- FDA data suggest that one third to one half of modern antidepressant trials do not distinguish a known effective drug from a placebo (Temple and Ellenberg, 2000)

- Same for
  - Analgesics, anxiolytics, antihypertensives, hypnotics, antianginal agents, ACE inhibitors, Beta blockers………..
How about Meta-Analysis?

- If meta analysis shows effect for drug, can it be used as the for ACET comparisons?
  - Even if meta analysis shows overall effect, many component studies may have been null
  - No assurance that active treatment would have exceeded placebo in your trial
Advantages of 3 groups designs

• Two thirds get active treatment
• Allows comparison for natural history
• If we can not be confident that we can distinguish active treatment from placebo, we can not be sure we can distinguish an effective treatment from a less effective treatment.
Other Solutions

• Early escape trials
  – Valuable for some drug studies
  – May be less valuable for studies on behavior change

• Statistical Approaches
  – Bayesian (Simon, 1999)
  – Prior distribution of effectiveness taken from meta analysis and used for evaluation in ACET trials
Example Comparisons of Nomifensine, Imipramine and Placebo (FDA data)

Trial R301

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Summary

• Many interpret Declaration of Helsinki as meaning that placebo controlled trials are unethical
• ACET trials are the best alternative
• ACET trials have significant limitations
• On a scientific level, there are few alternatives to Placebo-Controlled trials