

# Ethics of Placebo-Controlled Trials

Franklin G. Miller, Ph.D.

Department of Bioethics

National Institutes of Health

# Disclaimer

- The views presented are mine and do not reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

# The Problem

- Placebo-controlled trials (PCTs) raise ethical concerns when proven effective treatment exists.
- However, PCTs despite proven effective treatment are common to test new treatments for psychiatric and neurological conditions and for a wide range of treatments to relieve pain.

# Overview

- Examine critically two leading arguments against placebo-controlled trials (PCTs) when proven effective treatments exist.
- Present criteria for ethical justification of PCTs that withhold proven effective treatment.

# Background

- Ethical concerns voiced about control groups not receiving treatment since 1940s.
- Recent debate intensified in 1994 following NEJM Sounding Board by Rothman and Michels.
- Revision to Declaration of Helsinki, October 2000.

# Declaration of Helsinki

- Principle 29: “The benefits, risk, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.”

# WMA Note of Clarification

- “A placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
  - Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method, or
  - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.”

# Arguments Against PCTs

- Argument from therapeutic obligation of physicians, invoking principle of clinical equipoise
- Argument from scientific/clinical merit

# Therapeutic Obligation

- Use of placebo controls when proven effective treatments exist violates duty of physicians to offer optimal medical care.
- When standard treatment (S) has been proven better than placebo (P), it is unethical to test investigational treatment (I) against P, which is known to be inferior to S.

# Clinical Equipoise

- Randomized controlled trials (RCTs) are ethical only if there is uncertainty in the expert medical community about the relative therapeutic value of the investigational and control treatments (and the standard of care).

# Trial of St. John's Wort (SJW)

- RCT comparing SJW, sertraline, and placebo in major depression (JAMA 2002;287:1807).
- There was equipoise between SJW and sertraline, but not between sertraline and P.
- Use of placebo randomized patients to treatment known to be inferior.

# Critique

- The problem with appeal to the therapeutic obligation in RCTs and the doctrine of clinical equipoise is that they confuse the ethics of clinical trials with the ethics of medical care.

# Ethical Distinction Between Clinical Trials and Medical Care

- RCTs differ from medical care:
  - Purpose
  - Characteristic methods
  - Justification of risks

# Purpose of RCTs

- To produce generalizable knowledge about treatment efficacy and safety by controlled experimentation in *groups* of patients with the aim of promoting improved medical care.
- Contrasts fundamentally with goal of medical therapy to provide personal care for *particular* patients.

# Characteristic Methods

- RCTs include randomization, blinding, placebos, protocols restricting treatment flexibility, and research procedures to measure study outcomes.
- These methods employed to answer scientific questions are foreign to the ethos of medical care.

# Justification of Risks

- RCTs include procedures for scientific purposes that carry risks of discomfort or harm to subjects without a prospect of benefit to them. These are justified by anticipated value of knowledge.
- In medical care, the risks of diagnostic and treatment interventions are justified by potential medical benefits to patients.

# Critique of Clinical Equipoise

- Given the basic differences between clinical research and medical care, obligations of clinical investigators are not the same as obligations of physicians in clinical practice.
- Investigators have duty to avoid harming or exploiting research participants, not therapeutic duty to provide optimal medical care.

# Critique Continued

- It is important to recognize that the need for uncertainty to justify conducting an RCT is not the same as the principle that patients should never be randomized to treatment known to be inferior.
  - There must be uncertainty about whether I is better than P.
- It doesn't follow that P is unethical when proven effective treatment exists.

# Critique Continued

- Consider PCT of new treatment for allergic rhinitis.
- What counts ethically in evaluating placebo controls is not “denial” of treatment but risks of harm and exploitation of participants.

# Argument from Scientific Merit

- When proven effective treatments exist, there is no clinical or scientific value in testing I against P.
- We want to know whether I is as good or better than S, not whether it is better than “nothing.”

# Critique

- Double-blind, placebo-controlled RCT is the most rigorous test of treatment efficacy.
- To test symptomatic treatments for many chronic conditions there are strong methodological considerations in favor of PCTs.

# Conditions that Favor PCTs

- Fluctuating symptoms and spontaneous remission
- High rates of placebo response: e.g., 30% in depression; 43% in irritable bowel syndrome.
- Partial efficacy of existing treatment
- Standard treatments not consistently superior to placebo in PCTs

# Methodological Problems with Active-Controlled Trials

- Problem with trials to demonstrate equivalence or “noninferiority.”
- If there is no statistically significant difference between I and S, two conclusions are possible:
  - Both I and S were effective;
  - Neither I nor S were effective.
  - Without placebo control, it is difficult to discern which conclusion is correct.

# SJW Trial

- Active controlled equivalence trial of SJW vs sertraline would pose problems of internal validity or “assay sensitivity.”
- It is worthwhile to determine if SJW is better than P, despite demonstrated efficacy of standard antidepressants.

# Trial Results

- Neither SJW nor sertraline had superior efficacy to P (N = 340).
- Without P, it might have been concluded that SJW is effective in treating major depression and equivalent to sertraline.

# Benefits of PCTs

- Stronger internal validity than active controlled equivalence trials in conditions with high rates of placebo response.
- More efficient
- Permit determination of whether adverse events are due to treatment or condition.

# Science Versus Ethics

- It might be argued that ethical norms should trump methodological considerations.
- However, scientific validity is a fundamental ethical protection.
- No person should be subjected to risks in study that lacks scientific validity.
- Methodological considerations in favor of PCTs and against ACTs are ethically relevant.

# Ethical Criteria for PCTs

- Scientific merit and clinical value
- Risks not serious or excessive
- Safeguards to minimize risks
- Informed consent

# Scientific Merit

- PCT should not be conducted if it is not needed to answer valuable research question or assure scientific validity of a scientifically valuable study.
- IRBs should require detailed scientific justification of placebo controls.

# Risk-Benefit Assessment

- Risks of P from withholding treatment must be minor or not severe.
- Value of knowledge to be gained from trial must be sufficient to justify risks.

# Risks of Placebo in PCTs of Antidepressants

- Large-scale meta-analysis of FDA database of trials of antidepressants, encompassing several thousand patients:
  - Those randomized to P not at significantly greater risk of suicide or attempted suicide.
  - Mean symptom reduction on P of 31% versus 41% for investigational and standard drugs.

Khan et al. Arch Gen Psychiatry 2000;57:311-17.

# Safeguards for Minimizing Risks

- Excluding subjects at higher risk of clinical deterioration
- Shortest trial duration necessary to test study hypotheses
- Careful procedures for monitoring
- Rescue medications available in response to symptom exacerbation
- Reasonable criteria for trial discontinuation in case of adverse events

# Informed Consent

- Assurance of capability to give informed consent
- Problem of “therapeutic misconception”

# What Do Participants Need to Understand?

- Participating in research
- Nature of study
- Meaning of “placebo” and rationale for use
- Random assignment
- Blinding
- Risks of symptom worsening
- Risks of lack of improvement
- Alternatives

# Conclusions

- Determining when placebo controls are justified depends on recognizing the ethically relevant differences between clinical trials and medical care.
- PCTs are often methodologically indicated and are not necessarily unethical when proven effective treatment exists.

# Conclusions

- Justifying PCTs despite the existence of proven effective treatment requires
  - Thorough risk-benefit assessment
  - Scrupulous informed consent
  - Careful monitoring of subjects.