Sham-controlled Trials: Ethical and Policy Considerations

Franklin G. Miller, Ph.D.
Department of Bioethics
National Institutes of Health
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Overview

• Historical background
• Critical examination of ethical concerns with use of sham controls
• Methodological rationale
• Risk-benefit issues
• Informed consent
• Policy considerations
Sources


Landmark Trials

• Ligation of internal mammary artery for angina (1959-1960)
• Fetal tissue transplantation for Parkinson’s Disease (1999-2001)
• Arthroscopic surgery for osteoarthritis of the knee (2002)
• Vertebroplasty for pain associated with vertebral fractures (2009)
Angina Trial

• Internal mammary artery ligation widely used to treat angina

• Investigators conducted 2 sham-controlled trials
  – Sham involved skin incision and local anesthesia
  – Substantial subjective improvement in both groups but no difference between ligation and sham

Henry Beecher

• Beecher lauded sham-controlled, double-blind angina trials in classic article, “Surgery as Placebo” (JAMA 1961;176:1102-7).
  – “Caution is essential in interpreting the results of new operations, since precision of evaluation can be achieved only with tests properly designed to rule out the bias of the patient or the surgeon.”
  – Unethical not to conduct rigorous evaluation of innovative surgical procedures.
Contemporary Debate

• Response to sham-controlled trials of fetal tissue transplantation for Parkinson’s Disease.
Risks in Sham Fetal Tissue Transplantation

• Freeman et al. (1999)
  – General anesthesia
  – Scalp incisions and burr holes in skull
  – Low doses of cyclosporine
  – Antibiotics
  – Radiation risks for PET scans

• Freed et al. (2001)
  – Local anesthesia
  – No immunosuppressive drugs
Criticisms of Sham-controlled Trials

“Using a sham surgery component . . . adds risks of foreseeable and preventable harm without a corresponding benefit to subjects in the control arm. As a result it is difficult to see how the use of sham surgery controls might be reconciled with the duty of personal care.”

Criticisms Continued

“It is undeniable that performing surgery in research subjects that has no potential therapeutic benefit fails to minimize the risks of harm. An alternative research design that did not involve sham surgery would pose a lower risk of harm to the subject in the control group.”

Ethical Concerns

• Do no harm
  – Sham procedures pose risk to patients without the potential for therapeutic benefit

• Minimizing risks
  – Sham-controlled trials pose greater net risks to subjects in control group than active-controlled trials comparing invasive procedure with medical or behavioral intervention
Critique of “Do No Harm”

• Confuses ethics of medical care with ethics of clinical research
  – The RCT is a scientific tool for evaluating treatment in groups of patients, not a form of personal therapy.
  – Central to ethics of clinical research is exposing subjects to procedures that carry risks to them without compensating prospect of benefit
    • Invasive procedures to measure study outcomes: biopsies, bronchoscopies, endoscopies, etc.
    • Sham controls no different in principle
Critical of Minimizing Risks

- Scientific validity is a basic principle of research ethics
- Risks should be minimized in context of valid scientific methods to answer clinically-relevant research questions
  - If RCT comparing invasive procedure with drug intervention not a valid design, then appealing to minimizing risks to criticize sham-controlled trials is irrelevant.
Critique continued

• Risks are minimized when there is no practicable alternative method of validly testing study hypotheses that poses less risks.

• Key questions:
  • Are risks of sham control excessive?
  • Can risks be justified by value of knowledge to be gained from the trial?
Methodological Rationale

- Sham-controlled trials permit double-blind assessment
  - Not possible for RCTs comparing invasive procedures with pharmacological or behavioral interventions
  - Sham controls desirable for subjective outcomes and placebo-responsive conditions to demonstrate that benefits result from physiological effects of procedure
Obesity and Sham-controlled Trials

• Obesity trials measure weight loss—an objective outcome
• Is there a need for sham-controlled trials?
  – Consider implantable gastric stimulator
  – Why not RCT comparing stimulator + nutritional counseling vs counseling alone?
Rationale for Sham Control

• Effort to lose weight may be influenced by psychological factors: motivation, expectation
  – Patients receiving invasive procedures may be more highly motivated and expect greater success
  – Masked sham intervention controls for these factors
Spectrum of risk in Sham Controls

- **Low risk:** acupuncture, transcranial magnetic stimulation
- **Modest risk:** minimally invasive surgery
  - Small skin incisions
  - Local anesthesia or sedating drugs
- **Moderate-Higher risk:** implantable devices, neural cell transplantation
Risk/Benefit in Stimulator Trials

• All patients receive implanted stimulator
  – Randomized to on vs. off
    • No added risks in off
  – Permits cross-over trials and open stimulator follow-up: prospect of benefit for all subjects
  – If device not beneficial, risks of continued implantation or removal
Risk-Benefit Assessment

• Have risks been minimized in context of valid methods to answer research question?
• Are risks of sham intervention within reasonable threshold of acceptable research risks?
  – No objective standards for limits to research risks
• Are risks of sham intervention justified by value of knowledge to be gained from trial?
  – Calls for judgment
Consent for Angina Trial

• “The patients were told only that they were participating in an evaluation of this operation; they were not informed of the double-blind nature of the study.”
  
  – No mention of randomization or use of sham procedure to evaluate real surgery

Arthroscopic Surgery Trial

• “All patients provided informed consent, which included writing in their chart, ‘On entering this study, I realize that I may receive only placebo surgery. I further realize that this means that I will not have surgery on my knee joint. This placebo surgery will not benefit my knee arthritis.’”

Deception

• Sham-controlled trials involve elaborate deception
  – Arthroscopic surgery trial: “The surgeon asked for all instruments and manipulated the knee as if arthroscopy was being performed. Saline was splashed to simulate the sounds of lavage.”

• Subjects should be told that deceptive techniques will be employed
  – Use of deception consistent with informed consent
Why do Patients Volunteer?

• No systematic data
• Possible reasons
  – Access to experimental treatments not otherwise available
  – Interest in helping others
• In arthroscopic surgery trial, 44% of eligible patients declined consent, suggesting no undue pressure to participate.
Summary: Key Ethical Questions

• Is research question clinically relevant and important?
• Is use of sham control methodologically necessary or desirable?
• Have risks been minimized?
• Are risks of sham acceptable and justified by value of knowledge?
• Will informed consent be obtained?
Policy Considerations

- Invasive procedures often introduced into clinical practice without rigorous assessment of effectiveness
  - FDA doesn’t regulate innovative invasive procedures (without devices)
  - Regulation of devices often less rigorous than drugs
  - Little or no incentive for industry to sponsor RCTs
  - Insurance plans often do not demand rigorous evidence
Policy Measures

- Stronger regulation of devices, consistent with regulation of drugs
- Making coverage of innovative procedures conditional on participation in RCTs (or at least use of registries)—coverage with evidence development (CED)
CED for Invasive Procedures

• Setting priorities for CED in context of RCTs
  – Seriousness of condition and poor outcomes from existing treatments
  – Large eligible population
  – Procedure carries substantial risks
  – Procedure ripe for evaluation: evidence of benefit promising but not definitive
  – High cost of intervention
  – Available trial sponsor
Conclusions

• Sham-controlled trials may be justified:
  – Methodologically necessary to produce valid results
  – Risks not excessive

• FDA and health insurance plans should foster rigorous efficacy assessment of invasive procedures before they are made available in clinical practice.