Patients Are Not a Means to an End: The Ethics of Placebo-Controlled Trials

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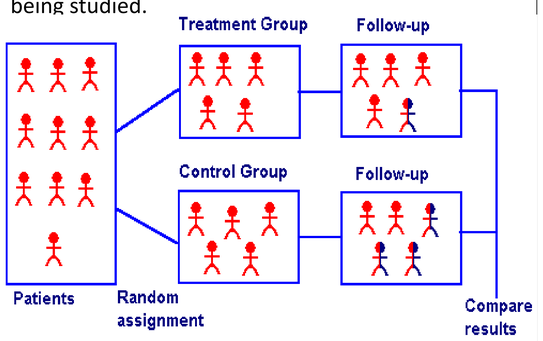
Introduction

The placebo effect is an improvement in a patient's condition caused by the expectation that a treatment will be helpful, rather than the true effect of the treatment. **Randomized controlled clinical trials (RCTs) attempt to provide therapeutic benefits for patients who need it, while recording data about treatment effects.** Researchers desire to minimize all forms of bias or convolution of data: demographic variables are minimized with randomization, observer bias is minimized with blinding, and sample sizes are preferred to be large to make data more statistically accurate. Attempting to minimize placebo bias has resulted in an orthodoxy of RCTs using placebo controls. In these studies, one group of subjects receives a placebo, usually in the form of saline injections or an inert pill, and one group of subjects receives the new treatment being examined. The major ethical problem with PCTs is that **minimizing placebo bias is the goal of researchers designing placebo controlled trials, and the means to this goal is providing patients seeking treatment with inadequate healthcare**. This project examines the arguments posed by placebo advocates as well as criticisms of these arguments. Ultimately, the dangers and ethical issues associated with withholding treatment from placebo group research subjects, as well as the existence of ethical criteria that allows for active-control trials (ACTs) as an alternative lead to the thesis that **placebo controlled trials (PCTs) should not be used when a standard treatment exists for the disease state in question**.

Basic Terminology

Randomized controlled trials: study design that randomly assigns participants into an experimental group or a control group; as the study is conducted, the only expected difference between the control and experimental groups is the outcome variable being studied.



FDA: this agency approves or denies whether drugs can be available for physicians to prescribe to patients after clinical trials have been conducted

Placebo treatment: a false treatment in the form of an inactive substance like sugar, distilled water, or saline solution. It allows for comparison to make sure drugs are not "effective" simply because a patient has the expectation that it will be helpful.

Institutional Review Board(IRB): committee which oversees research to ensure proper ethical, legal, and institutional conduct. IRBs approve or deny the initiation or continuation of trials, and researchers are held accountable by these committees.

Phillip's paradox: placebo-controlled trials are only useful when the experimental drug is not effective; if the experimental group is doing very well, the trial is more likely to be unblinded by subjects or investigators. If everyone knows which group is which, the results can be uninterpretable because of the possible expectancy effect (few studies check whether blinding is maintained!).

Traditional Philosophy

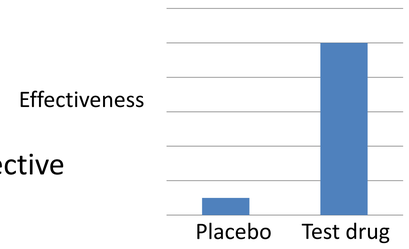
- **Utilitarianism**- more like clinical research, especially with placebo controls
  - Greatest net good for all those affected by research (presumably more accurate trial data)
  - Future-directed
  - Community > individual
  - PCT advocates argue that research is different than medicine and should have different rules
  - to allow for scientific progress (the **difference position**)
- **Kantian deontology-** more like clinical medicine
  - People are not a means to any goals
  - Individual > community
  - Immoral to make exceptions for certain groups– maxims are universally applied
- Active controlled trials
  - Allow researchers to operate with Kantian approach
  - Patient autonomy and adequate treatment

Kantianism	Utilitarianism
Motive/means	Consequences
Autonomy	Pleasure/ happiness
Chooser's POV	Impersonal POV
Categorical imperative	Utility calculation

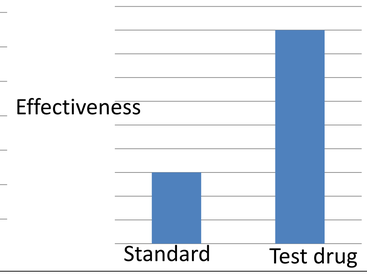
Active Controlled Trials and Clinical Equipoise

- ACTs– more ethical than PCTs
  - Design: test drug group compared with standard treatment control
  - Standard treatment control: treatment currently used by physicians for disease state of interest
  - All patient-subjects receive adequate treatment
    - No inert placebo controls
- **Clinical equipoise**– ethical standard
  - Est. by Benjamin Freedman in 1990
  - State of equipoise = genuine uncertainty about which drug is more effective
  - Clinical equipoise: medical community is not in agreement about which drug is more effective
  - PCTs can never meet equipoise requirement– placebo is not a treatment
  - ACTs with standard treatment controls can comply with equipoise ethics standard

Abstraction of a PCT result



Abstraction of an ACT result



Justifications for PCTs

- PCT advocates argue that PCTs can be safe and nondeceptive, therefore ethical
  - Safe: **minimization of risks**
  - Nondeceptive: obtain **informed consent**

Criticisms of Justifications

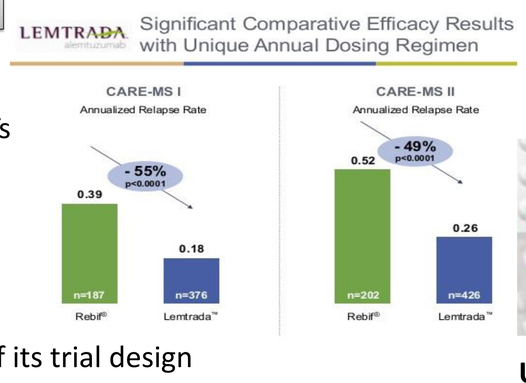
- Problems with minimizing risks as a justification
  - Variable valuation of "excessive risk" among researchers
  - Variable valuation of "excessive risk" between researchers and patient-subjects
  - IRBs use risk-benefit analysis for health concerns of patient-subjects
- Problems with informed consent as a justification
  - **Therapeutic misconception**
    - Patients feel cared for in clinical research setting
    - Motives for trial participation are not altruistic

The therapeutic misconception: Does this look like treatment, or an experiment?

Dr. Charles Weijer compares the **difference position** to Dr. Jekyll & Mr. Hyde: are you receiving treatment from a physician or from a researcher?

Legal Background and Incentives for Placebo Orthodoxy

- U.S. Department of Health and Human Services (HHS) vs Food and Drug Administration (FDA)
  - HHS guidebook for IRBs encourages ACTs and clinical equipoise
  - FDA shows preference for PCTs, **enforces** preference with ability to reject drug applications that do not use PCTs
- Examples of FDA rejecting ACT tested drugs
  - 1982 beta blocker tested against FDA-approved control
  - 2013: Lemtrada
    - Prevention of multiple sclerosis relapse
    - ACT used because test drug has obvious side effects that would unblind study (**Phillip's paradox**)
    - Tested against FDA-approved control, Rebif– Lemtrada did better than Rebif but was rejected because of its trial design
    - Another application takes years and over $100 million to follow "gold standard" of PCT
  - Both examples have excessive risk for placebo group patient-subjects
  - Both examples are very similar though 30 years apart



Update: the FDA reversed its decision about Lemtrada in November 2014!