



Ethics in the Design of Clinical Research

Jeremy Sugarman, MD, MPH, MA
Berman Institute of Bioethics
Johns Hopkins University
Baltimore, Maryland USA



Overview

- Randomization
- Placebos



A Case

Oncologists at a referral hospital in Taiwan want to evaluate a promising therapy for its efficacy in treating head & neck cancer. Although their scientific training suggests the need for a randomized, controlled trial, they are reluctant to do so because they believe it would be impossible to obtain informed consent because if they share this design with the patients, the patients will seek care elsewhere, probably from traditional healers.



Working with Randomization

- The problem
- Why use randomization?
- Conflicts associated with randomization
 - Research design
 - The tight relationship of clinical care and research



The Problem

- Uncontrolled observations may not be valid
 - The humbling history of medicine
 - The existence of marked clinical variation
- Controlled observations may threaten validity



Why Use Randomization?

- Minimize observer bias
- Minimize patient selection bias



Conflicts Related to Research Design

- Theoretical/Individual equipoise
- Clinical equipoise



Theoretical Equipoise

- “Theoretical equipoise exists when, overall, the evidence on behalf of two alternative treatment regimens is exactly balanced.”
- Evidence derives from literature, experience, theory, and instinct
- Held by an individual



Problems with Theoretical Equipoise

- Not suited for a complicated world
- Sensitive to the investigator's perception
- Personal and idiosyncratic



Clinical Equipoise

- “There is no consensus within the expert clinical community about the alternatives to be tested.”
- Consistent with decided treatment preferences of an investigator
- Medicine is social rather than individual
- Clinical equipoise does not require concealing information from subjects



Tensions Associated with Randomization

- Conflicts related to research design
- Conflicts related to the tight relationship of care and research
 - Conflicting obligations
 - Practical challenges



Conflicting Obligations

- Clinician
 - Patient welfare
 - Loyalty and fidelity
- Investigator
 - Acquisition of knowledge
 - Objectivity



Practical Challenges

- Informed consent
- Preserve individual treatment
- Permit treatment preferences



Informed Consent

- ❑ Reluctance to approach patients with uncertainty
- ❑ Reluctance to have treatment selected by chance
- ❑ The therapeutic misconception
- ❑ Cultural barriers



Practical Challenges

- Informed consent
- **Preserve individual treatment**
- **Permit treatment preferences**

Vertical Transmission Studies and Placebo Controls

- US study 076
 - The regimen
 - Oral AZT during pregnancy
 - IV AZT during labor and delivery
 - No breast feeding
 - The results
 - Decreased vertical transmission to 8%
- Contemporaneous trials in Africa and Asia
 - Lurie and Wolf
 - Angell: Tuskegee analogy
 - Angell M, The ethics of clinical research in the third world. *NEJM* 1997; 337: 847-849



Declaration of Helsinki

(October 2000)

- “The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.”



Research Design and Placebos

- Why?
 - Smaller sample size
 - Improved assessments of efficacy and safety
- When?
 - No known effective treatment
 - Others?

Placebo-Controls in Short-Term Clinical Trials of Hypertension

Sana M. Al-Khatib, Robert M. Califf, Vic Hasselblad, John H. Alexander, Douglas C. McCrory, Jeremy Sugarman

Science 2001; 292: 2013-2015



Background

- Short-term placebo-controlled trials for mild to moderate hypertension are common, despite claims that they are ‘unethical’
- ICH would seem to permit such trials, “if withholding the effective treatment leads to no serious harm and if patients are fully informed about available therapies and the consequences of delayed treatment.”



Methods

- Medline search, 1/97-12/98
- Inclusion criteria
 - RCTs
 - Mild to moderate hypertension
 - Non-pregnant adults
 - Placebo use
 - Trial duration <20 weeks
 - Primary data
- Articles abstracted

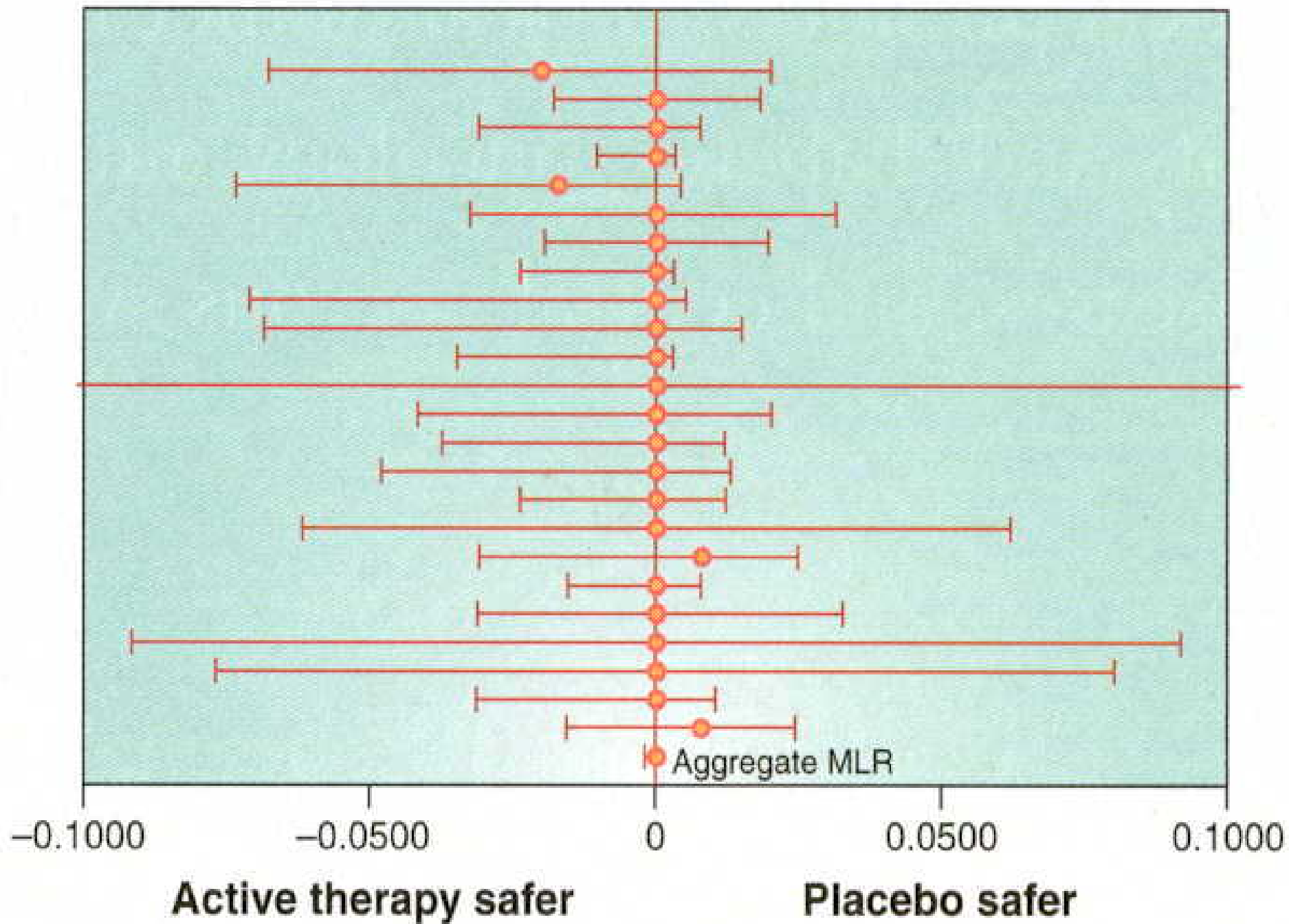


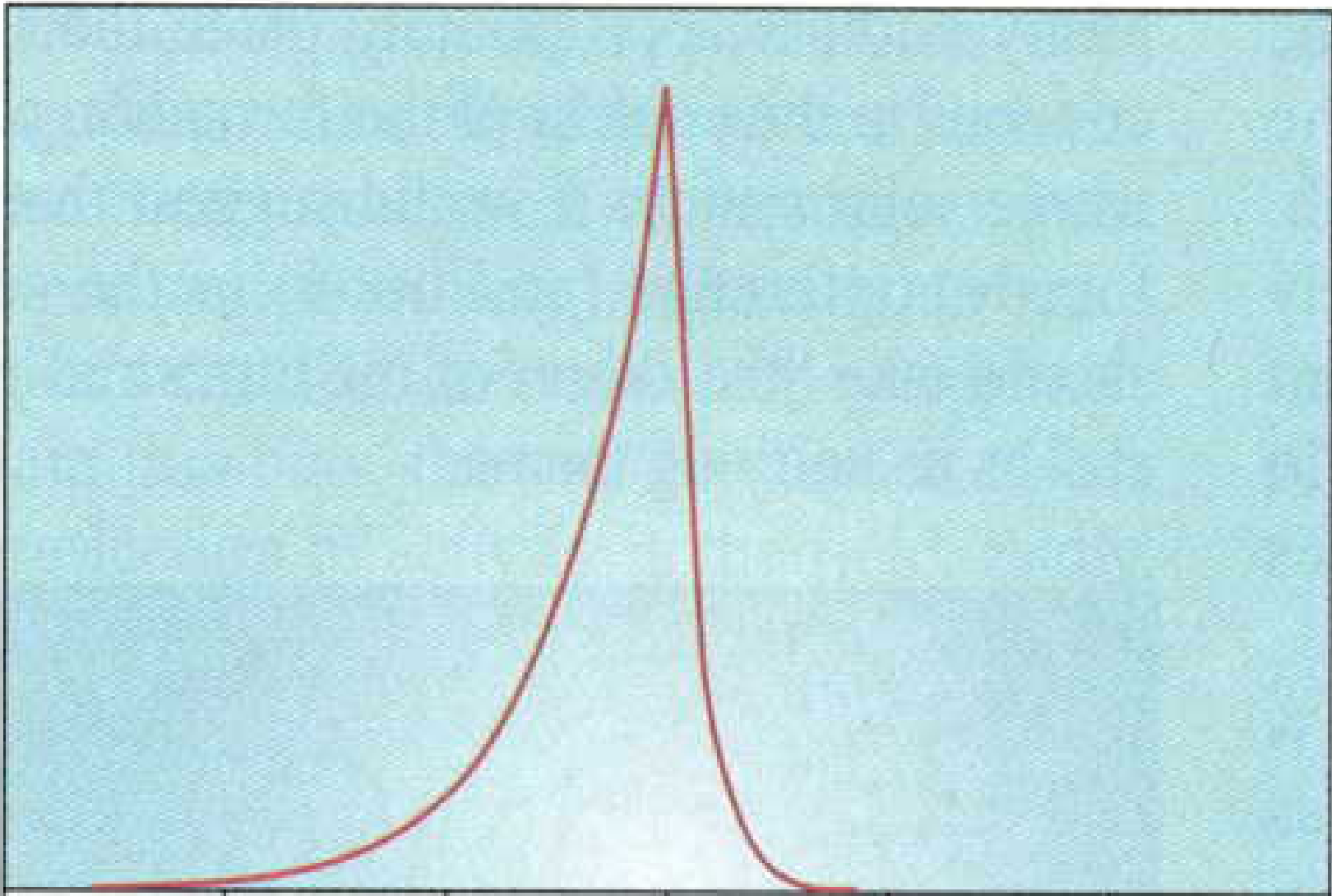
Results

- 267 postings
- 80 met inclusion criteria
- 25 provided adequate data for abstraction
- Sample sizes 20-734
- Total sample of 6409
- Power to detect 2.5 in 1000 difference in treatment arms

Serious Adverse Events by Treatment Group

SAE	Active	Placebo
N	4,878	1,604
Death	2	2
Stroke	2	0
MI	2	3
CHF	0	0
Total	6	5





-0.006

-0.004

-0.002

0

0.002

0.004

0.006

Active therapy safer

Placebo safer



Analyses

- Maximum-likelihood method
 - difference=0, 95% CI: -0.002 to 0.0006
- Bayesian posterior analysis
 - 50th percentile for the posterior distribution of the difference = -0.0004 ; 95% credible set limits: -0.003 to 0.0006



Explanation of Findings

- Trials are of short duration
- Only patients with mild or moderate disease
- Patient-subjects closely monitored



Lessons

- When medical treatments involve long-term benefits, determining whether placebo-controls are appropriate involves understanding the duration of treatment to confer such benefits – this is an empirical question
- General edicts concerning placebo use need to be sensitive to the real risks and benefits involved



FOOTNOTE:

NOTE OF CLARIFICATION ON PARAGRAPH 29 of the WMA DECLARATION OF HELSINKI

- **The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. *However, 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.*

- **All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.**

http://www.wma.net/e/policy/17-c_e.html



Declaration of Helsinki (2008)

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.



Conclusions

- The design of research raises important ethical issues
- Attending to the ethical aspects of research design can help meet investigators' ethical obligations towards those who are willing to participate in this research