

Ethical Issues in Clinical Research

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Overview

- Research Design
  - Randomization
  - Placebos
  - Confidentiality
  - Selection of Subjects
- Informed Consent



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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.



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### Working with Randomization

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



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### The Problem

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



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### Why Use Randomization?

- Minimize observer bias
- Minimize patient selection bias



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### Conflicts Related to Research Design

- Theoretical/Individual equipoise
- Clinical equipoise



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### 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



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### Problems with Theoretical Equipoise

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



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### 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



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### Tensions Associated with Randomization

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



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### Conflicting Obligations

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



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### Practical Challenges

- Informed consent
- Preserve individual treatment
- Permit treatment preferences



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### Informed Consent

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



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### Practical Challenges

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



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**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

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**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.”

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**Research Design and Placebos**

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

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**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](http://www.wma.net/e/policy/17-c_e.html)



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### 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.

<http://www.wma.net/en/30publications/10policies/b3/index.html>



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### Declaration of Helsinki (2013) Use of Placebo



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

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

<http://www.wma.net/en/30publications/10policies/b3/>



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### Confidentiality

- Why?
  - Desire for balanced recruitment
  - Desire for “good” information
  - Protect participants from social risks: insurance, jobs, housing, and the law
- When?
  - Any research posing potential social and some economic risks
- Challenges?
  - Must be considered in the design of research
  - Strategies may be expensive



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### Shifting Claims/Justice & Subject Selection

- AIDS activism
- Cancer activism



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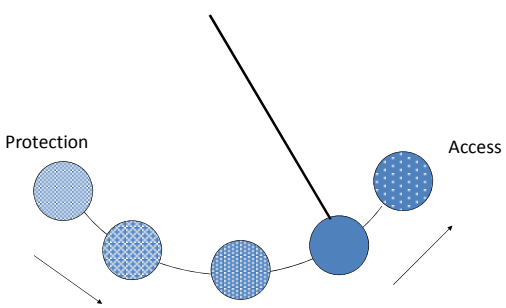
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**Justice as Access**

- The 'vulnerable sick'
- Children
- Women
- Minorities

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**Subject Selection**

- Why?
  - Generalizability
  - Justice
- When?
  - Disease or condition is of relevance to the population or population subgroup
- Challenges?
  - Statistical power
  - Recruitment and retention

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**Two Senses of Informed Consent**

- Autonomous authorization
- Social rules of consent

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### Autonomous Authorization

- Ethical principle of respect for persons
- Right to liberty



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### Two Senses of Informed Consent

- Autonomous authorization
- Social rules of consent



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### Social Rules

- Consent of minors
- Special forms
- Witnesses



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Informed Consent Process

**Threshold**

- Decision-making capacity



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Informed Consent Process

**Threshold**

- Decision-making capacity
- Voluntariness



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Informed Consent Process

**Information**

- Disclosure

**Threshold**

- Decision-making capacity
- Voluntariness



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## Informed Consent Process

**Information**

- Disclosure
- Understanding

**Threshold**

- Decision-making capacity
- Voluntariness

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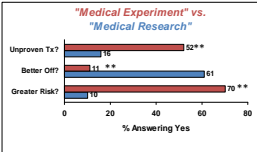
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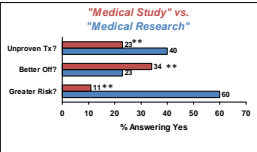
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## How do patients understand terminology?


*"Medical Experiment" vs. "Medical Research"*




*"Medical Study" vs. "Medical Research"*





*"Clinical Investigation" vs. "Medical Research"*



*"Clinical Trial" vs. "Medical Research"*



Slide courtesy of Dan Nelson  
Sugarman, et al, IRB 20:1-7, 1998

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## Informed Consent Process

**Information**



- Disclosure
- Understanding

**Authorization**

- Indication of agreement
- Consent forms:
  - Consistent with disclosure
  - Readable

**Threshold**

- Decision-making capacity
- Voluntariness

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**Concluding Comments**

- The design and conduct of research is associated with important ethical issues
- Attending to these issues can help meet investigators' ethical obligations towards those who are willing to participate in research

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