

# Ethics in the Design of Clinical Research

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# Overview

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- Randomization
- Placebos
- Confidentiality
- Selection of subjects
- Risks and benefits



# A Case

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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

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



# The Problem

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- 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?

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- Minimize observer bias
- Minimize patient selection bias



# Conflicts Related to Research Design

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- Theoretical/Individual equipoise
- Clinical equipoise



# Theoretical Equipoise

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- “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

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



# Clinical Equipoise

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- “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

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



# Conflicting Obligations

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



# Practical Challenges

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- Informed consent
- Preserve individual treatment
- Permit treatment preferences



# Informed Consent

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



# Practical Challenges

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



# Vertical Transmission Studies and Placebo Controls

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- 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)

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- “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

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



## FOOTNOTE:

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

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- **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)



# Declaration of Helsinki (2008)

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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.



# Confidentiality

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- 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



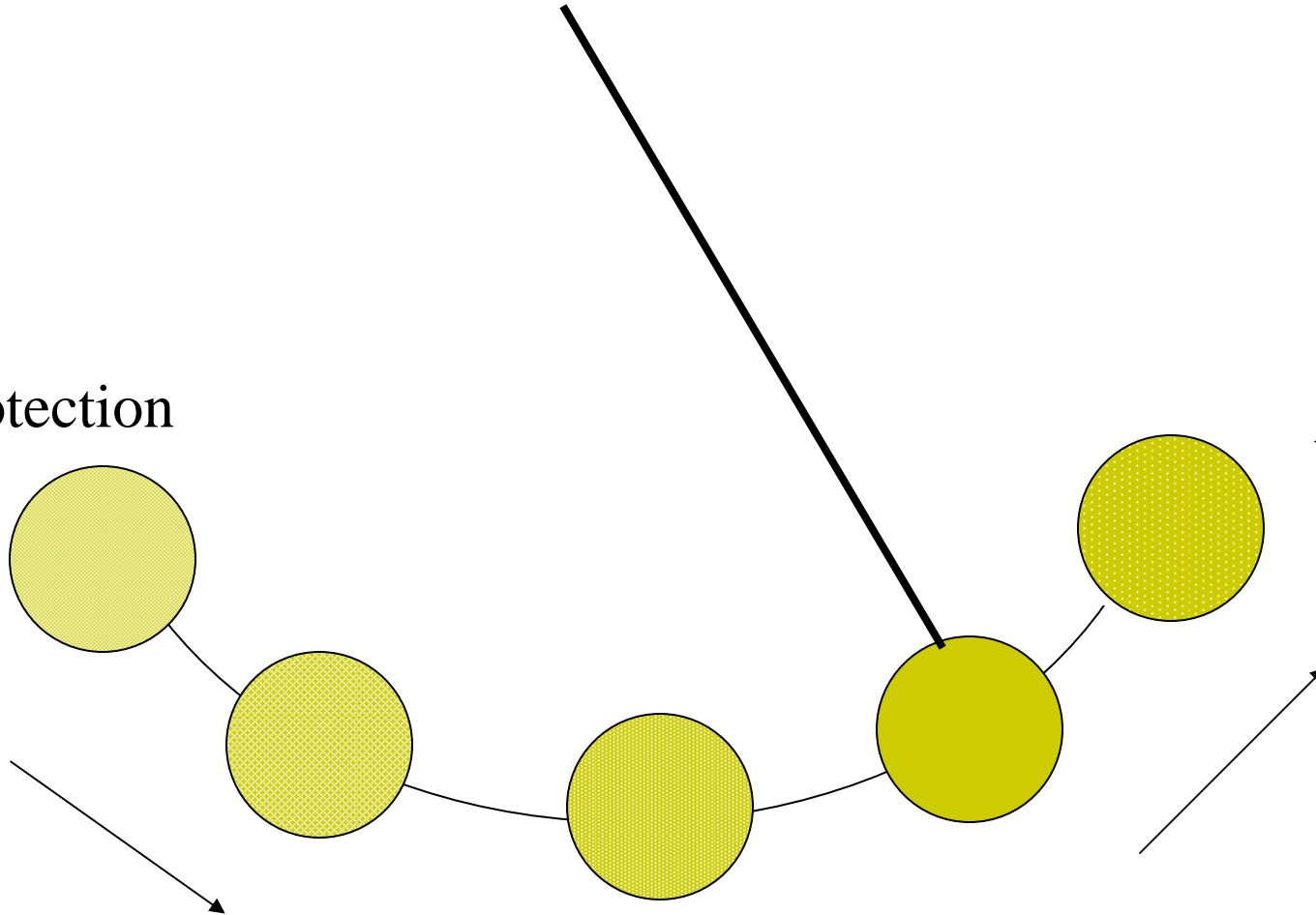
# Shifting Claims about Justice and Subject Selection

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- AIDS activism
- Cancer activism

Protection

Access





# Justice as Access

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- The ‘vulnerable sick’
- Children
- Women
- Minorities



# Subject Selection

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



# A Case

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- Endemic hypothyroidism in West African nation
- Randomized trial of iodinated salt



# Risks and Benefits

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- Traditional attention to risk partially eclipsed by concerns of consent and benefit
- Recognized by numerous international bodies
  - Risks to subjects are minimized
  - Risks to subjects are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may be expected to result
- Attention to welfare as well as rights



# Risk

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- “The possibility of suffering harm or loss”
- Risk does not mean harm!



# Risks

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- Types
- Quantification
- Level



# Types of Risk

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- Physical
- Psychological
- Social
- Economic



# Quantifying Risk

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- Likelihood
- Severity
- Duration



# Level: Making Risk Assessments

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- Empirical data
- Experts



# Minimizing Risks

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- ❑ Qualified personnel
- ❑ Substitution of procedures
- ❑ Monitoring
- ❑ Exclude especially susceptible subjects



# Benefits

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- Types
- Quantification
- Level



# Types of Benefit

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- Direct
- Collateral
- Aspirational



# Direct Benefit

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- Arising from receiving the intervention being studied



# Collateral Benefit

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- Also called “indirect” benefit
- Arising from being a subject, even if one does not receive the experimental intervention
  - Medical care
  - Gratification
  - Compensation



# Aspirational Benefit

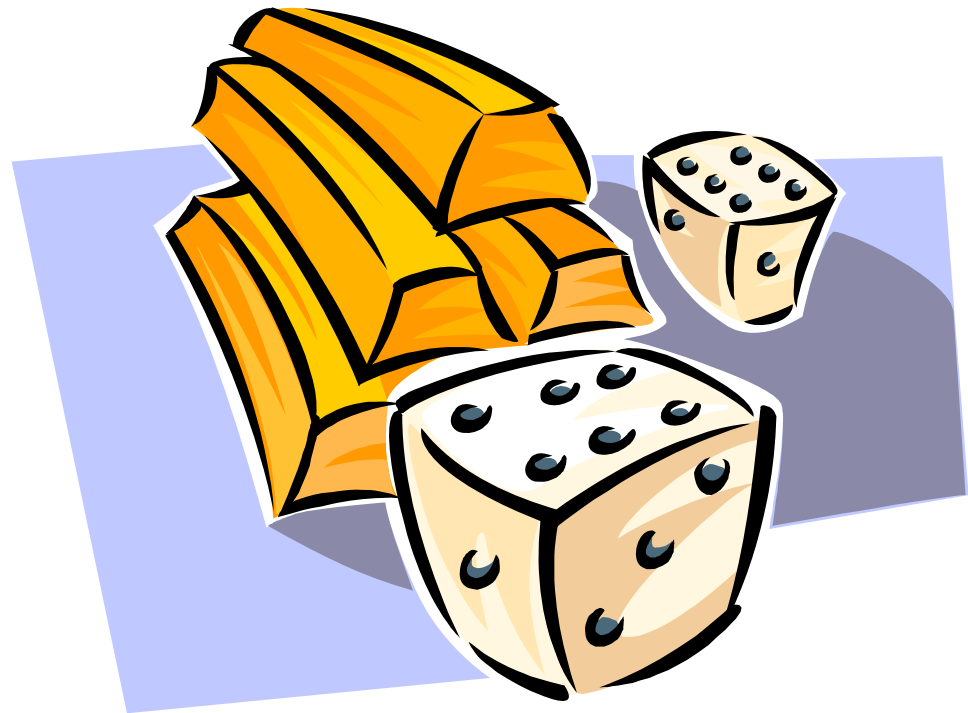
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- Benefit to society and to future patients
- Arises from the results of the study

# Quantifying Benefits

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- Likelihood
- Magnitude
  - Size
  - Duration





# Level of Benefit

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- What is the nature of the benefit according to type of benefit?
  - Primary outcome measures
  - Secondary outcome measures



# Maximizing Benefits

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- Principle of beneficence
- Implications for informed consent
  - Avoid ambiguity
  - Avoid the therapeutic misconception
- Considerations with respect to justice



# Incommensurability in Balancing Risks and Benefits

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- Risks and benefits may affect different domains of health status
- Risks and benefits may affect different parties
  - Risks may be born by one individual to benefit another
  - Risks may be born by individuals to benefit society
  - Risks may be born by society to benefit individuals



# Summary Comments Regarding Risks and Benefits

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- Although balancing risks and benefits can be difficult, or impossible, there is an obligation to minimize risks and maximize potential benefits in research
- To do this task well requires a nuanced evaluation of risks and benefits
- Such an evaluation not only promotes the welfare of subjects but also enhances consent and the accuracy of claims about justice



# Conclusions

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- 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