Ethics of Power and Sample Size

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Learning Objectives

1. **Describe basic ethical concepts underlying trial design.**
2. **Define 3 key concepts important for ethical sample size determinations**
   - **Informed consent**
   - **Equipoise**
   - **Therapeutic misconception**

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Learning Objectives

3. **Understand ethical concerns in *over*powered studies**
4. **Understand ethical concerns in *under*powered studies**
5. **Understand the importance of early sample size and power planning**

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Learning Objectives

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Ethical issues affecting study design:

1. **Informed consent**
2. **Equipoise**
3. **Therapeutic misconception**
4. **Ethical balance**

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Informed Consent:
Protects research participants

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What is equipoise?

Hint: it's not the steroid used for race horses…

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Equipoise:
Between treatment arms of a study

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Null hypothesis:
Treatment arms are no different

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Therapeutic misconception:
Confuse research with treatment

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Research does not promise medical benefits to participants.

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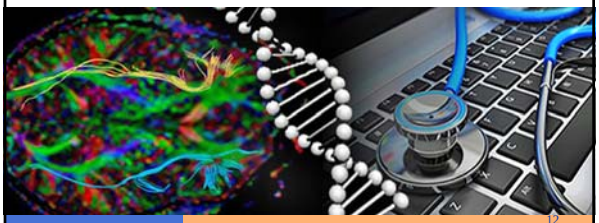
Factors Contributing to Therapeutic Misconception

Investigators: Overly optimistic

Participants: Misunderstanding risks, benefits, limitations



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Study Design: Maintain Ethical Balance

VALUE
to society and individuals ≥ **BURDEN**
to individuals

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What benefits accrue to participants?

- **Promise of helping others (altruism)**
- **Possibility of effectiveness**
- **Incidental care, diagnostics, payment**

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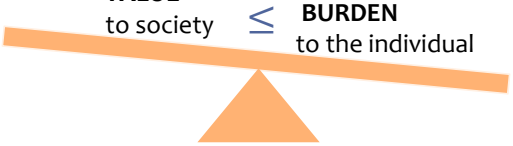
Minimal Benefit

VALUE
to society ≤ **BURDEN**
to the individual



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Cumulative Benefit

VALUE to society ≥ **BURDEN** to the individual

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Institutional Review Boards
IRB

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Inappropriate power and sample size can upset the ethical balance

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Why Most Published Research Findings Are False
John P. A. Ioannidis
PLoS Med. 2005 Aug; 2(8): e124.
Published online 2005 Aug 30. doi: 10.1371/journal.pmed.0020124
PMCID: PMC1182327

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Causes of Underpowered Studies

- **Efficacy vs effectiveness**
- **Promising early results**
- **Grantsmanship**
- **Funding restrictions**
- **More cynical reasons…**

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Example: Power calculated assuming perfect adherence to assigned treatment

- **Adherence is rarely perfect in clinical trials.**
- **One should calculate power under real world assumptions about adherence rates.**

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Underpowered studies fail to maintain ethical balance

All risk to individuals, no benefit to society, wasted resources

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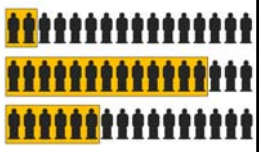
Researchers are responsible for forecasting realistic sample sizes in grant applications

- **Must account for potential loss to follow-up.**
- **Must recruit the sample size projected in grant to answer the research question!**



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Usually unethical to choose to do a trial that is underpowered

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Yet, underpowered studies are very common… especially in social sciences

"…failures to replicate may not be failures at all, but rather are the result of low statistical power in single replication studies, and the result of failure to appreciate the need for multiple replications in order to have enough power to identify true effects."

Lenth, 2001

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Why might you consider doing a trial that is underpowered?

Hard and expensive to recruit participants

And hey, underpowered studies might still contribute to overall scientific knowledge, right?

N.B. Much more likely if it's possible to combine results with other studies…

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OR

Underpowered studies might inspire discussion and further research.

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ETHICAL PROBLEMS WITH OVERPOWERED STUDIES

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Overpowered studies expose a greater number of individuals to burden than necessary

Burden to individuals increased, no increase in value to society, waste resources

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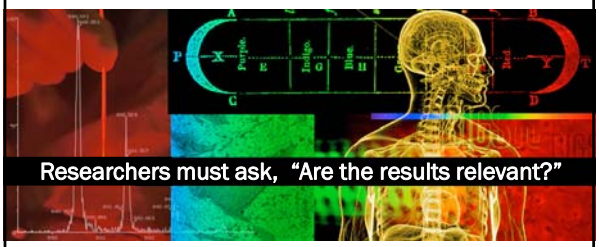
An overpowered study may detect statistically "significant" differences without clinical significance



Researchers must ask, "Are the results relevant?"

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Overpowered studies are also common… especially in drug development

Celik and Yazici (2014) list 40 examples and conclude: "Most RCTs in RA enroll more patients than needed. This is costly and has the immediate consequence of exposing needless number of patients to potential harm."

Why?

Lenth, 2001

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Studying multiple aims simultaneously may confound sample size selection

- **Sufficient power for one endpoint may result in too much power for another endpoint.**
- **Researchers must balance the risks and rewards of each research question.**
- **Participant input is useful in ethically balancing risks and rewards.**

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To be ethical…

- Sample size must be adequate to **answer the research question.**
- Unethical!
  - If sample too small, the research does **not** answer the question, puts participants at **risk unnecessarily, wastes resources.**
  - If sample too large, puts participants at **risk unnecessarily** and **wastes resource.**

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DISCUSSION