Ethics of Power and Sample Size

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Learning Objectives

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

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Learning Objectives

- Understand ethical concerns in *over*powered studies
- Understand ethical concerns in *under*powered studies
- Understand the importance of early sample size and power planning

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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:

- Informed consent requires that individuals freely agree to participate after being thoroughly informed of the:
  - purpose, risks, and benefits of the research
  - foreseeable limitations to the value of the research
  - if the study requires a sample size that will be difficult to recruit

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Equipoise

- Equipoise is a state of genuine uncertainty regarding whether study arms are equally useful or different; when we are genuinely uncertain (or there is legitimate disagreement) about whether treatment A is better or worse than treatment B.
- It is ethically required because it would be unethical to do a study of a treatment that the scientific community is already fully convinced is effective (or ineffective)
- NOT THE SAME AS than null hypothesis

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Therapeutic misconception

- This is the idea that a participants confuse treatments with research
- In reality, these two are not the same:
  - Treatment is the administration of a known or presumed effective solution to a problem
  - Research is conducted in order to develop effective solutions to problems and advance scientific knowledge

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Factors Contributing to Therapeutic Misconception

- Investigators: Overly optimistic
- Participants: Misunderstanding risks, benefits, limitations

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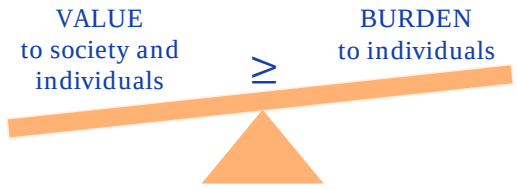
Study Design: Maintain Ethical Balance



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What benefits accrue to participants?

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

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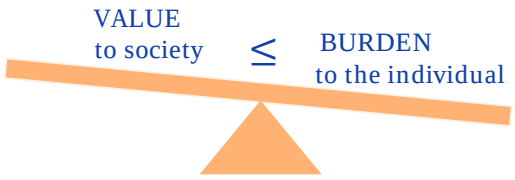
Minimal Benefit



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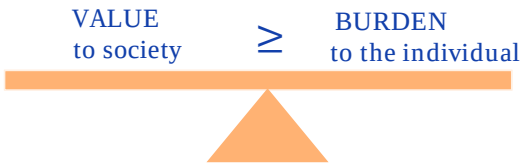
Cumulative Benefit



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Institutional Review Boards (IRBs)

- IRBs: responsible for evaluating the benefit-to-risk balance for proposed studies
- Most proposed research studies involving human participants must be approved by an IRB
- Often, the IRB will make recommendations for how to make adjustments to the study protocol to achieve balance, rather than simply rejecting or approving a study
  - Most commonly, these adjustments will relate to the informed consent process

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ETHICAL PROBLEMS WITH UNDERPOWERED STUDIES

Causes of Underpowered Studies

- Efficacy vs. effectiveness
- Misleading 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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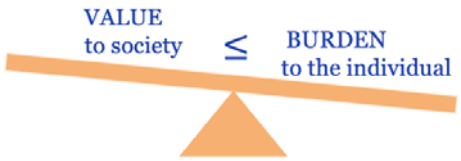
Underpowered studies fail to maintain ethical balance



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

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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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It is usually unethical to choose to do a trial that is underpowered

- **Reasons:** It might simply be impossible to accrue a large enough sample for the study
- **Example:** Recruitment in a population that is mistrusting of participation in research
- Another study design is probably necessary to do the research

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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?
  - Much more likely if it's possible to combine results with other studies
- Can inspire discussion/further research

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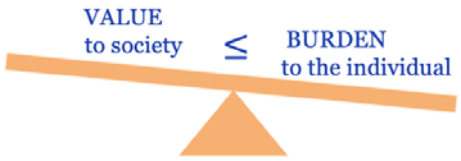
ETHICAL PROBLEMS WITH OVERPOWERED STUDIES

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

Are the results relevant? Do They matter?

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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?** Cynical reasons...

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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Summary

- To be ethical:
  - Sample size must be adequate to **answer the research question**.
- You are being unethical if:
  - Sample too small, the research does **not** answer the question, puts participants at **risk unnecessarily, wastes resources**.
  - Sample too large, puts participants at **risk unnecessarily** and **wastes resource**.

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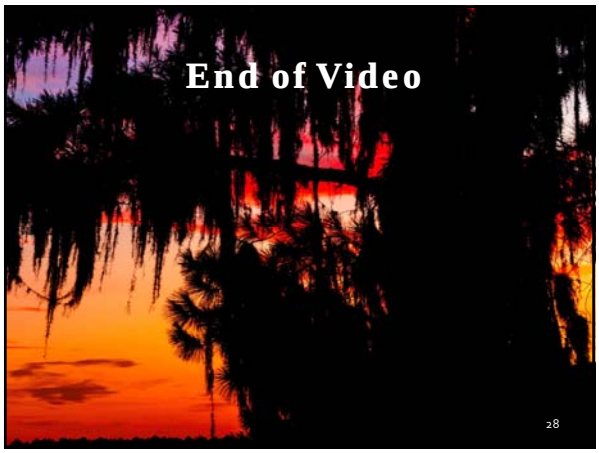
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