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Placebos, randomization, and financial incentives – oh my! Balancing ethical considerations in clinical research

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Learning Objectives

1. Describe eight benchmarks for ethical clinical research
2. Discuss how empirical data illustrates limitations of ethics regulations of randomization
3. Identify elements of a proposed research study that warrant ethical deliberation

Outline

1. Introduction to a framework for ethical clinical research
2. Case studies: what to do when benchmarks conflict
3. Group discussion and practice applying the framework

Please vote:

Do you consider yourself an ethically responsible researcher?

"Isn't ethics for people who have bad motivations?"

- Not just about preventing egregious violations - no such thing as the "ethics police"
- Also offers guidance, identifies potential challenges

Please vote:

Have you ever faced an ethical challenge in your research that was outside the scope of the IRB?

"Aren't there regulations for that?"

- Research ethics analysis helps flesh out responsibilities above the regulatory floor

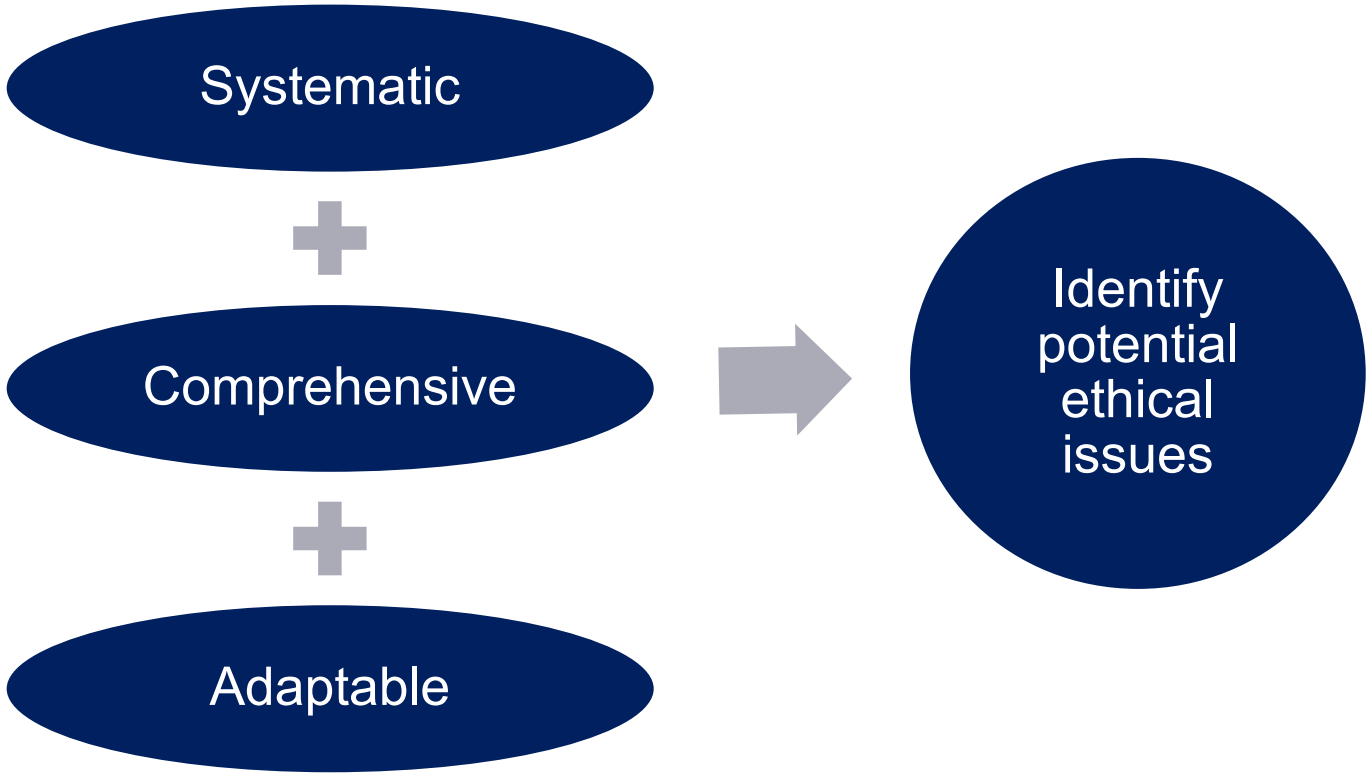
Please vote:

Have you ever raised an ethics issue to a colleague or PI?

"Is it really my job to worry about ethics?"

- Yes!
- Ethics analysis is important for all research team members
- Framework can empower researchers to identify and think through potential issues

A framework for ethical clinical research

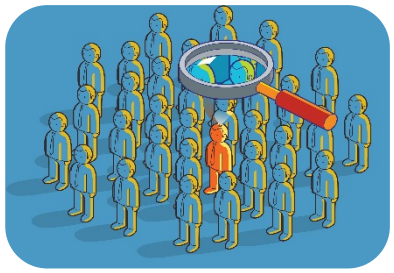


Eight benchmarks for ethical clinical research

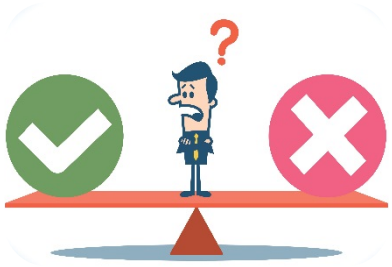
Collaborative partnership

Social value

Scientific validity



Fair subject selection



Favorable risk/benefit ratio

Independent review

Informed consent

Respect for participants and communities

Collaborative partnership

- Partner with the community in in planning, conducting, and overseeing research
- Share benefits with the community

Social value

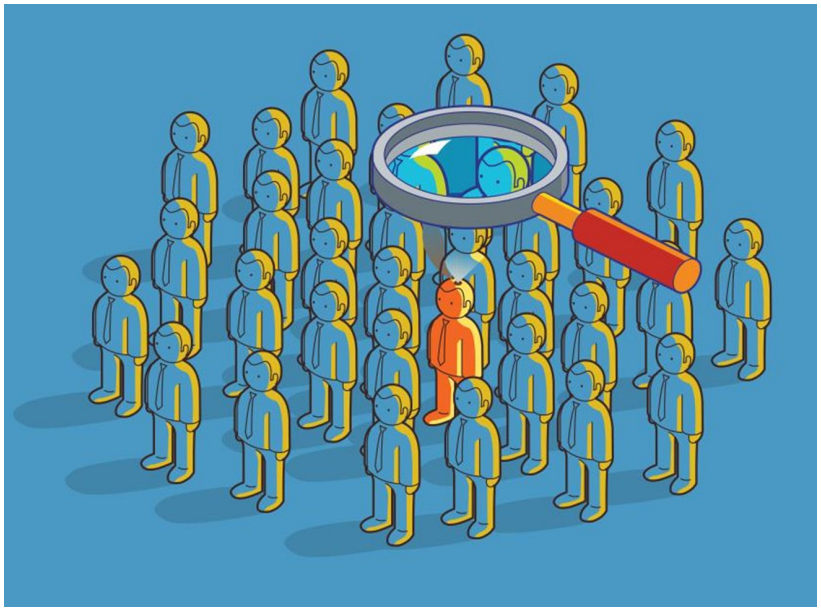
Improvements in health or generalizable medical knowledge for participants, community, and/or future patients

Scientific validity

- Reasonable possibility that research will produce valid scientific results
- Justifies resources used and risks/burdens undertaken

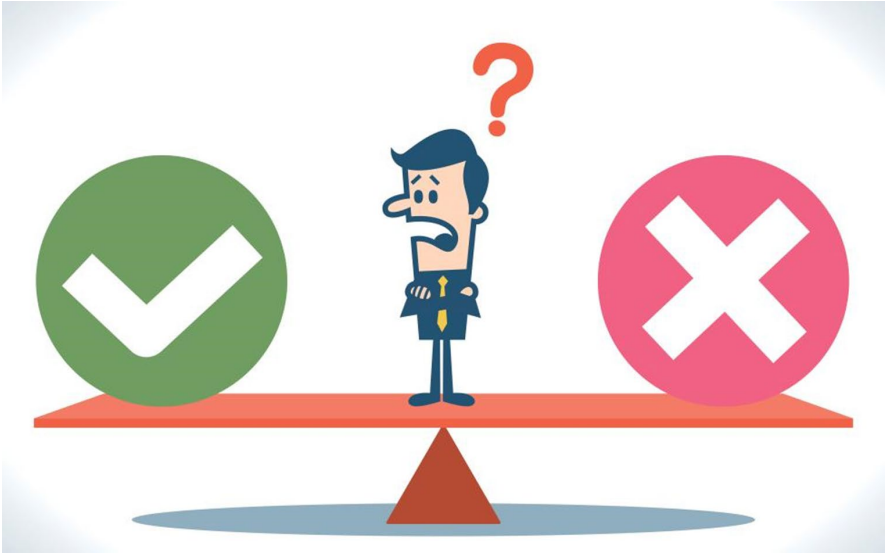
Fair subject selection

- Scientific objectives, not vulnerability or privilege, guide inclusion criteria and targeted populations
- Consider distribution of burdens and benefits of research



Favorable risk/benefit ratio

- Identify, assess, and minimize risks
- Identify and enhance potential benefits
- Weigh risks and benefits



Independent review

- Minimizes the impact of conflicts of interest
- Assures society that research is ethically appropriate and demonstrates trustworthiness

Informed consent

- A process (not just a form) by which people decide whether to take part in a study
- Serves multiple functions, including: providing transparency, allowing control, protecting welfare, building trust

Respect for participants and communities

Ongoing ethical requirements beyond consent, including:

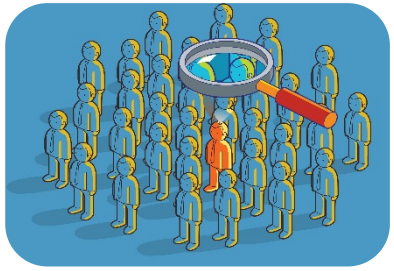
- Confidentiality
- Right to withdraw
- Consideration of group harms

Questions?

Collaborative partnership

Social value

Scientific validity



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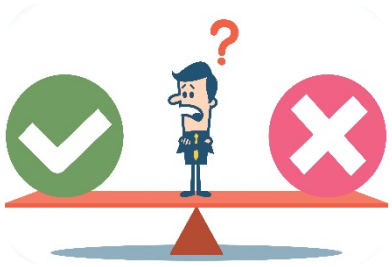


Favorable risk/benefit ratio

Independent review

Informed consent

Respect for participants and communities

Case: Randomization and risk (SUPPORT)

- Clinical guidelines (2003) recommended oxygen saturation targets in premature infants be set between 85-95%, but lots of practice variation within this range
- Researchers wanted to know if outcomes (retinopathy of prematurity, death) are better in upper vs. lower range
- Protocol randomized patients to upper vs. lower range; double-blinded using modified pulse oximeters

"The investigators incorrectly believed that because all infants were randomized to oxygen levels within the standard range it follows that the study involved no more than minimal risk.

The risks of the randomization made it more likely that there would be differences in the outcomes of the two groups including death, neurologic problems and ROP."

– Office for Human Research Protections, Letter to SUPPORT Investigators, 2013

Key ethical questions

- Does randomizing patients within the range of usual care introduce (more than minimal) risk? Why?
- What risks should be disclosed to potential participants and how?

"[Randomized controlled trials] offend common sense and upset our psychological well-being. **We hate to think that doctors don't know what is best**.

If doctors truly don't know what is best, … they must not be good doctors. Or, more disturbingly, if they do know what is best and they are still willing to choose a treatment by flipping a coin, then they are abdicating their fiduciary responsibilities."

– John Lantos, Randomized Trials Are Deeply Offensive, Am J Bioeth 2020

"The odd thing about such controversies is that everybody knows that doctors are often wrong and that medical recommendations change over time. … **Doctors can be massively and collectively wrong**."

– John Lantos, Randomized Trials Are Deeply Offensive, Am J Bioeth 2020

Two perspectives

Randomization is inherently risky

- Precludes clinical judgment of physician who has knowledge of patient, setting
- Hard to define true "clinical equipoise" in a constantly evolving system

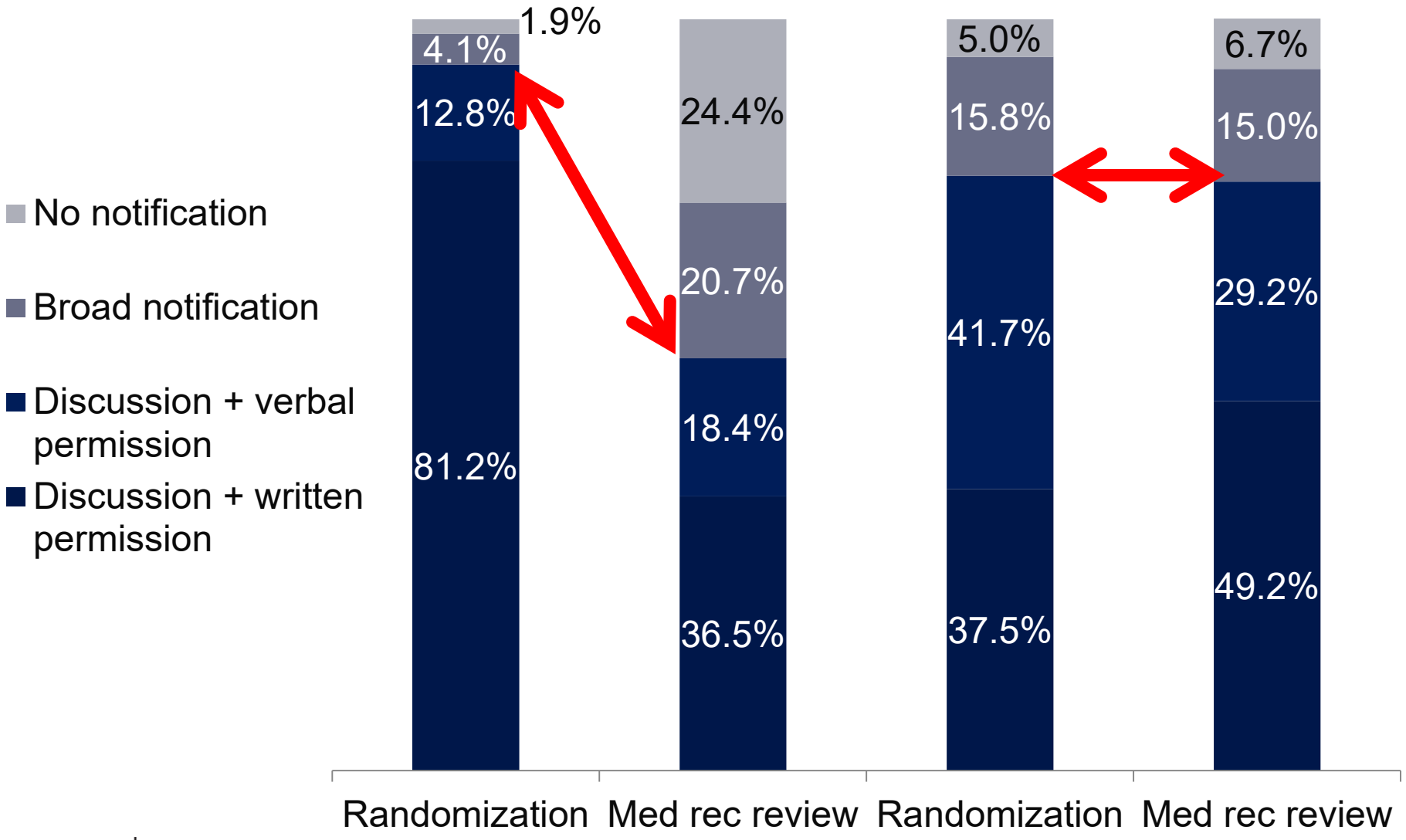
Randomization does not add risk

- Clinical risks exist regardless of whether a patient is in research
- Studying an uncertain outcome doesn't make it a risk

Empirical data: Surveys of patients, IRBs

In a [randomized/medical record review] study of two antihypertensive drugs that are both acceptable in clinical care, what approach to consent should be used?

- No notification
- Broad notification
- Verbal consent
- Written consent


No notification
Broad notification
Discussion + verbal permission
Discussion + written permission
1.9%
4.1%
12.8%
81.2%
24.4%
20.7%
18.4%
36.5%
5.0%
15.8%
41.7%
37.5%
6.7%
15.0%
29.2%
49.2%
Randomization
Med rec review
Randomization
Med rec review
IRB professionals
Patients

Randomization and risk: Empirical data

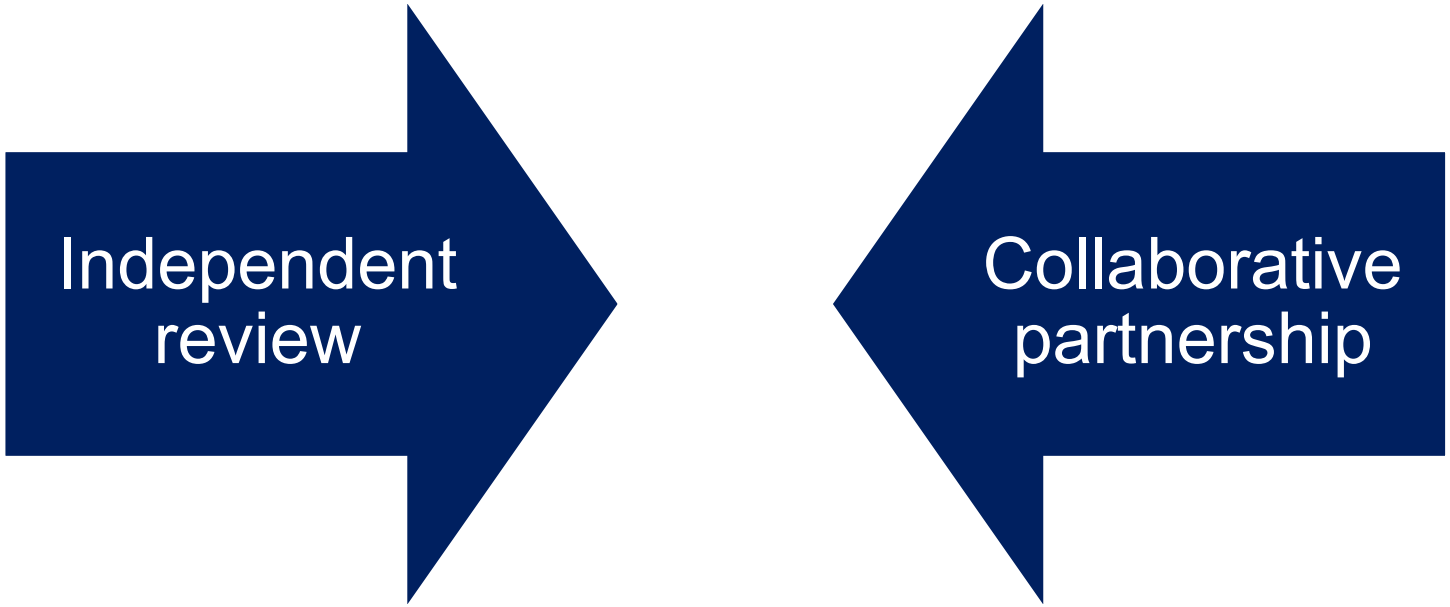
IRBs: randomization is special; focus on format of consent

Patients: just ask my permission; format doesn't matter

"Signing those forms was my first official act as her mother … The only thing I remember about any of those forms was how it felt to write next to my name that I was her mom."

– Kelly Benham, Oct 18, 2013, Tampa Bay Times

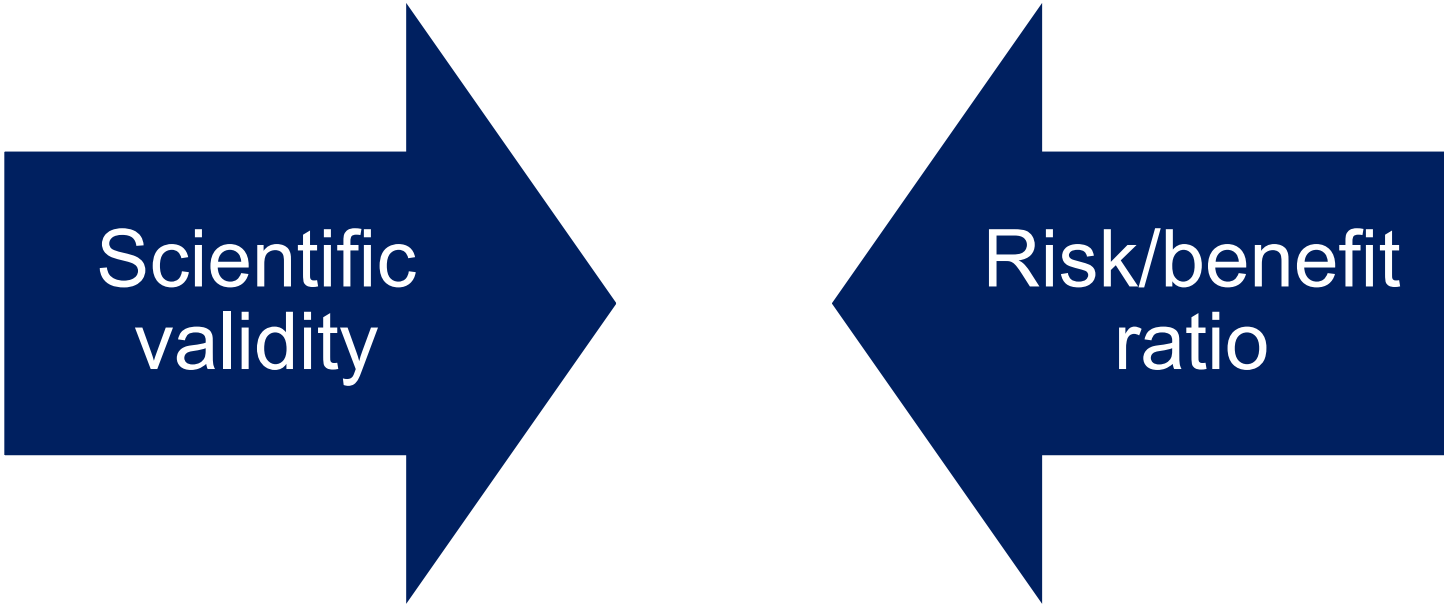
Conflicting benchmarks



Case: Placebos (ESSENCE)

- Randomized, double-blind, multicenter, 96 week study to evaluate a drug for Duchenne muscular dystrophy
- Intervention requires weekly IV infusions of drug or placebo
- One study site is requesting the ability to use a central venous access port instead of IV

Conflicting benchmarks



Scientific validity

- Randomized placebo-controlled trials = “gold standard”
- Controls for effects of treatment that don’t depend on the treatment itself (placebo effect)
- Can reduce biases, such as confirmation bias, placebo effect, observer effect
- Blinding requires that the two arms be treated the same (i.e. receive the drug/placebo in the same way(s))

Favorable risk/benefit ratio

- Risks of IV:
  - Underlying disease causes difficulty with PIV access
  - Increased anxiety/emotional trauma leading up to IV placement
  - Repeated and frequent placement
- Risks of central line:
  - Requires anesthesia for surgical placement/removal
  - Infection
  - Mechanical failure
- Benefits: intervention arm vs. placebo arm

Balancing in practice

- Explore other study designs
- Involve the relevant community (collaborative partnership)
  - How do parents/patients perceive the societal benefit versus individual risk?
- Determine what elements of study design are crucial for scientific validity and which can be sacrificed

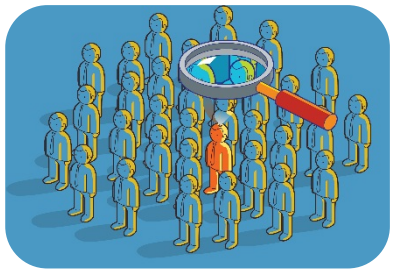
Case: Financial incentives in a human challenge study

- Healthy volunteers are paid up to $2500 to participate in a malaria human challenge study to test the efficacy of an anti-malarial drug
- Participants are exposed to malaria-carrying mosquitoes, then randomized to receive the experimental drug vs. placebo (all later receive treatment)
- Participants come in for regular blood draws for 6-8 weeks

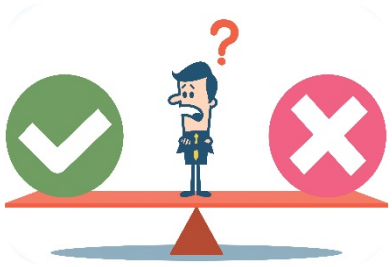
Collaborative partnership

Social value

Scientific validity



Fair subject selection



Favorable risk/benefit ratio

Independent review

Informed consent

Respect for participants and communities

Ethical questions

- Do the societal benefits outweigh the individual risks? (*social value, favorable risk/benefit ratio*)
- Do the financial incentives unduly influence decision-making and/or entice lower income individuals to join? (*fair subject selection, informed consent)*
- How much does it matter what participants think about this? (*collaborative partnership*)

Thank you!

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Research ethics consult service: iths.org/bioethics


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