

Risk-Benefit Assessment in Clinical Research

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Belmont Report

- “Systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible.”
- “The nature, probability and magnitude of risk should be distinguished with as much clarity as possible.”
- “Assessment of risks and benefits requires careful arrayal of relevant data.”

Scope of Talk

- In this talk, I will focus on the risks and benefits of clinical research for individual participants.
- Related issues: aggregate risks; aggregate benefits; 3rd parties; post-trial benefits.

Terms of Art

- 'Risks' and 'benefits' refer to all the good and bad things that can happen to participants, factored by their likelihood.
- 'Risks' refer to certain harms (pain of a needle stick), possible harms, and burdens (waiting).
- 'Benefits' refer to definite benefits, possible benefits, and decreased burdens.

Proposed Framework

1. Ensure value of interventions/study
2. Identify and minimize the risks
3. Identify and enhance the benefits
4. Benefits to participants justify the risks?
5. If yes: the intervention/study is acceptable (with respect to participant risks/benefits)
6. If no: are the 'net' risks acceptable?

Rid, Wendler. KIEJ 2011; 21:141–179

Component Analysis

- Clinical research studies are composed of different elements or interventions. For example, a clinical trial might administer an experimental treatment, require five clinic visits, and take blood 6 times.
- IRBs should apply the framework to the individual interventions, and then apply it to the study as a whole.

Research Interventions

- Studies often include clinical interventions and research interventions. For example, 3 blood draws may be for research and 3 for routine clinical care.
- For the most part, IRBs should focus on the risks and benefits of the research interventions.

US Regulations

“In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).”

45CFR§46.111 (2)

Clinical Interventions

- Typically, IRBs can assume that clinically indicated interventions pose acceptable risks.
- Does participation in the research alter the risk/benefit profile of clinically indicated interventions (e.g. experimental treatment increases the risks of standard treatments)?

Step 1: Social Value

- Research interventions should have the potential to gather valuable information.
- This evaluation requires expertise (e.g. knowledge of the disease, the intervention, alternatives) and is inherently speculative.

Step 1: Social Value

→ Should IRBs make comparative value judgments within or across studies?

Lack of clear prioritization “could easily lead to a situation where none of the trials would be able to recruit sufficient patients”

Beavogui et al Clin Trials 2016; 13:73-78.

Step 2: Identify/Minimize Risks

- The next step is to identify and minimize the risks of the research interventions.
- This evaluation should consider all the risks the interventions pose, including physical, psychological, social, and economic risks.

Challenge

- To identify the risks, one needs to know the impact of the interventions on participants.

→ Research is designed to evaluate the impact of the interventions on participants.

Approach: Consider relevant precedents: same class of drugs, similar mechanism of action, etc.

Another Challenge

- To decide whether to approve a study, IRBs must evaluate the risks and potential benefits *before* the study begins.
- But: the risks (and benefits) of research procedures often depend on who enrolls (e.g. good kidney function).

Responses

- To address this concern, studies can exclude those who face excessive risks.
- It also is important to monitor participants to ensure that risks remain acceptable during study participation.

The Implied Comparison

- Risk and benefit judgments rely on comparison to some baseline.
- For example: Does a phase II study of a treatment that has been shown safe and offers a small chance of helping participants offer the potential for clinical benefit?

Defining the Baseline

- It depends on what the individuals would experience absent the research.
- If, outside the research, the individuals would receive a drug that offers a high chance of cure, then the phase II study may be overall risky rather than beneficial.

Importance of Context

- To evaluate the risks of research, it is important to have reliable information on existing care for the participants.
- A trial may be risky in some places, but potentially beneficial in others.

Determining the Baseline

- Individuals may have relevantly different baselines for determining risks.
- Should IRBs determine the risks of a study by comparing the interventions to the expected alternative OR the appropriate alternative?

Lead Paint Studies

- Expose children who live in homes with lead paint to partially lead paint abated homes.
- Risky study? Beneficial study?

Ross. JLME. 2002;30(1):50-7

Minimize Risks

- Once risks have been identified, minimize them.
 - Blood draws: look away, jiggle cheek, EMLA, take research bloods during clinical draw.
- Minimizing risks can undermine social value (mandate fewer blood draws) and raise concerns of fairness (exclude participants without good venous access).

Step 3: The Potential Benefits

- Next identify the potential benefits of the research interventions.
- As with risk determinations, focus on the potential benefits above and beyond what individuals would receive absent the research (e.g. in clinical care).

What Counts as a Benefit?

- Many research studies offer financial incentives and compensation.
- Does payment count as a benefit to participants?

Difference

- Most commentators argue that IRBs should consider only the clinical or ‘direct’ benefits of research, not any indirect, inclusion, or financial benefits.
- But: IRBs are supposed to consider all the risks, including financial ones.

The Philosophers' Clinic

- Study in which participants paid \$100 for a research biopsy, but will have to pay \$100 for antibiotics if the site gets infected.
- Most commentators regard the potential \$100 costs as (economic) risks of the research, but do not regard the \$100 payment as a benefit.
- Does this difference make sense?

Enhance Benefits

- Once the potential benefits have been identified, enhance them.
- For example, limit the study to individuals who are very ill (or limit it to less ill individuals to minimize the risks).

Step 4: Risk-Benefit profile

- Determine whether the benefits to participants justify the risks, and whether the risk/benefit profile of the intervention (study) is at least as favorable as the available alternatives.
- If YES: the intervention (study) is acceptable (with respect to participant risks and benefits).

Justifying Risks

- What does it mean for the benefits of research participation to "justify" the risks?
- The ethical question is whether the risks exceed the benefits for participants.
- Hence: assess whether the benefits are equivalent to, or outweigh, the risks (i.e. no 'net' risks).

Informed Clinician Test

- How do we determine whether the benefits are equivalent to, or outweigh, the risks?
- There is no algorithm for making this determination.
- Informed Clinician Test: Would an informed clinician recommend that potential participants undergo the intervention?

The Assessment

- If the clinician would recommend the intervention, the potential benefits justify the risks (no net risks).
- If the clinician would not recommend it, the potential benefits do not justify the risks.
- These interventions pose 'net' risks.

Fallacy of the Package Deal

- Many commentators argue that the potential benefits of a research intervention can justify only the risks that it poses (not the risks of other interventions in the same study).
- In particular, the potential benefits of the treatment being tested cannot justify the risks of research procedures in the study (e.g. biopsies).

Justification and Challenge

- This approach precludes investigators from adding risky and unrelated biopsies to a study that offers potentially life-saving treatment.
- But: what about a study of an experimental treatment for cancer that requires a research biopsy to assess the treatment?

Necessary Interventions

Clinical Necessity: Experimental treatment requires an initial biopsy to ensure it's safe; Overall risk-benefit profile is favorable.

Research Necessity: Assessing the experimental treatment requires a follow-up research biopsy; Overall risk-benefit profile is favorable.

Should these be treated differently?

Net Risks

- If the intervention (study) poses net risks: Are the net risks acceptable or excessive?
 - Are the net risks justified by the social value of the intervention (study)?
- Should the order of these bullets be reversed?

Net Risk Research

- Some commentators argue that whether net risks are acceptable depends on whether the intervention (study) is “therapeutic” (intended or designed to benefit participants) or is given with “therapeutic warrant”.

Weijer and Miller

“clinical trials often contain a mixture of interventions...some are administered on the basis of evidence sufficient to justify the belief that they may benefit research subjects...others are given without therapeutic warrant. They are administered solely for the purpose of answering the scientific question. As this distinction is morally relevant, IRBs must apply separate moral standards to their assessment of therapeutic and non-therapeutic procedures.” Nat Med 2004;10:570-571

Two Standards

- On this view, therapeutic interventions are allowed only when they offer a favorable risk-benefit profile.
- Non-therapeutic interventions (e.g. research blood draws) are allowed even when they pose some net risks.

Clinical Equipoise

- This ‘dual track’ view implies that the risk-benefit profile of therapeutic interventions must be at least as favorable as that of the available alternatives.
- If this is right, clinical equipoise is an ethical requirement for research involving therapeutic interventions.

Problem

- Proposal to compare a new, expensive treatment to an older, cheaper treatment with a single research lumbar puncture.
- Dual track analysis: Lumbar puncture probably acceptable; Older treatment unacceptable if it has even a slightly worse side effect profile (e.g. slightly greater chance of nausea).

Alternative

- For protecting participants, the level of net risks matters, not whether the net risks are from a therapeutic or non-therapeutic intervention.
- This suggests equipoise is not an ethical requirement on clinical research.
- It also points to the need for a better way to evaluate net risks.

Net Risks Test

- 1) Does the research intervention pose net risks?
- 2) If so, are the net risks acceptable and justified?
- 3) Are the cumulative net risks of the study acceptable and justified?

Wendler, Miller. JME 2007; 33:481–486

Minimal Risks

- Most guidelines place limits on the level of allowable net risks, especially for research with individuals who cannot consent (e.g. children).
- Net-risk research interventions typically are permitted when the risks are not greater than minimal.

Minimal Risk Defined

- Many regulations (Council of Europe, Uganda, CIOMS, British MRC, Canada Tri-Council, U.S., Australia and South African MRC) define 'minimal' risks based on the risks of daily life.
- On this standard, risks are minimal when they are no greater than the risks individuals ordinarily encounter in daily life.

Charitable Participation Standard

- Many risks in daily life are justified by the associated benefits (e.g. snow skiing).
- Define minimal risks based on the risks in daily life that are *acceptable* for children in activities to benefit *others* (e.g. appropriate charitable activities, car trips for others).

Wendler. Hastings Center Report 2005; 35:37–43

Limits on Risks?

- Can higher net risks be justified by potential benefits *to others*?
- Study that poses higher risks in children, but has high social value (category 407/50.54)?
- Study that poses high risks in competent adults, but has high social value?

Thresholds for Competent Adults

- No limits: competent adults can decide
- Altruistic activities (organ donation): Less likely benefits, more people Miller, Joffe JME 2009;35:445-449
- Public service (routine risks to firefighters) London AJ. Stat Med 2006;25:2869-85
- Strict limits: social benefit judgements unreliable, we cause the harms, understanding uncertain

Summary

- Risk-benefit evaluations are vital to ensuring ethical clinical research.
- Using a systematic approach can help to protect participants while allowing valuable and appropriate research.
- Important questions remain!