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

- I will focus on 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 the good things 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. Do benefits to participants justify the risks?
5. If YES: the intervention/study is acceptable
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 we make comparative value judgments within or across studies? For example, should an IRB reject a study because the investigator could do a more valuable study instead?

→ Who should make these assessments?

Prioritization

Lack of prioritization by researchers and IRBs could result in trials being unable to recruit a sufficient number of patients for EBOLA trials.

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

Given limited resources, institutions need COVID-19 prioritization committees.

Meyer et al. Clin Trials 2021;18(2):226-233

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.

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

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.

- Does a phase II study of a treatment that has been shown safe and offers a small chance of helping participants medically qualify as a potential for benefit study?

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 risky.

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.

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.

Example

- Experimental drug for a serious condition with few effective treatment options.
- Drug poses a risk of significant bleeding that requires transfusion.
- Include or exclude individuals with bleeding disorders? Low platelets? Not willing to be transfused?

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 that can offset risks?

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.

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 what participants would get otherwise (relevance of available alternatives).

- If YES: the intervention (study) is acceptable.

Informed Clinician Test

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

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).

Randomized Trials

- What about placebo controlled trials?
- Do they offer a prospect of direct benefit to participants who are randomized to the placebo arm?

Miller, Wendler, Wilfond. J Pediatr 2003;142:102-107

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)?

Wendler, Miller. JME 2007; 33:481–486

Minimal Risks

- Many critics argue that it is unethical to expose individuals who cannot consent (e.g. children) to research risks to benefit others.
- Most guidelines permit this research when the risks are ‘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.

Views of the US Public

- Survey of representative sample of 1658 members of US public (RR= 66.1%).
- Approximately 91% approved of a research blood draw in minors, and approximately 69% approved of a research bone marrow biopsy.

Net-Risk Standard

- How do we determine what level of net risks is acceptable for competent adults?
- Based on clinicians' obligations? Researchers' obligations? What people will consent to?
- Does it matter whether the participants are healthy or affected (e.g. kidney biopsy study)?

Thresholds for Competent Adults

- No limits: competent adults can decide.
- Strict limits: social benefit judgements unreliable, we cause the harms, understanding uncertain.
- Altruistic activities (organ donation)

  Miller, Joffe JME 2009;35:445-449
- Public service (routine risks to firefighters)

  London AJ. Stat Med 2006;25:2869-85

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!