Risk-Benefit Judgments in Clinical Research

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Belmont Report

“The idea of systematic, non-arbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research.”

Scope of Talk

- I will focus largely on the evaluation of risks and benefits for subjects enrolled in research.

- Other issues that deserve more attention: minimizing aggregate risks; enhancing aggregate benefits (e.g. increase study N); risks and benefits to family, to host communities.

Proposed Framework

1. Ensure value of interventions and study
2. Identify and minimize risks
3. Identify and enhance potential benefits
4. Do potential benefits to subjects justify the risks/burdens they face?
5. If yes: intervention/study is acceptable (with respect to subject risks/benefits)
6. If no: ensure ‘net’ risks are not excessive

Component Analysis

- Clinical research studies are composed of different elements or interventions. For example: experimental treatment, five clinic visits, 6 blood draws.

- IRBs should apply the framework to the individual interventions, and then apply it to the study as a whole.

Focus on Research

- Clinical studies often are a mix of standard of care interventions and research interventions. For example, 3 blood draws may be for research and 3 for clinical care.

- For the most part, IRBs should focus on 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)**

Focus on Research

- Typically, IRBs can assume that standard of care procedures are acceptable.

→ Does the research alter the R/B profile of the clinical interventions (e.g. research add-on intervention undermines the standard treatment)?

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).

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 the 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/study.

→ Since research is designed to evaluate interventions, often few data available.

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 potential benefits) of research procedures often depend on who enrolls (e.g. good kidney function).

Responses

- To address this concern, exclude those who face excessive risks.
- It also is important to (independently?) monitor subjects to ensure that risks remain appropriate for those who enroll.

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 subjects qualify as prospect of 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 and potentially beneficial in others.

Lead Paint Studies

- Some children grow up in houses with lead paint.
- Randomize families with young children to a home with no lead paint or to a partially abated home.
- What is the risk level of this study?

Risk Questions

→ Individuals may have relevantly different baselines for determining risks.

→ Determine risks compared to expected alternative care OR appropriate one?

→ There may be limits on research not grounded in protecting subjects from risks.

Minimize Risks

- Once the risks have been identified, “minimize” them (take research bloods during clinically indicated needle sticks).

→ Minimizing risks can undermine social value (mandate fewer blood draws) and raise concerns of fairness (exclude subjects without good venous access?).

Step 3: The Potential Benefits

- Next identify the potential benefits of the research interventions.
- As with the 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 potential benefit to subjects?

Disanalogy

- 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.

Dave's Research Clinic

- Study in which subjects paid $100 for a research biopsy, but will have to pay $100 for antibiotics if the site gets infected.

- Most commentators regard any potential costs of research as (economic) risks, but do not regard payments as potential benefits.

Enhance Benefits

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

Step 4: Risk-Benefit profile

- Determine whether the potential benefits to subjects justify the risks they face, 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 subject risks and benefits).

Informed Clinician Test

- When do potential benefits of an intervention ‘justify’ (‘outweigh’) the risks?

- Informed Clinician Test: What would an informed clinician recommend regarding the intervention?

→ For herself or for her mother?

The Assessment

- If the clinician would endorse the intervention for the subjects in question, the potential benefits justify the risks (no net risks).

- If the clinician would regard the intervention as contrary to subjects' clinical interests, the potential benefits do not justify the risks (poses net risks).

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 two bullets be reversed?

Net Risk Research

- Some commentators argue that whether net risks are acceptable depends on whether the intervention/study in question is “therapeutic” (intended or designed to benefit subjects) 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 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 a worse side effect profile (slightly greater chance of nausea).

Alternative

- For protecting subjects, what matters is the risk-benefit profile, not whether the intervention is categorized as therapeutic or non-therapeutic.

- This suggests that equipoise is not an ethical requirement, but a device for evaluating risks and benefits (as well as the social value of the research).

Net Risks Test

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

Minimal Risks

- Most guidelines place limits on allowable net risks, especially for research with individuals who cannot consent (e.g. infants).
- Non-beneficial research interventions typically are permitted 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 encounter in daily life.

Charitable Participation Standard

- Many risks in daily life justified by the associated benefits (snow skiing).

- Define minimal risks based on risks in daily life that are *acceptable* in activities to benefit *others* (e.g. appropriate charitable activities, car trips for others.

→ What about minimal risk to fetuses?

Dave's Clinic Once More

- Can higher net risks be justified by potential benefits *to others*?
- Is it acceptable to conduct a study that poses high risks to subjects, but has very high social value?

Fallacy of the Package Deal

- Many commentators argue that the potential benefits of one intervention should not be allowed to justify the risks of other interventions in the same study.

- The potential benefits of the treatment being tested cannot justify the risks of research procedures in the study.

Justification and Challenge

- This approach has the virtue of precluding investigators from adding unrelated and risky biopsies to a study that offers possibly live-saving treatment.

- But: what about a study of a new treatment for cancer that requires two research bone marrow biopsies?

Necessary Interventions

Clinical Necessity: Experimental treatment requires an initial bone marrow biopsy; Overall R/B profile is favorable.

Research Necessity: Assessing the experimental treatment requires a bone marrow biopsy; Overall risk-benefit profile is favorable?

Summary

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