

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.”

Proposed Framework

1. Ensure social value
2. Identify and minimize risks
3. Identify and enhance potential benefits
4. Do potential benefits to subjects justify the risks they face?
5. If yes: research acceptable (with respect to risks and benefits)
6. If no: ensure 'net' risks are not excessive

Component Analysis

- Clinical research studies are composed of different elements or interventions.
- 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 composed of a mixture of standard of care interventions and research interventions.
- For the most part, IRBs should focus on the research interventions.

Focus on Research

- There is typically no need to apply the framework to clinically indicated procedures (important for research on standard interventions).
- Does the research alter the R/B profile of the clinical interventions (e.g. fixed doses)?

Step 1: Social Value

- Research interventions should have the potential to gather valuable information.
 - Requires expertise (e.g. knowledge of the disease, the intervention, alternatives).
 - Should IRBs make comparative value judgments within or across studies?

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 information on the impact of the study.

→ Since research is designed to evaluate the impact of interventions, there often are few data available for this purpose.

→ How do we include the level of data (or certainty) in risk evaluations?

Another Challenge

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

The Implied Comparison

- Risk and benefit judgments (implicitly) rely on comparison to some baseline.
- Does breathing the somewhat polluted air at the research site qualify as a risk of participation in the study?

Defining the Baseline

- Typically, the comparison is to what we would expect the individuals to experience absent the research.
- Breathing the “research” air typically is not a risk because we assume individuals would breathe similar air absent the research.

Lead Paint Studies

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

Risks

- Individuals may have relevantly different baselines for determining risks.
- To what extent is the choice of the risk baseline an ethical one?
- There may be limits on research that are not grounded in protecting subjects.

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, consider only those 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 will be paid \$100 to undergo a research biopsy, but will have to pay for any research injuries.
- Most regard the potential need to pay for injuries as an (economic) risk, but do not regard the \$100 as a benefit when evaluating individual risks and benefits.

Consider only Direct Benefits?

- Non-direct benefits inappropriate to research.
- Money in particular can commodify research participation.
- Other benefits are more in the control of investigators, hence, may be manipulated in exploitative ways.

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 risks and benefits).

Net Risk Research

- Are research interventions acceptable when the risks exceed the potential benefits to subjects?
- Some argue that it depends on whether the intervention is “therapeutic” (intended or designed to benefit subjects) or is given with “therapeutic warrant”.

Weijer and Miller

“Component analysis builds on the recognition that 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 have a negative or unfavorable risk-benefit profile.

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 useful 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, how great are the net risks?
- 3) How great are the cumulative net risks?

Pose Net Risks?

- Does the potential for benefit of undergoing the intervention justify the risks?
- If so, is the risk-benefit profile at least as favorable as the risk-benefit profile of the available alternatives?

Informed Clinician Test

- What does it mean for the potential benefits of an intervention to ‘justify’ (or ‘outweigh’) the risks?
- Informed Clinician Test: What recommendation would an informed clinician make regarding the intervention in question (for herself or her mother)?

The Assessment

- If the clinician would be indifferent, or would endorse the intervention, 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 has social value and poses no net risks it is acceptable.
- If the intervention poses net risks: Are the net risks acceptable or excessive?
- Are the cumulative net risks of all the interventions included in the study acceptable and justified by the social value of the study?

Acceptable Net Risks

- If the cumulative net risks are low, which is usually what is allowed, and the study has important social value, the social value will justify the risks (the risks will be reasonable).
- What if the net risks of a research intervention are high (e.g. research biopsy of the liver)?

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.
- For example, investigators should not add unrelated and risky biopsies to a study that offers possibly live-saving treatment.

Necessary Interventions

Clinical Necessity: Study requiring a central line to give the experimental treatment;
Overall R/B profile is favorable.

Research Necessity: Study requiring a biopsy to test the experimental treatment;
Overall risk-benefit profile is favorable?

Evaluation

- Are these two studies acceptable?
 - Are they ethically different?
- The package deal may not be a fallacy in at least some cases where the added intervention is necessary for the study.

Dave's Clinic Once More

- Can high research risks be justified by potential benefits *to others*?
- Is it acceptable to conduct a study that poses high risks to subjects (liver biopsy in healthy volunteers) but has very high social value?

Higher Net Risks

- For individuals who cannot provide voluntary informed consent, most guidelines place strict limits on the level of allowable net risks.
- Most guidelines do not include specific risk limits for research with competent adults.

One More Challenge

- Assessment of risks requires an estimate of the level of risk. For example, to determine the risk level of a study involving lumbar puncture (LP), we need to estimate how bad it would be to have an LP headache.
- → People may have different judgements of how bad an LP headache is

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.

Proposed Framework

1. Ensure social value
2. Identify and minimize the risks/burdens
3. Identify and enhance the potential benefits
4. Do the potential benefits to subjects justify the risks/burdens they face?
5. If Yes: the research is acceptable (with respect to risks and potential benefits)
6. If No: ensure the 'net' risks are acceptable