The Ethics in Risk-Benefit Judgments

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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.”

P

Background: P is a newly identified compound. In the laboratory, P shows activity which suggests the potential to inhibit angiogenesis and tumor growth.

Prior Experience

- In a series of 17 patients with renal cell cancer, P has shown some tumor shrinkage and stable disease.

- P appeared to be well tolerated with the most common adverse events being hypertension, diarrhea, nausea, fatigue, and hair depigmentation.

Phase 1 Study of P

- Determine the maximum tolerated dose and dose limiting toxicities of P;
- Characterize the pharmacokinetic and pharmacodynamic profiles of P;
- Document any antitumor activity in patients enrolled in the study.

Interventions

- P given orally once a day for 21 days.
- Dose escalation across subjects.
- A small amount of blood will be collected daily to evaluate P in subjects‟ blood.

The Ethical Challenge

Question: When is it acceptable to expose individuals to risks in clinical research studies, such as the phase 1 study of P?

Answer: When participation involves their contributing to a valuable project, and the risks are not excessive.

Importance

- To ensure clinical research is ethical, IRBs (and others) must evaluate the risks and benefits of individual studies.
- Challenge: develop a systematic framework to make these evaluations.

Components Analysis

- Clinical research studies are composed of different elements or interventions (administration of P; daily blood draws).

- IRBs should evaluate the risks and benefits of the individual research interventions, and then evaluate the risk/benefit profile of the research interventions collectively.

Benefits and Harms

- Benefits are events or experiences that advance an individual‟s interests (stopping tumor growth would be good for subjects).

- Harms are events or experiences that set back an individual‟s interests (experiencing nausea would be bad for subjects).

Potential Benefits and Risks

- *Potential* benefits refer to the chance of experiencing a benefit in a context (chance of inhibiting tumor growth by taking P).
- R*isks* refer to the chance of experiencing a harm in a context.
- Potential benefits and risks are a complex function of the probability, magnitude, and duration of the benefit or harm in question (chances of nausea, how bad, for how long).

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: the research is acceptable
6. If no: ensure net risks are not excessive

Focus on Research

- Apply the framework to the research interventions in the study.
- For R/B evaluation, assume that clinically indicated procedures are acceptable.

→ Does the research alter the R/B profile of any of the clinical interventions?

Step 1: Social Value

- To be ethical, research interventions should have the potential to gather socially valuable information.

→ Making this determination often requires significant expertise, including knowledge of the disease, the intervention, and the available treatments (e.g. how valuable is blocking tumor growth).

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 of research, one needs information on the impact of the intervention in question.

→ Since research is designed to evaluate the impact of interventions (e.g. study of P is evaluating its side effects), there often are few data available for this purpose.

Another Challenge

- To decide whether to approve a study, IRBs must evaluate the risks and potential benefits prospectively.

→ The risks (and potential benefits) of research procedures often depend on who undergoes them (e.g. good kidney function to clear P?).

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 (cf. airline/ventilator study).

Caution: Dave‟s Research Clinic

- Assume children in school get taunted on average 5 times a day.
- Risk level of a study that takes children from school and taunts them 3 times?
- Potential for benefit (less chance of suffering from taunting)?

A Real Example

- Many children grow up in houses with no lead paint; some grow up in houses with lead paint.

- Randomize families with children to a home with no lead paint or to a partially abated home.

→ Individuals may have relevantly different baselines; there may be limits on research that are not grounded in protecting subjects (e.g. minimizing risks to them).

Which Risks to Whom?

- Most regulations focus on the risks research interventions pose *to subjects*.

- Family proposes to drive 20 hours with a sick sibling to participate in study.

→ Research participation may involve non-research risks; research may pose risks to individuals other than 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 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?

- Presumably, financial payments to subjects do not count as part of the social value of clinical research studies.
- Does the fact that payments can advance the interests of subjects imply that payment counts as a 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 of P to individuals who are very ill (or might limit to more healthy 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 is at least as favorable as the available alternatives.

- If YES: the intervention is acceptable (with respect to risks and benefits).

Non-therapeutic 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 given with „therapeutic warrant").

Two Standards

- On this view, therapeutic interventions (administration of P?) are allowed only when they offer a favorable R/B profile.

- Non-therapeutic interventions (the research blood draws) are allowed even when they have a negative or unfavorable R/B 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.

Justification

- The assumption that clinical equipoise is an ethical requirement uses different standards for the risks of therapeutic and non-therapeutic interventions.

- Is there a reason to do this: physician obligations, therapeutic misconception?

Problem

- Proposal to compare a new, expensive treatment to an older, cheaper treatment using 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 R/B profile, whether the intervention is categorized as therapeutic or not.

- 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 (recommend receiving P or not)?

The Default

- If the clinician would regard the intervention as contrary to subjects‟ clinical interests, the potential benefits do not justify the risks.

- If the clinician would be indifferent, or would endorse the intervention, the potential benefits justify the risks (i.e. prospect of benefit intervention).

Cumulative 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?
- Are the cumulative net risks of 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 tumor added to study of P)?

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?

Vulnerable Subjects

- For individuals who cannot provide voluntary informed consent, most guidelines place strict limits on the level of allowable net risks.

- Typically the net risks must be minimal or negligible. The U.S. regulations also allow a „minor increase" over minimal risk for research with children (in some cases).

Minimal Risk: Definition

“*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

45CFR46

Ever Met One?

- What about doing the study in rational normal, reasonable adults?
- Can they make this decision?
- Should we do this to them?

Applying Framework to Study of P

1. Ensure social value: Need more/better cancer agents; Value of inhibiting growth? Is P sufficiently promising?

2. Identify/minimize risks: Few data; Data on renal cell patients relevant to other cancer patients? Require good kidney function; Must have no standard treatment options; Fairness?

3. Identify/enhance benefits: Few data; Data on renal cell patients sufficient to consider prospect of benefit? How much of a benefit is inhibiting tumor growth?

Applying the Framework to Study of P

4. Do potential benefits justify risks? Would an informed clinician judge the chance of inhibiting tumor growth to justify the chances of hypertension, diarrhea, nausea, fatigue, and hair depigmentation?

5. If YES: administration of P is acceptable with respect to risk/benefit assessment.

6. If NO, ensure „net" risks not excessive: Low risk of hypertension, diarrhea, nausea, fatigue, and hair depigmentation acceptable? Risks of few extra blood draws is minimal.