

Evaluating the Risks and Benefits of Clinical Research

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Phase 1 Study of P

Background: in the laboratory, P shows broad activity which suggests the potential to inhibit angiogenesis and tumor growth.

Goals: determine the MTD and DLT of P; characterize the PK and PD profiles of P; document any antitumor activity in patients enrolled on the study.

Previous Results

- In a small series of patients with renal cell cancer, P has shown some tumor shrinkage and stable disease.
- P appears well tolerated with the most common adverse events being hypertension, diarrhea, nausea, fatigue, and hair depigmentation.

Eligible Subjects

- Patients with any metastatic solid tumor for which standard curative or palliative measures do not exist or are no longer effective.
- Patients must have adequate renal and bone marrow function.

Interventions

- P will be 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

- When can it be acceptable to expose individuals to risks in clinical research studies, such as the phase 1 study of P?
- When participation involves their contributing to an important project, and the risks are not excessive.

Importance

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

Components Analysis

- Clinical research studies are composed of different elements or interventions.
- IRBs should evaluate the risks and benefits of the individual research interventions and then evaluate the study as a whole.

Benefits and Harms

- Benefits are events or experiences that advance an individual's interests.
- Harms are events or experiences that set back an individual's interests.

Potential Benefits and Risks

- *Potential* benefits refer to the chance of experiencing a benefit in a given context; *risks* refer to the chance of experiencing a harm in a given context.
- Potential benefits and risks are a complex function of at least the probability, magnitude, and duration of the benefit or harm in question.

Proposed Framework

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

Step 1: Social Value

- To be ethical, research interventions should have the potential to gather information important for improving health and well-being.
- Making this determination often requires significant expertise, including knowledge of the disease, intervention, and available treatments.

Step 2: Identify the Risks

- The next step is to minimize and evaluate the risks of the research, including the physical, psychological, social, and economic risks.
- For this purpose, identify which interventions qualify as research interventions; clinically indicated procedures can effectively be ignored.

Challenge

- To evaluate 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, there often are few data available for this purpose.

More Challenges

- Minimizing risks can undermine the social value of the research (e.g. fewer blood draws) and raise concerns of fairness in some cases of exclusion.
- IRBs make evaluations before studies begin, yet the risks (and potential benefits) of research procedures often depend on who enrolls (e.g. intact immune system? claustrophobic?)

The Implied Comparison

- Risk and benefit judgements implicitly rely on comparison to some assumed 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 or ventilator study).

Caution: Dave's Research Clinic

- Assume children in school get taunted on average 5 times a day.
- Does a study that proposes to take children out of school for a day and taunt them 3 times pose risks? Does it offer the potential for benefit?

Minimize Risks

- Once the risks of the research procedures have been identified, minimize them.
- For example, when possible rely on the results of a prior scan or biopsy rather than take a new one.

Step 3: The Benefits

- Next determine the potential benefits of the research interventions.
- As with the risk determination, 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 a social benefit of research.
- 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, when evaluating the risk-benefit profile for subjects, IRBs should consider only the clinical or direct benefits of research procedures, not any indirect, inclusion or financial benefits of participation.
- But, IRBs are supposed to consider all risks, including financial ones. Is this difference justified?

Dave's Research Clinic

- I propose a study in which subjects will be paid \$100 to undergo a research biopsy and they will have to pay for any research injuries.
- Most commentators would regard the need to pay for injuries as a risk, but would not regard the \$100 as a benefit to subjects when evaluating individual risks and benefits.

Consider only Clinical 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.
- Payments not a value of the research, but can benefit subjects.

Enhance Benefits

- Once the potential benefits to subjects and society have been identified, enhance them.
- For example, a study of a new treatment may focus on individuals who most need the treatment.

Step 4: Risk-Benefit profile

- Determine whether the potential benefits to subjects justify the risks.
- Is research acceptable when the risks exceed the potential benefits to subjects?

One Approach

- Some commentators argue that the answer depends on whether the intervention/study is therapeutic or nontherapeutic.
- Therapeutic interventions are intended to benefit, designed to benefit, or offer the potential for benefit to subjects.

Clinical Equipoise

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

Oops

- Many problems with this view.
- Most notably, the distinction between therapeutic and non-therapeutic is unclear, and it is not clear why the risks of therapeutic interventions should be treated differently than the risks of non-therapeutic interventions.

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) its risks?
- Informed Clinician Test: What recommendation would an informed clinician caring only about individuals' clinical interests make regarding the intervention or study in question?

The Default

- If the clinician would regard the research as contrary to individuals' clinical interests, the potential benefits do not justify the risks.
- If the clinician would be indifferent, or would positively endorse the research, the potential benefits justify the risks (prospect of benefit).

Cumulative Net Risks

- If the intervention/study 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?

Is the Package Deal a Fallacy?

- Can high research risks be justified by the potential benefits of other interventions in the study (fallacy of the package deal)?
- Should IRBs prohibit risky research biopsies, even when they are necessary for scientific purposes and the overall risk-benefit profile of the study is favorable for subjects?

Dave's Clinic

- Can high research risks be justified by potential benefits *to others*?
- Is it acceptable to conduct a study that poses very high risks to subjects (e.g. a 1 in 500 chance of death) but offers the potential to identify a way to cure AIDs or Alzheimer disease?

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.

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 Seen One?

- What about doing the study in normal, healthy, rational, reasonable, adults?

Applied to Phase 1 study of P

1. Ensure social value: paucity data
2. Identify and minimize risks: prospective, competes with value, issues of fairness
3. Identify and enhance benefits: prospective
4. Do potential benefits to subjects justify the risks they face: default and how evaluate
5. If yes: the research is acceptable
6. If no: ensure risks are not excessive: package deal, should there be limits on research risks and how should the limits be defined