Risk Benefit Assessment

Cristina E. Torres, Ph.D.

UP-NIH Faculty and FERCAP Coordinator

Definition of Risk

- The term risk refers both to the probability of a harm resulting from an activity and to its magnitude.
- `Risk' often stands for the combined probabilities and magnitude of several potential harms.

Categories of Risks

- Physical risks
  - Bodily harm
  - simple inconvenience
- Psychological risks
  - Emotional suffering
  - breach of confidentiality
- Social risks
  - Employment or social discrimination
- Economic risks
  - Financial costs related to participation

Definition of Benefit

- **A benefit refers to any sort of favourable outcome of the research to society or to the individual**

- **In practice, 'benefit' often stands for the combined probabilities and magnitudes of several possible favorable outcomes**

Potential Benefit

- **Physical benefits**
  - **Improvement of disease**
- **Psychological benefits**
  - **Comfort from suffering**
  - **Feeling of helping others in the future?**
- **Economic benefits**
  - **Financial benefits related to research participation?**
- **Benefit to science/society**
  - **Generalizable knowledge**
  - **Effective interventions in the future**
  - **Change in practice standards decreasing morbidity and mortality**

Assessing Risks & Benefits

HOW?

Systematic Assessment

- Benefits and Risks must be “balanced” and shown to have a “Favorable Ratio”
- The ideal:
  - Quantitative Techniques for scrutiny (?)
  - Those making decisions to have thorough understanding of all aspects of research
  - Rigorous and precise assessment of research

Levels of Risk-Benefit Assessment

- Risk-Benefit assessments to **individuals**
- Risk-Benefit assessments to **society**
  - Knowledge gained + Benefit to participants
  - Misuse of societal resources + Risks to participants

Magnitude of Risks and Benefits

- Magnitude of potential harm and potential benefits
  - Organ dysfunction versus slight discomfort
  - Cure versus tumor shrinkage

- Duration of potential harm and potential benefits
  - One time harm versus long-term level of harm
  - Indirect from chemotherapy (acute infection versus chronic fatigue)

Categories of Risk

- **Category 1 - Minimal Risk**
- **Category 2 - Greater than Minimal Risk with prospect of direct benefit**
- **Category 3 - Minor increase over minimal Risk but no prospect of direct benefit to individual but likely to yield generalizable knowledge to subjects**
- **Category 4 - Research not fitting in any category, but presents an opportunity to understand, prevent, alleviate a serious problem affecting the health or welfare**

Category 1 - Minimal Risk

- **Risk is so small that it can be ignored, may be equated with risk accepted in everyday life & to which a person is already exposed**
- **Examples**
  - **Physiological experiments involving exercise, collecting urine, measurements of weight/height, collection of nail clippings or small samples of hair, developmental assessment, routine physical examination, observation of behavior or changes of diet, or obtaining a single peripheral venous blood sample from an adult or bigger child.**

Category 2 - More than minimal risk

- **Prospect of direct benefit**
- **Risk should be justified by anticipated benefits**
- **Anticipated benefit-risk must be favorable than alternatives**
- **Example**
  - **Examples of more than minimal risk would include procedures such as spinal taps, biopsies and behavioral interventions likely to cause psychological stress.**

Category 3 - More than minimal risk and no prospect of direct benefit

- Intervention will yield generalizable knowledge about the condition or disease, which may be of vital value in understanding of subjects condition
- Adequate provisions and safeguards in place

Category 4 - Research not fitting in any category

- Research presents an opportunity to understand, alleviate a serious problem
- Non-therapeutic research
- Careful Review and safeguarding
- Monitoring
- Informed Consent/ assent from minors

Risk – Benefit Assessment

- An inexact science
- Degree of uncertainity
  - lack of precision inherent in risk/benefit analysis
- However, it may not be difficult to reach a conclusion
- Risk Evaluation
  - Probability or relative magnitude of harm.
  - Process of combining the results of risk identification and estimation with the *perceptions of those involved*.
  - It is the perception of a risk formed by patient that is of overriding importance compared with investigator's perception

Risk Assessment in Protocol Review

- Scientific Review
  - Identify and minimize risks as much as possible by using procedures that are consistent with sound research design.
  - It is important to emphasize that study design might affect risks and hence, ethics committee must be knowledgeable about methodology

Risk Assessment in Protocol Review

- Ethical Review – a holistic process that examines risks and benefits in all relevant parts of the protocol
  - Objectives
  - Research Design
  - Number of Subjects
  - Distribution and method of randomisation
  - Inclusion exclusion criteria
  - SAE management and reporting
  - Consent form & questionnaires if any
  - Source of funding

Risk Assessment in Protocol Review

- Ethical Review – a holistic process that examines risks and benefits in all relevant parts of the protocol
  - Risk /benefit ratio- direct/ indirect/ no benefit/ society
  - Privacy & confidentiality
  - Subject / Vulnerable Protection
  - Equitable selection
  - investigator qualifications/ facilities
  - COI management
  - Recruitment materials- ADVERTISEMENTS
- Continuing review/ monitoring

Research Objectives

- Purposeful
- Direct benefit/ indirect benefit/ benefit to science
  - Targeted to individual subjects/ community
  - By way of medical examination/ sharing information/ talking
  - Generation of knowledge, improvement in Science
- Scientific soundness is essential to make a study ethically viable.
  - Likely importance of the information which is sought.
  - Investigator should describe the relevance of research

Previous Information Required

- Animal studies/ invitro testing results
- Previous clinical study results if any
- Proposed research to be built on previous knowledge

Research Design

- Appropriateness of the scientific design of a study
  - Endpoints defined
  - Adequate duration of participation of subjects
  - Appropriate selection of controls
  - Randomization to eliminate bias
  - Inclusion / exclusion criteria adequate
  - Subject size and statistical assumptions

Issues in Study Design

- Do IRB/IECs know how to judge scientific adequacy? – need for members/consultants with appropriate expertise
- Study with flawed design need not be undertaken
- Scientifically valid design with ethical concerns – alternative design may be required to minimize risks

Placebo design issues

- Intervention being used in a study should not be regarded as a new treatment but as something with unproven effects
- Length of time to receive the intervention (no more, no less) should be based on the exposure that is necessary to produce statistically valid measures of good and bad effects
- Any decision to use the intervention in patients is based on a prediction or hope of a good outcome rather than on scientific evidence

Placebo design issues

- Clinical equipoise – when an unbiased expert is genuinely uncertain whether the treatment will be better than a placebo; well-being of patients not compromised for science
- Placebo controls are most likely to raise ethical concerns when the condition being studied is serious—especially if it is fatal
- Study design may require placebo control for the study to yield useful knowledge

Placebo design issues

- Placebo-controlled trials may be faster and cheaper, and need fewer participants, to achieve a given level of certainty about the research hypothesis
- Placebo designs may be favoured by trial sponsors to show that their new product is safe and effective than having to demonstrate that it is superior to products already approved.

Other design issues

- Natural experiments – Tuskegee studies, observational studies without informed consent
- Misleading marketing studies – testing a drug against a competitor drug (at lower dosage or with an unintended population)

D. Subject Selection

- Fair subject selection criteria
- Subjects likely to benefit from the research
- Objective of research should be relevant to needs of the people
- The first requirement for IRB/IEC is to ensure that it fully comprehends a protocol's design: what information the research study seeks to gain, how it proposes to do this, and what effect its choice of design has on participants relative to alternative designs.

Subject Selection

- Appropriateness of subject population
- Involvement of vulnerable groups
  - Is it necessity ?
- Secondary subjects
- Statistical considerations
  - Data analysis methods
  - Sample size sufficient to be statistically significant
  - Interim analysis
  - Data safety committee monitoring

Inclusion – Exclusion Criteria

- Inclusion exclusion criteria
  - **Age**
  - **Gender**
  - **Pregnancy**
- Selectively include subjects most likely to yield an answer
- Select subjects equitably
- Exclude subjects
  - who can predictably confound the answer
  - who might be at an increased risk

Minimize Risks

- **Choice of least vulnerable population to achieve results**
- **Appropriate screening of potential subjects**
- **Reasonable number of visits to monitor expected benefit**
- **Minimal number of subjects in non-treatment/ placebo arms**
- **Minimising predictable risks**
- **Using tests and procedures to avoid risk to subjects (collecting extra samples)**
- **Avoid subject deception (Debriefing and counseling)**

Minimize Risks

- Follow up care
- Define stopping/withdrawal criteria
- Allow rescue medications and procedures
- Define safety committee role to perform interim assessments
- Provide serious adverse events management
- Address potential for exploitation (commercial/ other)

Considerations

- Inhumane treatment never justifiable
- Risks may not be eliminated but minimized to achieve research objective
- Significant risk to be justified in terms of benefits, voluntariness for participation ensured
- Appropriateness of including vulnerable groups

Reducing Risk and Enhancing Benefits

- Conducting research consistent with the standards of good clinical practice
- Substitution of procedures
- Use of qualified personnel
- Monitoring
- Excluding subjects that are especially susceptible to harms associated with study
- Useful guide is probably whether or not members of Committee would consent to participate in research if they or members of their families were eligible

E. Risk and benefit

- Challenging moral dilemmas
  - when participants are placed at risk of harm, or are burdened by discomfort or distress,
  - without prospect of obtaining any personal benefit at all:
  - the knowledge obtained is solely for the benefit of others.
  - Benefit to healthy volunteers

Risk and benefit

- Ensure that potential participants are given a full and honest account of the harms and benefits that may occur in the consent form if they agree to join a study
- If conscientiously executed, the consent process will permit prospective participants to weigh the potential for harm against the prospect for benefit, if any.

Risk and benefit

- Make a judgment when the net prospects for the participant are negative.
  - studies that do not have a therapeutic aim regarding participants
  - studies in which the probability and/or extent of benefit is smaller than that for harm.