Risky Business: Assessing Minimal Risk in Research

Kristina Borror, Ph.D.
Director, Division of Compliance Oversight
Overview

- Regulatory Background
- How We Assess Risk
- Unpacking “Minimal Risk”
- “Fixed” vs “Relative” Standards of Minimal Risk
- Study Design and Risk
- Minimal Risk and Expedited Review
- Minimal Risk and Informed Consent
- Minimal Risk and Subpart B, C & D
Minimal Risk

- *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.
  
  – 45 CFR 46.102(i)
How We Assess Risk
Ropeik’s 14 Factors that Affect our Perception of Risk

- Trust vs. lack of trust
- Imposed vs. voluntary
- Natural vs. human-made
- Catastrophic vs. chronic
- The dread factor
- Hard to understand
- Uncertainty
- Familiar vs. new
- Awareness
- A known victim
- Future generations
- Does it affect me?
- Risk vs. benefit
- Control vs. no control
Evaluating the Risks of Clinical Research
Annette Rid; Ezekiel J. Emanuel; David Wendler
*JAMA*. 2010;304(13):1472-1479

“Because intuitive judgments of risk are subject to well-documented cognitive biases, this approach raises concern that research participants are not being adequately protected. To address this situation, we delineate a method called the systematic evaluation of research risks (SERR). which evaluates the risks of research interventions by comparing these interventions with the risks of comparator activities that have been deemed acceptable.”
The 4-Step Process of Systematic Evaluation of Research Risks

1. Identify the potential harms posed by the research intervention.
2. Categorize the magnitude of each potential harm using the harm scale.
3. Quantify or estimate the likelihood of each potential harm.
The 4-Step Process of Systematic Evaluation of Research Risks (continued)

4. Compare the likelihood of each potential harm from the research intervention with the likelihood of potential harms of the same magnitude occurring in an appropriate comparator activity. If the likelihoods of the potential research harms are all comparable, then the risks of the research intervention do not exceed the risks of the comparator activity.
Is there an objective way to compare research risks?
John Rossi, Robert M Nelson
doi:10.1136/medethics-2011-100194

“… we suggest that the most defensible method for risk comparison may be one that is deliberative. A deliberative method relies on discourse rather than rigid algorithms to come to judgements about risk comparisons.
Unpacking “Minimal Risk”
Unpacking Minimal Risk

- *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.
“Probability and Magnitude”

• How likely (or unlikely) is the harm to occur?
• How severe would the harm be, if it occurred?
“Harms and Discomforts”

- The IRB's evaluation of the harms and discomforts of the research should consider:
  - the nature of the study procedures,
  - other study characteristics,
  - subject characteristics (subject susceptibility, vulnerability, resilience and experience), and
  - steps taken to minimize risk.
“Anticipated in the Research”

- To determine if a study is minimal risk, one must first estimate the anticipated harms and discomforts of the research for the proposed study population.
“Greater in an of Themselves”

• The anticipated harms and discomforts of the research for the proposed study population must then be compared to a standard, and if they are lower, or the same, then the study is no more than minimal risk.
“Ordinarily Encountered in Daily Life”

• Are the activities of the research more similar to the kinds of activities one normally encounters in daily life?

• Are the risks of the research similar to the kinds of activities one normally encounters in daily life?
  – If so, then this the likely the best standard to compare the research risks to.
“During the performance of routine physical examinations or tests”

- Are the activities of the research more similar to the kinds of activities performed during routine physical examinations or tests?
- Are the risks of the research similar to the kinds of activities performed during routine physical examinations or tests?
  - If so, then this the likely the best standard to compare the research risks to.
“During the performance of routine psychological examinations or tests”

- Are the activities of the research more similar to the kinds of activities performed during routine psychological examinations or tests?
- Are the risks of the research similar to the kinds of activities performed during routine psychological examinations or tests?
  - If so, then this the likely the best standard to compare the research risks to.
• Do the activities of the research have to be ordinarily encountered in daily life, or performed as part of routine physical or psychological examinations or tests in order to be considered minimal?

NO!

But the risks of those activities must be commensurate.
What Risks Need to be Considered by the IRB?

• The IRB should consider only those risks and benefits that may result from the research.

• The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
“Fixed” vs “Relative” Standards of Minimal Risk
Should IRBs use a “uniform” / “fixed” standard for determining minimal risk or a “relative” standard? (in relation to the daily life of the population to be recruited or enrolled in a particular research study)
From the Preamble to the Regulations

• “HHS in the proposed regulations used the terminology ‘healthy individuals.’ In light of the public comments on this, however, HHS has reworded the final regulation to reflect its intention that the risks of harm ordinarily encountered in daily life means those risks encountered in the daily lives of the subjects of the research.”

45 CFR 46
Federal Register Vol. 46 No. 16
January 26, 1981
Preamble, p. 8373
Estimate of the study’s risk

(a) Minimal Risk threshold is fixed to an estimate of the risks of daily life for the average, healthy person in a safe environment.
Estimate of the study’s risk

Studies 1-4 differ only in subject characteristics

(b) The minimal risk threshold is adjusted based on the risks of daily life of the subject sample or subject pool.
Which is More Protective of Subjects, Fixed or Relative Standard?

• OHRP has never issued official guidance regarding the definition of minimal risk on its website. However, when asked, OHRP recommends use of the healthy person standard when applying the provisions of Subpart A of 45 CFR 46.
Summing Risks

- If there are X number of procedures in a study, and the risks of each procedure is no greater than minimal, is the risk of the research as a whole minimal?
  - That depends.
  - Need to look at all the risks together and see if the risks as a whole are no greater than those of daily life (or physical or psych exams or tests).
Study Design and Risk
Criteria for IRB Approval of Research

• Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. (§46.111(a)(1))
Criteria for IRB Approval of Research (continued)

• Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. 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).  
  ($46.111(a)(2)$)
Minimizing Risk

• All study personnel qualified and kept up to date with changes in the protocol
• Additional protections in place for vulnerable subjects or less vulnerable subjects should be used
• Procedures with less associated risk are substituted whenever possible
• Procedures used will already be performed for treatment or diagnosis
• Subjects appropriately monitored to ensure their safety
• UPs promptly reported
• Subject withdrawal criteria appropriate
• A timely treatment plan is in place
Are “Standard of Care” Procedures Minimal Risk?

• That depends.
  – Are the risks of the procedures no greater than those of daily life (or physical or psych exams or tests)?
  – Are the procedures going to be done anyway for clinical care? Does the research dictate or constrain the way the procedures will be done?
Minimal Risk and Expedited Review
Expedited Review

• Expedited review procedures for certain kinds of research involving no more than minimal risk (§46.110)

• The Secretary, HHS, has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure.

• An IRB may use the expedited review procedure to review some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk.
Expedited Review Categories

- The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
Minimal Risk and Informed Consent
§46.116(d) Waiver of Informed Consent

- An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent if the IRB finds and documents that:

  (1) The research involves **no more than minimal risk** to the subjects;

  (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

  (3) The research could not practicably be carried out without the waiver or alteration; and

  (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
§46.117 Waiver of Documentation of informed consent

An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds:

– the research presents no more than minimal risk; and

– the research involves procedures that do not require written consent when performed outside of a research setting.

OR

– the principle risks are those associated with a breach of confidentiality concerning the subject’s participation in the research; and

– the consent document is the only record linking the subject with the research
Minimal Risk and Research Involving Pregnant Women and Fetuses
§46.204 Research involving pregnant women or fetuses

- Previous studies done for assessing potential risks to pregnant women and fetuses
- Risk to fetus caused solely by interventions with prospect of direct benefit for woman or fetus; or, risk to the fetus is not greater than minimal and the purpose is to develop important biomedical knowledge which cannot be obtained by any other means
- Any risk is the least possible for achieving the objectives of the research
- No prospect of direct benefit for woman or fetus
  - Risk to fetus no greater than minimal
  - Development of important biomedical knowledge
Minimal Risk and Research Involving Children
Research Involving Children Categories (1)

- §46.404- No greater than minimal risk
  - Child assent
  - Parental permission

- §46.405- Greater than minimal risk, prospect of direct benefit
  - Risk justified by anticipated benefit
  - Relation of anticipated benefit to risk at least as favorable to the subjects as that presented by available alternative approaches
  - Child assent
  - Parental permission
Research Involving Children- Categories (2)

• §46.406- Minor increase over minimal risk, generalizable knowledge about subject’s disorder or condition
  – Minor increase over minimal risk
  – Experience reasonably commensurate
  – Likely to yield generalizable knowledge
  – Child assent
  – Parental permission
Research Involving Children- Categories (3)

- §46.407-Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children
  - can be approved if the Secretary/Commissioner consults with panel of experts.
Minimal Risk in Research Involving Prisoners
Definition of Minimal Risk in Subpart C

• The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.
Considerations for Risk in Research Involving Prisoners

• Note difference in definition of minimal risk between Subpart A and Subpart C

• Categories of permitted research involving prisoners are no more than minimal risk or require Secretary consult and published notice in the FEDERAL REGISTER
Contact Information

- OHRP telephone: 240-453-6900
  1-866-447-4777
- OHRP e-mail: ohrp@hhs.gov
Office for Human Research Protections

THANK YOU for protecting Human Subjects!