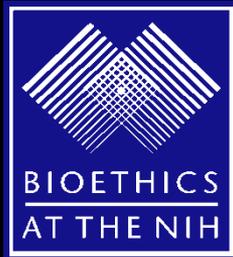


Application of the Minimal Risk Standard in Pediatric Research

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David Wendler
Department of Bioethics
NIH Clinical Center

Acceptable Research

- Some research offers subjects a risk-benefit profile that is at least as favorable as indicated clinical care.
- This research is acceptable with respect to risks because it does not make subjects prospectively worse off.

Net Research Risks

- Other research poses 'net' risks: risks that are not justified by the potential benefit for subjects.
- This research poses risks to subjects for the potential benefit of others.

Net Research Risks

- Some experimental procedures offer no potential benefit to subjects. All the risks of these procedures are net research risks.
- For example: purely research biopsy.

Net Research Risks

- Other procedures (e.g. chemotherapy) offer subjects a prospect of benefit.
- These procedures still pose net risks if:
 - 1) the potential benefits to subjects do not justify the risks, or
 - 2) the risk-benefit profile is not as favorable as that of available alternatives.

Two Questions

- 1) Why is it acceptable to expose children to research risks to collect data that might benefit others?
- 2) What risks are acceptable in this context?

Minimal Risk

- Many agree that net research risks in children are acceptable when they are sufficiently low and the research is valuable.
- Sufficiently low risks are often termed 'minimal'.

Procedural Approach

- To determine which risks are minimal we might simply describe a study and ask reasonable people: is this acceptable in children?
- There are reasons to think this approach is not effective.

Survey IRB Chairpersons (%; N=188)

| | MR | >MR |
|-------------------------------|-----------|---------------|
| MRI | 48 | 44 |
| Survey Sexual Activity | 44 | 48 |
| Allergy Skin Testing | 23 | 70 |

What's Going On?

- There are several problems with a purely procedural approach.
- First, we are very bad at evaluating absolute risks.
- Is a 1 in 2,334 risk of moderate harm acceptable or excessive?

Beware the Saber Toothed Tiger

- In addition, our bare intuitive judgments of risks rely on heuristics (e.g. familiar things are safe and unfamiliar things are risky).
- This approach can be problematic, especially when evaluating the risks of research (which often are unfamiliar).

Regulatory Definition

- The regulations provide a way to try to address the shortcomings of purely intuitive judgment: compare the risks of research to other risks.
- Definition: Minimal risk means the risks are not greater than those encountered in daily life or during routine examinations.

Regulations and Ethics

- This definition gives us two uses of ‘minimal’ risk:
 - Risks that are approvable under the regulations
 - Risks that are ethically acceptable
- First step: Clarify the regulatory definition (then consider to what extent it captures which risks are ethically acceptable).

'Procedural' Interpretation

- Some assume the 'risks of daily life' refers to the risks of procedures and activities children ordinarily face in daily life.
- Hence: if an experimental procedure is not ordinary, it poses greater than minimal risk.
- NO: A study of Reiki may be minimal risk

'Type of Risk' Interpretation

- Others assume the 'risks of daily life' refers to the types of risks children ordinarily face (e.g. risk of a bruise).
- If children do not ordinarily face a type of risk, it is greater than minimal.
- NO: A risk of negative energy transfer may be minimal.

The Ethical Concern Again

- We are trying to protect pediatric subjects from excessive net risks.
- It is the level of net risk that matters.

Risk Level Approach

- Does the level of net research risk exceed the level of risk children face in ordinary activities of daily life?
- Objective interpretation: Compare research risks to the level of risk faced by average, healthy children in daily life.

Regulations and Ethics

- Are risks that satisfy the objective interpretation of the minimal risk definition also ethically minimal?
- Two reasons for concern.

Caveat #1

- The risks of many activities in daily life (e.g. mountain biking) are acceptable because the activities offer compensating benefits.
- The risks of these activities do not provide an appropriate standard for assessing the risks of non-beneficial pediatric research.

Caveat #2

- Daily life poses some risks to average, healthy children that are inappropriate, such as the risks of driving while intoxicated.
- These risks do not provide an appropriate standard for assessing whether the risks of non-beneficial pediatric research are ethically acceptable.

Charitable Participation Standard

- The minimal risk standard should be limited to risks in daily life that are *acceptable* for average children to face in the context of activities designed to benefit *others*.
- Examples: car trips for others, charity car wash, selling cookies for Oxfam, shoveling neighbor's sidewalk.

81 Children (ages 7-14, RR= 69.2%)

- Children in research preferred to help other children by participating in non-beneficial research than in a charitable activity (76.5% vs 23.5%; 95% CI, 0.56-0.97).
- The parents of these children also preferred that their child help others by participating in research.

Wendler, Jenkins. Arch Peds Adol Med 2008; 162:9-14

177 Subjects (ages 13-17; RR= 95.2%)

- 68.9% felt they were making an important contribution; 80.8% felt proud to be doing so.
- Respondents were equally willing to face risks to help others in research or in a charitable activity.

Wendler, Abdoler, Wiener, Grady. *Pediatrics* 2012; 130:692-699.

Procedural Implementation

- To implement the (objective, charitable) minimal risk standard, we might simply compare the risks of the respective activities.
- Is a research lumbar puncture riskier than shoveling a neighbor's sidewalk?

Benefits of a Method

- A better approach would be to develop a method to systematically compare the respective risks.
- We could then base our normative judgment on the results of this comparison (rather than simply judge the respective risks themselves).

Requirements

- To implement the minimal risk standard systematically, we need:
 - 1) Data on risks of research procedures
 - 2) Data on the risks of appropriate 'charitable' activities for children
 - 3) A way to compare the two

SERR

- We are working on a method to more systematically compare the level of net research risks to the level of risk posed by ordinary and appropriate ‘charitable’ activities in daily life.

Rid, Emanuel, Wendler. JAMA 2010; 304:1472-1479.

General Idea

- Risks are a function of the magnitude of possible harm (severity, duration, reversibility), and the likelihood of experiencing that harm (as the result of a research procedure).
- Compare likelihoods to likelihoods and magnitudes to magnitudes.

Comparisons

- Comparing likelihoods is relatively straightforward, but requires some judgment (1 in 3,000 risk greater than 1 in 3,200?).
- Comparing the magnitudes of different harms is more difficult, and would benefit from a systematic method (is an LP headache worse than an ankle sprain?) .

Level

Example

Risk Daily Life

Negligible

Bruise

100K/ 100K

Minor

Common cold

22,000/ 100K

Moderate

Bone Fracture

70/ 100K

Significant

Knee instability

8/ 100K

Major

Rheumatoid Arthritis

0.008/ 100K

Severe

Paraplegia

0.03/ 100K

Catastrophic

Death

0.2/ 100K

Systematic Comparison

1. Skin biopsy may lead to infection (technology changes may change the risks).
2. Infection would be a minor harm
3. Moderate anxiety is a minor harm from common activities of daily life
4. Likelihood of infection = X
5. Likelihood of moderate anxiety from activities of daily life = 10,000 per 100,000
6. Does X exceed 10,000 per 100,000?

Some Comments

- Complicated: so probably not for IRBs
- Requires data: so collect it
- Requires judgment: determining magnitude of harms, are data sufficient, what is close enough, do data apply
- More work needed (e.g. how evaluate “tradeoffs” when numerous possible harms).

How Many Standards?

- Often assumed that the minimal risk threshold is the same for all children.
- On this approach, we might implement the minimal risk standard by comparing research risks to the risks faced by 10 year olds in the context of 'charitable' activities.

Concern

- Very young children cannot understand research; this approach may be under-protective for them.
- Many teenagers can understand; this approach may be over-protective for older children.

Responses

- We could use a sliding scale of risk as children mature.
- This would be complicated.
- In addition, the crucial distinction is whether the subjects can understand the research.

Two (not Double) Standards

- It is appropriate for older children who understand (and agree) to face greater risks for the benefit of others.
- Set a general age threshold (e.g. 13), or evaluate specific children.

Wendler. Arch Ped Adol Med 2009; 163:115-118.

Summary

- Focus on added net research risks
- It is the level of net risk that matters
- Allow greater net risks in adolescents
- More work needed to collect data and develop methods to help IRBs and others assess when pediatric research poses minimal risk