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# Minimal risk in pediatric research

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# The Role of Minimal Risk in the Federal Research Regulations

- ▶ For categories of pediatric research are approvable under the federal regulations:
  - ▶ 46.404 Research not involving greater than **minimal risk**.
  - ▶ 46.405 Research involving greater than **minimal risk** but presenting the prospect of direct benefit to the individual subjects.
  - ▶ 46.406 Research involving greater than **minimal risk** and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
  - ▶ 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.

# Minimal Risk as a Threshold Concept

- ▶ Minimal risk—not ethically problematic, unless the research is poorly designed.
- ▶ More than minimal risk—additional justification is needed, such as direct benefits to the participants (46.405) or benefits to the participants' class (46.406), or important problem affecting children's health (46.407).

# Definition

- ▶ 46.102(i) 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.

# Applying the Definition

- ▶ What are the risks of the research?
- ▶ Physical, psychological (pain, distress, embarrassment)
- ▶ Net risks (total, cumulative)
- ▶ Risks of the research vs. risks of clinical procedures being done as part of therapy

# Applying the Definition

- ▶ Risks of routine physical and psychological examinations or tests.
  - OHRP expedited review categories. These are 14 years old and need to be updated.
  - The NIH Clinical Center has guidelines that we use at NIH.
  - Not all risks can be assimilated under this concept.
- ▶ Risks of daily life.
  - Whose daily life is it?
  - Relative standard vs. absolute standard.
  - The relative standard is ethically problematic because it can lead to exploitation and unequal protections.
  - Can you quantify the risks of daily life?

# Applying the Definition

- ▶ There are disagreements about how to interpret minimal risk.
- ▶ Shah et al study of 188 IRB chairs.
- ▶ 81% classified a single blood draw as minimal risk
- ▶ 53% classified an electromyogram as minimal or minor increase over minimal, while 41% said it was more than a minor increase over minimal.
- ▶ 23% said allergy skin testing is minimal risk, 43% said it is a minor increase over minimal risk, and 27% said it is more than a minor increase over minimal risk.

Shah S, Whittle A, Wilfond B, Gensler G, Wendler D. How do institutional review boards apply the federal risk and benefit standards for pediatric research? JAMA 2004; 291(4):476–82.

**Table 4.** Cumulative Risks in the Daily Lives of Healthy Children, by Age Group\*

Harm	Cumulative Risk per Million Children per Day				
	<1 y	1-4 y	5-9 y	10-14 y	15-19 y
Death	1.5	1.5	1.4	1.4	10
Hospitalization	1.0	1.3	1.7	2.1	6.0
Emergency department visit	6.4	16.4	26.0	36.1	64

\*The cumulative risks healthy children face in an average day is calculated based on the risks of 1 "riskier" round-trip in a car, 1 instance of bathing, and 1 instance of playing on a playground for children aged 0 through 4 years or the risk of participating in basketball for children aged 5 through 19 years.

- ▶ Wendler et al attempted to quantify the concept of the risks of daily life by looking at typical children's activities, such as riding in automobiles, sports, and bathing/swimming.
- ▶ An interesting analysis but unclear how it could be translated into IRB practice. Would IRB members/chairs quantify the risks of a study and compare them to these numbers? Should they?
- ▶ Wendler D, Belsky L, Thompson KM, Emanuel EJ. Quantifying the federal minimal risk standard: implications for pediatric research without a prospect of direct benefit. JAMA 2005; 294(7):826-32.

# An Example

- ▶ NIEHS and Children's Hospital of Philadelphia collaborating on an observational study of breast feeding vs. bottle (cow's milk) vs. bottle (soy milk) in infants.
- ▶ Parents have already made their feeding choice prior to entering the study.
- ▶ Trying to understand how soy isoflavones, which have estrogen-like activity in the body, affect infant development and health.
- ▶ Variety of physical and behavioral measurements.
- ▶ Infants followed from birth up to nine months (boys) or seven months (girls); toddlers enrolled at 12 months and followed until 24 months.
- ▶ Infants must be healthy, full term, singleton birth.
- ▶ 6ml blood collected at weeks 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36 (boys).

# An example

- ▶ IRB was concerned about the risks of the blood collection.
- ▶ A single collection of 6ml was within NIH Clinical Center guidelines and was regarded as minimal risk, but the cumulative effect of collecting blood was a concern, especially at 8 weeks, when infants are at an increased risk for anemia, due to switching from fetal hemoglobin to adult hemoglobin.
- ▶ IRB required a heel stick (1 ml blood) at 6 weeks to measure hemoglobin. Infants who are anemic will not provide blood at 8 weeks.
- ▶ IRB was also concerned about the stress of repeated venipunctures on infant and mother, and limited this to no more than three attempts per blood draw.
- ▶ The IRB approved the study a minimal risk study once these changes were made to the protocol.

# An example

- ▶ The IRB thought the study was justified, because it was well-designed and was addressing an important pediatric health concern.
- ▶ But since there were no direct benefits to the infants, risk was an issue.
- ▶ It was no at all clear that this study would have been approvable if it were not classified as minimal risk, because it would then fall under 46.406 and it was not clear that the infants had a disorder or condition (they were healthy).
- ▶ The IRB made stipulations to protect the infants from harm, which helped ensure it would be a minimal risk study.
- ▶ Feeding soy milk to infants may pose some risks, due to estrogen disruption, but this was not viewed as a risk of the study, because these the parents had already decided to feed their infants soy milk. This was a natural history/observational study, not an experimental one.