

# Understanding Minimal Risk

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# Why is Minimal Risk So Important?

- It is the threshold for determining level of review (Issue 8)
- Determines, in part, what is on list of research eligible for expedited review (Issues 10-13)
- Implicitly determines what is on exemption (excused?) list (Issue 14-18)

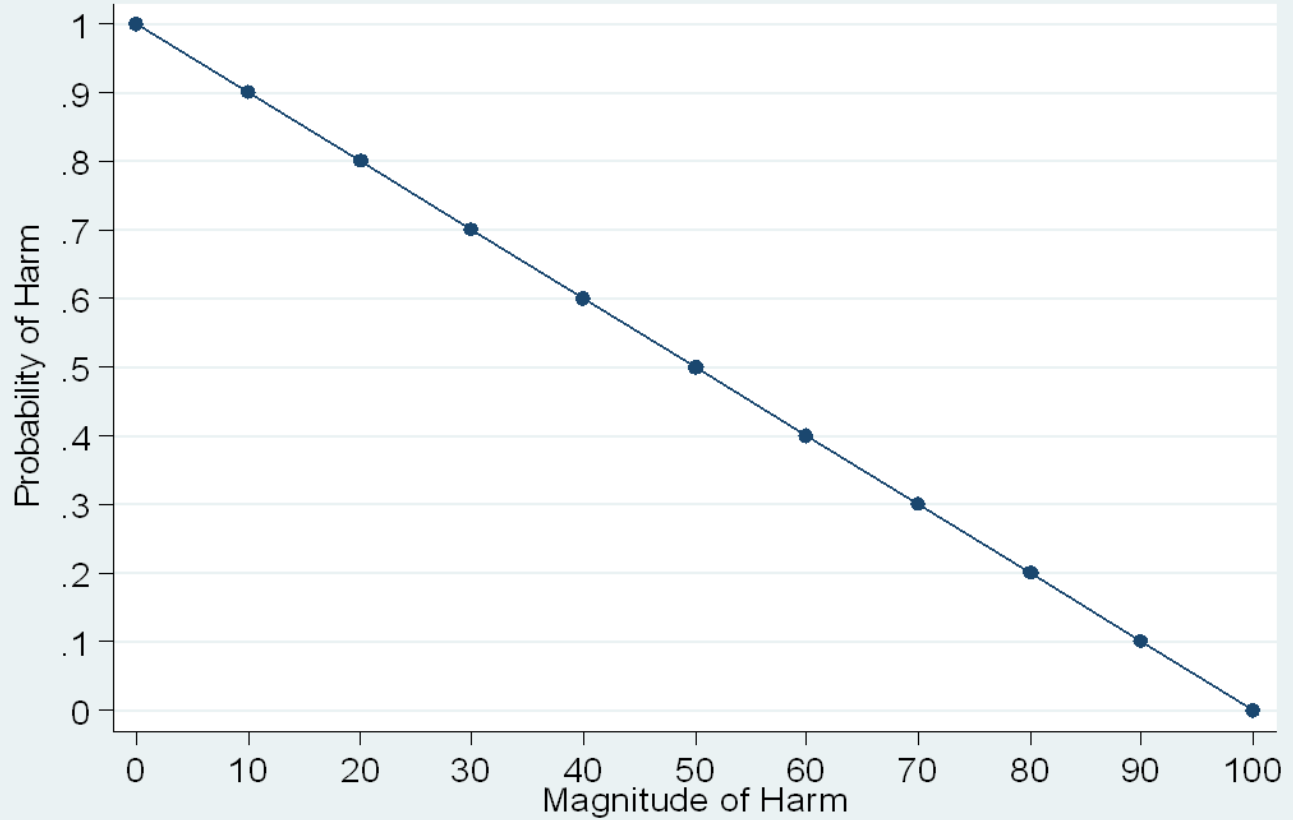
# Definition of Minimal Risk in Common Rule

- *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.*

# What part of “minimal” don’t you understand?

- Both IRB’s and investigators seem to have trouble with the definition. Why?
- It seems clear enough: worst harm should not be serious and probability of harm should decrease as magnitude of harm increases.
- Here is a simple graph that conveys that idea.

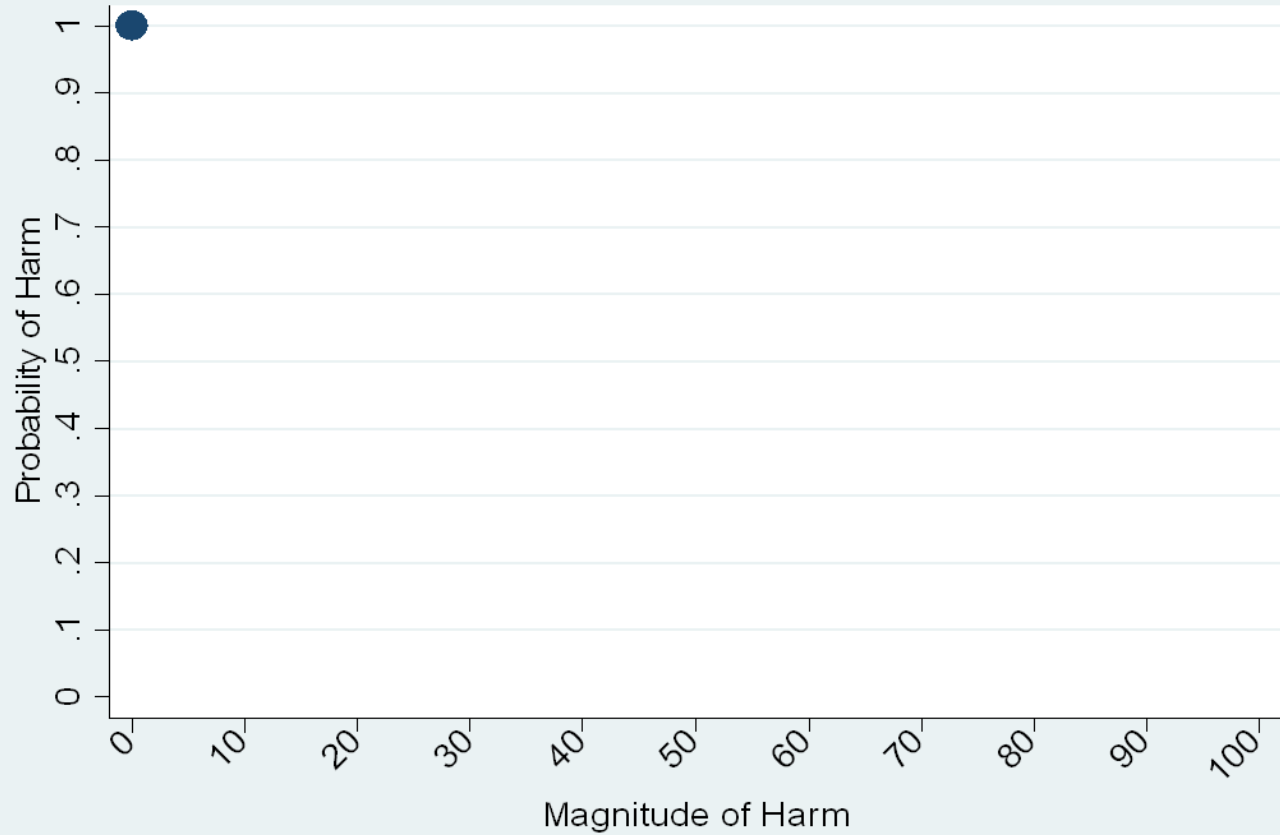
## What the Common Rule Implies



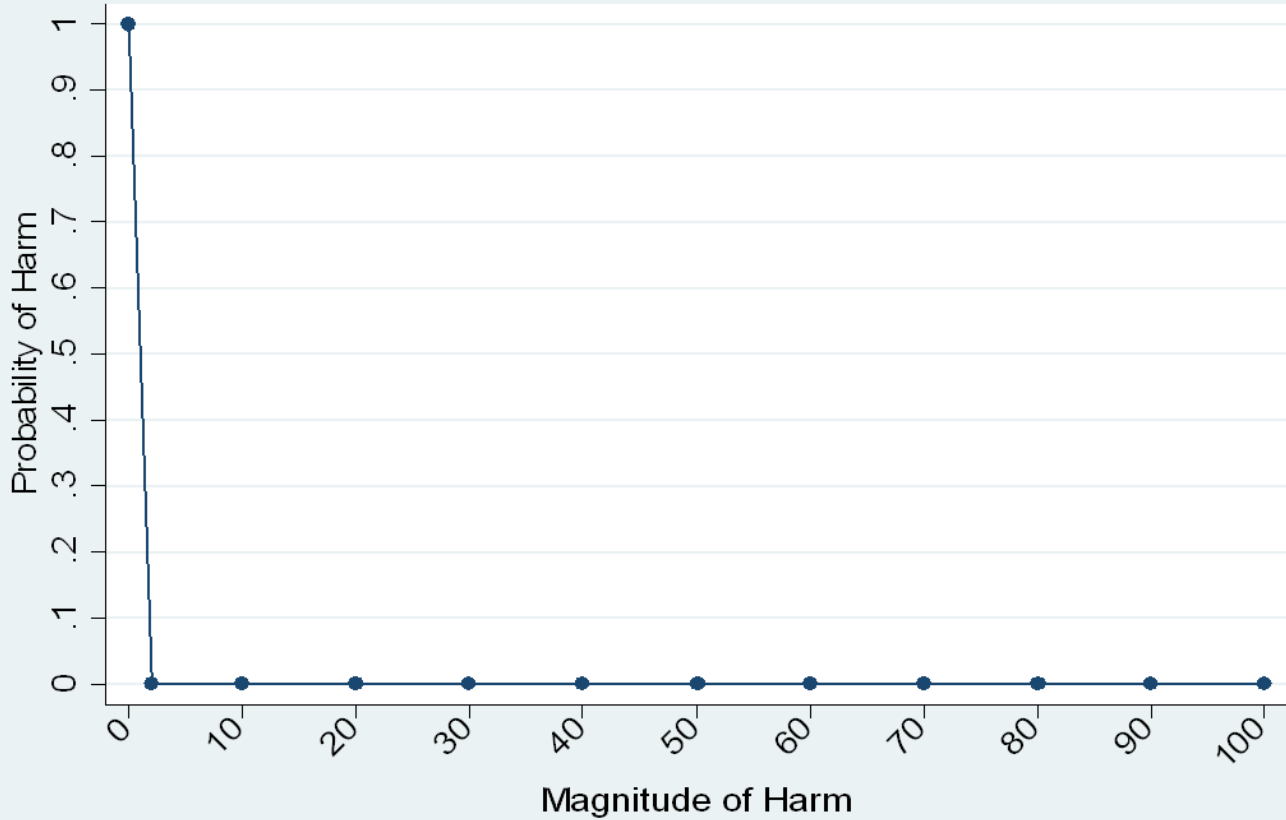
# Problems in Drawing a Graph Like This

- What, exactly, do we mean by probability?
  - Probability distribution found after aggregating over many similar studies?
  - Hypothetical probability distribution for the study under review?
- What, exactly, do we mean by magnitude of harm?
  - The numeric scale is obviously arbitrary.
  - The daily life standard is an attempt to anchor the scale.

## What the regulations don't say

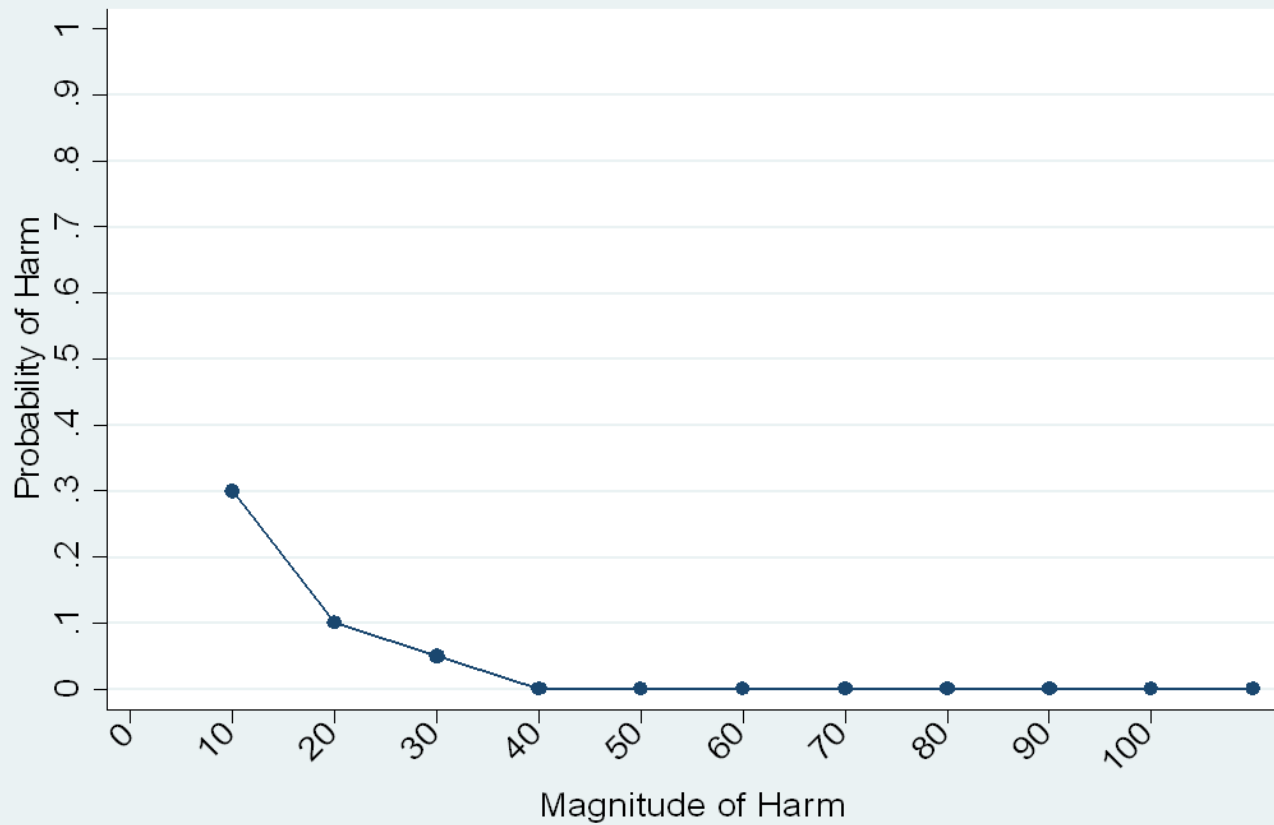


# What many people think is meant by 'minimal risk'





## A somewhat more realistic view



# Problems with the Definition

- The biggest problem is that although the definition is clear enough, the term “minimal risk” is cognitively complex and tends to be used without reference to the definition.
- It is very easy to slip into an assumption that *both* the magnitude of harm and the probability of harm should be “minimal.”
- The CFR implies, but does not make explicit that *by definition* “[harms] “ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” are, over time, encountered by everyone with virtual certainty, that is, with a probability of 1.

# Why is the concept of minimal risk “cognitively complex?”

- Probability is a notoriously difficult concept that many people, even sophisticated academics often do not fully understand or use consistently.
- Risk is even more difficult; in common language it has at least three meanings, which are often inter-mixed.

# Defining Risk

- It can mean the probability of an event occurring within a unit of time, that is during the period of exposure. This is the formal epidemiological definition.
- It can refer to a negative outcome, with or without a probability (loosely) implied. We refer to “risky behaviors.”
- It can refer to general uncertainty as in “this is a risky investment.”
- Hence, when we say “minimal risk” we may be dealing with all three issues, usually in unstated

# A classic example of the confusion that results

- *Sometimes economists distinguish between risk and uncertainty. Risk refers to a situation where we can list all of the outcomes and assign probabilities to them. Uncertainty refers to situations where we may neither be able to list the outcomes or assign the probabilities. Except where we make explicit distinctions, we will simplify our exposition by using the two terms interchangeably. (Footnote in a well know health economics text)*

# Defining Harm and Discomfort

- Common rule points us to routine physical and psychological exams.
- Other examples of daily life hassles:
  - Having to use PowerPoint to prepare a presentation
  - Getting a traffic ticket
  - Being involved in a minor “fender bender”
  - Dealing with a child’s routine illness
  - Having a minor argument at work
  - Losing something important e. g. keys.

# What investigators and reviewers should try to do

- Keep the distinction between risk (as probability) and harm (as magnitude) clear.
- Ask ourselves if we can state the worst harm(s) that can result in a study.
- Ask ourselves if we have some reasonable estimate of the probability of various harms.
- Build a more thorough research base that provides realistic probability estimates.
- Investigate perceptions of the magnitude of harm.

# Some issues that could use further work

- Surveys with sensitive questions
- Absolute versus relative risk and the problem of reference populations
- Voluntary versus involuntary exposure to risk
- Permanent versus transitory harm
- Probability of harm to a given person as opposed to the probability that at least one person will be harmed



# Surveys with sensitive questions

- My IRB experience is that reviewers tend to be skittish about questions involving intimate behaviors, criminal activities and the like for two reasons – accidental disclosure and psychological reactions to the questions.
- Proposed changes #16 and 17 appear to deal with disclosure.
- Clear guidance on consent and respondents right to refuse should deal with the latter.

# Absolute versus relative risk

- If we apply the “daily life” standard, whose life are we talking about?
- Many populations have much higher “background risks” than the investigator.
- Should we evaluate risk relative to “average people” or the population being studied?

# Voluntary and Involuntary Risks

- We all experience risks over which we have no control, e.g. an unpredictable illness.
- We also accept certain risks on a daily basis, e.g. whenever we get in a car.
- We ask respondents to voluntarily accept some risks in a study, usually at little or no benefit to themselves.
- But the daily life standard refers to risks that we accept with the expectation of some benefit.
- This is an ethical issue which might be explored further.

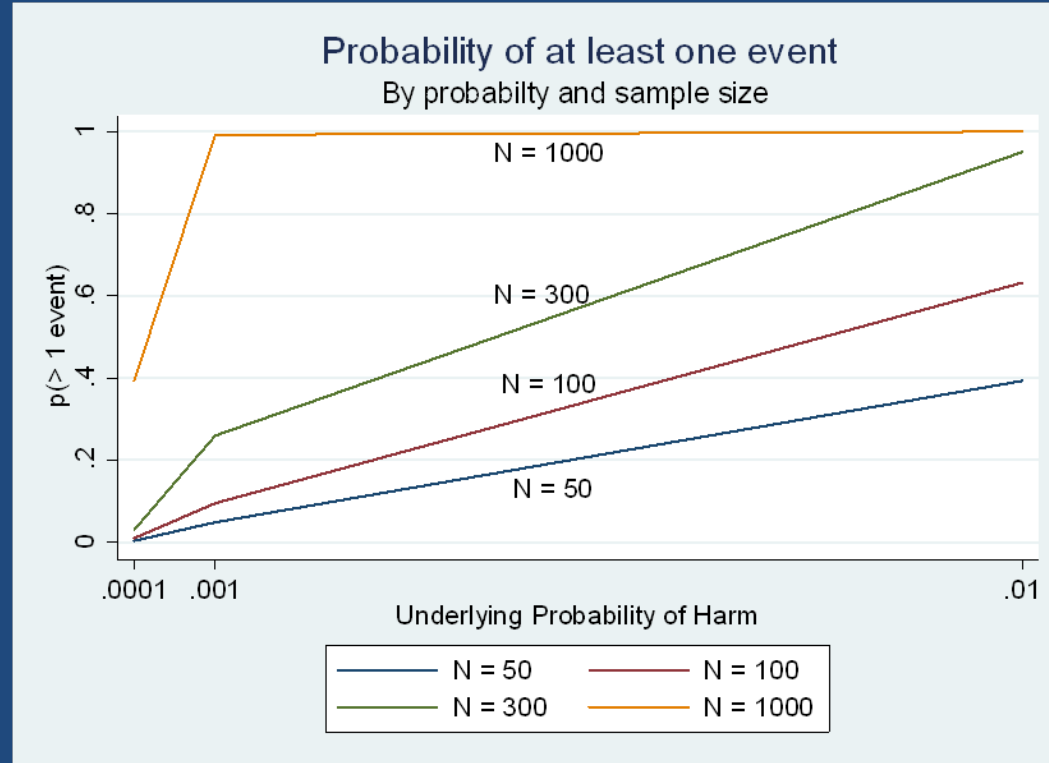
# Permanent versus transitory harm

- An unstated aspect of the “daily life standard” is that we assume the presumed harms are of low magnitude *and short lasting*.
- The discomfort of a medical exam is over once one is out the door or shortly thereafter.
- We can imagine permanent harm from a simple blood draw, e.g. an infection with long term consequences, but the probability of that, while non-zero, is extremely low.

# Harm to One Person versus Harm to at Least One Person

Samp. Size	p (harm)	P (0 events)	P (>0 events)
50	0.01	0.60653	0.39347
50	0.001	0.95123	0.04877
50	0.0001	0.99501	0.00499
100	0.01	0.36788	0.63212
100	0.001	0.90484	0.09516
100	0.0001	0.99005	0.00995
300	0.01	0.04979	0.95021
300	0.001	0.74082	0.25918
300	0.0001	0.97045	0.02955
1000	0.01	0.00005	0.99995
1000	0.001	0.36788	0.63212
1000	0.0001	0.90484	0.09516
5000	0.01	0.00000	1.00000
5000	0.001	0.00674	0.99326
5000	0.0001	UIC	0.39347

# Graphical representation of previous table



# How can this committee help?

- I suspect that it is unlikely that a new definition of minimal risk will appear. The concept is too deeply imbedded in the fabric of human subjects regulations.
- Perhaps this committee could elaborate the concept in its report.
- Given that, perhaps OHRP could issue official guidance which elaborates the definition and suggests how it might be applied more consistently.