

Making More Sense of "Minimal Risk"

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Although discussion often focuses on IRB review of high-risk protocols that may result in substantial harms to research participants, not all research involves high risks. Minimal risk protocols comprise a substantial number of protocols in universities that have flourishing research programs in the social sciences and education. Because some minimal risk protocols may be reviewed using an expedited review process, researchers may pursue "minimal risk" status for their projects.¹ IRBs must understand what constitutes "minimal risk" before they can determine whether a given research protocol involves merely minimal risks for each of the individuals who participate in it.²

Unfortunately, the definition of minimal risk in the federal regulations is ambiguous, allowing some research to be inappropriately characterized as "minimal risk" when in fact it requires greater oversight. Here I examine one misinterpretation.

The regulations define minimal risk as follows:

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 (CFR 46.102(i)).

Some clarification is required to

understand this definition. First, it should be clear that risk and harm are not the same concepts. Beauchamp and Childress note that harm is the "normatively neutral sense of thwarting, defeating, or setting back the interests of one party by causes that include self-harming conditions as well as the (intentional or unintentional) actions of another party."³ Thus though they may not be bad in an absolute sense, harms are, in general, perceived as *prima facie* wrong to inflict on others.⁴

Risk is "commonly expressed as the magnitude of some harm multiplied by the probability of its occurrence,"⁵ and can be represented in the following product formula:

$$\text{Harm} \times \text{Likelihood That Harm Will Occur} = \text{Risk}$$

While assigning numerical values to the magnitude or the likelihood of harm is problematic, in theory the magnitude of harm can be measured in terms of positive numbers (including zero), and the likelihood of harm can be measured in terms of a fraction, or percentage (including zero percent). Multiplying these two numbers would yield a positive number (again, including zero), the risk of harm. (In decision theory, this would be known as the "expected utility" of the state of affairs in question.⁶)

On this interpretation, there are three ways in which a low degree of risk can obtain in any given situation:

- 1) the magnitude of harm is low and the likelihood that the harm will occur is low; thus the level of risk is very low
- 2) the magnitude of harm is very

low, but the likelihood that the harm will occur is moderate or high; thus the level of risk is low

- 3) the magnitude of harm is moderate or high, but the likelihood that the harm will occur is very low; thus the level of risk is low

Minimal risk studies would be those in which the product of magnitude and likelihood of harms that would result from the study do not exceed the risks of everyday life.

Although applying the product formula is only one way to interpret the phrase "the probability and magnitude of harm" in the regulations, the National Human Research Protection Advisory Committee (NHRPAC) accepts the product formula, when it claims that "minimal risk" means that the worst harm that could occur in a study should not be very serious—even if

many subjects experience it, and, if the harm is serious, then the probability of any given subject experiencing it should be quite low."⁷

A final caveat should be noted when discussing minimal risks as the product of magnitude of harm and likelihood of harm. Harm can have a subjective component: different people may perceive differently both what counts as a harm and what is understood as the magnitude of that harm. For example, we recognize that embarrassment is almost universally seen to be harmful, but some people don't embarrass easily, if at all, while others are easily and profoundly embarrassed at the slightest provocation. Similarly, the probability of a given harm accruing to a given individual may be relative to that individual: we don't claim that the probability of getting into a car

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accident is the same for both for 17-year-old males and 40-year-old females.⁸

Challenging the Product Formula

Two case examples illustrate the pitfalls of using the product formula when assessing minimal risk:

CASE 1: The IRB reviews a study in which a 100-student, college-level biology lecture will be observed when a guest lecturer seemingly has an epileptic seizure during the first minutes of the two-hour class. After the guest lecturer is attended to and removed from the room, the regular professor resumes the class. Near the end of class, a pop quiz is administered on the day's lecture. Before the end of class the students are debriefed about the nature of the study, and are thanked for their cooperation in assessing the effects of stressful events on memory and retention of complex information. They are told that the "pop quizzes" will not figure into their final grades, as their names will be removed from the tests before grading takes place.

A waiver of consent is sought for this study, on the argument that it meets the requirements of 45 CFR 46.116(d): the study presents minimal risk, students' rights and welfare will not be adversely affected, and the phenomena being observed would be altered if the students knew that they were part of a study. The researchers claim that while practically every student is expected to become uncomfortable to some degree, this degree is so small, and so fleeting, that the study may qualify as minimal risk.

This study is in keeping with the second type of minimal risk research: the likelihood of harm is high—the researchers hypothesize that nearly all of the participants will experience some level of discomfort at what they see—but the degree of harm is believed to be very low. The students don't know the "guest lecturer," epileptic seizures are known to rarely

be life threatening, and the students will soon be told that the guest lecturer is just fine.

But consider a different scenario in which the product formula might suggest that the research is "low risk":

CASE 2: The IRB considers a study in which police officers are interviewed privately to discuss police corruption. All identifiers are removed from each of the interview transcripts, and the investigator is taking great care to protect the anonymity of each participant. However, if any individual responses were made known outside of the interviews, some participants could face termination of employment.

This study seems to conform to the third type of minimal risk study: the likelihood that harm will occur is very low, but the harm that may result is a moderate or perhaps even "serious" harm, to use NHRPAC's language.

One question raised by Case 2 is this: Should the risk of a particular harm to an individual be considered when evaluating minimal risk, or should merely the overall degree of risk to the participant cohort figure into the IRB's assessment? On one hand, the particular harm that may result from this study—loss of employment—is significant to the individual who experiences it. On the other hand, the likelihood of this harm occurring is very, very low. Using the product formula, this may qualify as a minimal risk study. Numerically, the risk may be comparable to, or even lower than, the risks posed in everyday life.

But this assessment is mistaken. Surely a person who lost employment as a result of the study would not agree with the assessment that this study posed merely "minimal risk." This stands in sharp contrast to Case 1, in which every one of the students would likely agree that the transient nature of the distress was sufficient to qualify this as a minimal risk study, despite the fact that the

distress was experienced by every participant.

If a police officer does lose a job after participating in the study described in Case 2, how could the IRB or the researcher reasonably have known this would happen? After the study is completed, it can be said with 100% certainty that a substantial harm will result from the study. So after the fact, the study is no longer minimal risk. But before the study takes place, isn't it appropriately assessed as minimal risk?

It is, of course, impossible for IRBs to use 20/20 hindsight when evaluating levels of risk. Whatever our means of assessing risk, they must be practical, because IRBs are called on to assess the risks of studies, early and often. Additionally, the 20/20 hindsight rule will absurdly render some high-risk research minimal risk, just as long as no one was actually harmed by the completed study. It is obviously a mistake to call a given phase I trial "minimal risk" because after the fact it turns out that there were no harmful consequences of that particular study. Phase I trials should be undertaken only with the greatest caution and oversight; claiming that such a study, with 20/20 hindsight, was merely minimal risk would be wrong.

Weighing Risks, Weighing Benefits

IRBs weigh the risks against the benefits of undertaking a given research project. Studies that have a negative risk/benefit ratio, wherein the risks of the study outweigh the benefits, are deemed unethical. Having a positive risk/benefit ratio, in which the benefits of the study outweigh the risks of the study, is a necessary, but not sufficient condition, for IRB approval. The implication is that risks and benefits are in some measure commensurate. If this is so, the way that benefits are measured will illuminate the ways in which risks are appropriately measured.

It isn't clear that we use a product

formula when calculating the benefits of a study, however. If we did, then there would be three ways in which a study could result in a high level of benefit, corresponding to the product formula for measuring risks:

- 1) the magnitude of benefit is high, and the likelihood of benefit is high;
- 2) the magnitude of benefit is very high, but the likelihood of benefit is low;
- 3) the magnitude of benefit is very low, but the likelihood of benefit is high.

In fact, we don't apply the product rule when calculating the benefits of research studies, for if we did, the third version of high benefit research would exist, when it in fact does not. Imagine a study that would, if successful, eliminate hangnails for the entire human race. On the third product formula above, this would be a study that would result in high benefits. Countless people are certain to benefit from this study. However, no IRB would allow, in the service of possibly eliminating hangnails, research that put individual participants at risk of serious harm.

Why not? Because we don't calculate risk in terms of harms to the entire population of individuals who may experience those harms. Rather, we calculate risk in terms of the degree of harm that may accrue to any given individual. Pancreatic cancer may affect only a very small number of people, but the harms of pancreatic cancer, for those who actually get pancreatic cancer, are great. Phase I studies of drugs that may treat pancreatic cancer are approved by IRBs, even though the risks in those phase I studies may be very high and the benefits will likely accrue to a future cohort of patients, not the actual research subjects in the phase I study.

Nancy King distinguishes between "direct benefit to subjects," which includes the benefits that research participants receive from the intervention under study, and "aspira-

tional benefit," which includes the benefits that accrue to future cohorts or to society.⁹ While the direct benefit in the phase I pancreatic cancer trial is very low, the aspirational benefit of such a trial may be great, even though only comparatively few people will receive those benefits. If IRBs used the product formula in calculating the risk/benefit ratio of such phase I studies, they might not approve them, because the risks are high, and while the benefits may also prove to be high, those benefits will ultimately accrue to only a few individuals. But for those few individuals, the benefits will be tremendous.

But wait—doesn't that look like a textbook application of the product formula: multiply the number of people affected (very few, in the case of phase I pancreatic cancer trials) by the degree of benefit that will result (very high) to find the benefits of the research (high)?

Yes, it does. But the application of the product formula in the case of hangnail research shows that it is not the product formula that correctly characterizes an assessment of the benefits, or risks, of a study. Rather, measuring risks and benefits requires an appreciation of the individual research participant's experience in taking part in the study, and the experiences of other individuals whose lives will be enhanced by this research.

The result is that the third version of a product formula for benefits—the magnitude of benefit is very low, but the likelihood of benefit is high, thus the benefits of the research are high—is mistaken. Such research shouldn't be considered "high benefit" because there are no individuals to whom a high benefit will accrue. The experience of each individual who benefits from this research is only a very minor benefit.

The third version of the product formula in measuring risk—the degree of harm is moderate or high, but the likelihood that the harm will occur is very low, thus the level of

risk is low—is similarly mistaken. There are individuals for whom this research could result in moderate or high degrees of harm, despite the very low likelihood of that harm occurring. Thus the research should appropriately be classified as exceeding minimal risk. The only research that is appropriately considered minimal risk is research in which the harms that each individual would experience as a result of participating in the research do not exceed the harms experienced by individuals in daily life.

The "Daily Life" Criterion

Measuring the risk in studies on the basis of the harms that accrue to individuals, rather than the harms as they are totaled across all of those who experience them, is in keeping with the "daily life" criterion used in the definition of minimal risk at 45 CFR 46.102(i). The daily life criterion is not without controversy. Kopelman believes it is a mistake to peg the daily life criterion to the experiences of research participants, for such a position results in different individuals being expected to endure greater research risks because they have high-risk occupations, or already have illnesses that require risky medical interventions on a daily basis.¹⁰ Others, such as Freedman and colleagues, interpret the daily life criterion as allowing for differential acceptable risks for individuals who experience different levels of risk in their daily lives, asking, "Minimal risk to what end, from whose point of view, and under which situations? On a semantic level, 'minimal risk' is relational, context-dependent."¹¹

Regardless of the appropriate interpretation, the daily life criterion calls on researchers to consider whether the risks each individual research participant will be exposed to exceed the risks of daily life. As Glass and Speyer-Ofenberg note, "[t]he risks of everyday life for

rational self-interested individuals offer some personal benefit,"¹² which is to say that they are risks that individuals undertake, and are traded against benefits individuals experience. Even King's aspirational benefits will ultimately be benefits experienced by individuals, whether future cohorts of patients or members of society. This is why the deception study described as Case 1 above is a minimal risk study. Though the total number of students who experience some discomfort from the study is high, it is a mistake to sum the amount of harm, because there is not "an increase of felt suffering" by any individual.¹³

Another point about the failure of the product formula emerges if we look further at Case 1. As described, 100 students will experience fleeting, low level harm in this study. Using the product formula, however, the implication is that increasing the number of participants may increase the risk of the study beyond minimal risk. Imagine performing the study in a room of 200, 300, or 400 students. Is it suddenly four times as risky? Not really. More accurately, it is four times more likely that someone in the room will experience some type of trauma exceeding those harms experienced in everyday life, because there are four times as many people in the room. But that is again an increase in the number of individuals experiencing that harm, not an increase in risk as understood using the product formula.

Those who accept the analysis offered by Freedman et al. might argue that my focus on the product formula is mistaken, that comparisons of risk are "not quantitative, but represent a categorical judgment that focuses upon the comparison of new experiences to those of everyday life."¹⁴ Rather than examining risks from a quantitative perspective, oughtn't we to use a more qualitative measure? Perhaps terms like minimal risk and moderate increment over minimal risk,

although seemingly quantitative, should be metaphorically applied to qualitative assessments.

Yet even if risks are understood qualitatively and not quantitatively, it must be the case that some risks are recognized as greater than others—some risks are minimal, some are greater than that. King, when describing three aspects of benefit that should be described in any consent form—nature, magnitude, and likelihood of benefit—does not commit to either a qualitative or quantitative measure. But even she uses quantitative language—"how long?" or "how great?"; "100 percent effectiveness" versus "a low incidence of effectiveness"¹⁵—despite remaining noncommittal about the quantitative or qualitative measurement of benefits, or risks. An objection to the analysis of the product formula on the basis that it is merely a quantitative assessment of minimal risk is mistaken. The product formula may be erroneously employed, even among those who adhere to a qualitative, and not quantitative, measure of risks and harms.

Nothing in the federal regulations explicitly requires or endorses the product formula, but ambiguity in the definition of "minimal risk" allows utilization of the product formula. And that may result in misapplications of the minimal risk label, such as is found in the NHRPAC's draft recommendations. The product formula, which mistakenly looks to the product of the magnitude of harm and the likelihood of harm in calculating risk, does not accurately capture what it is for a study to in fact be a minimal risk study. A clearer understanding of how the benefits of research are measured and an understanding of the daily life criterion make clear that risks should be understood in terms of the harms that are experienced by individuals, and not on the abstract and general basis of the product formula.

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