

Moral Problems in Assessing Research Risk

by Loretta M. Kopelman

In a recent contribution to *IRB*, "Thinking Clearly About Research Risk: Implications of the Work of Benjamin

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Freedman," Charles Weijer wrote a fine tribute to our late friend and colleague.¹ This comment is also intended to honor Benjamin Freedman and promote continued discussion of his excellent publications. In the course of this article and referencing an earlier article by Freedman, Fuks, and Weijer,²

Weijer criticized my analysis of the weaknesses of the definition of "minimal risk" that appears in the U.S. and other research regulations. The definition states: "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 and psychological examinations or tests." (45 CFR 46.102i).



This standard is pivotal in these rules, setting a foundation on which to assess potential harms and benefits in deciding if research is permissible. Approval is contingent on finding that subjects have been selected fairly and that the risks to subjects are minimized and reasonable in relation to anticipated benefits of the study to the subject or to society. In addition, IRBs can only approve pediatric studies having no more than a "minor increase over minimal risk"; this crucial upper limit is undefined, however. As risks increase, the regulations require increasingly more rigorous documentation of such features as informed and voluntary consent, potential benefits, and the nature of the risks of harm. The Council of International Organizations of Medical Sciences (CIOMS)³ has a similar definition, as do the United Kingdom, South Africa, Canada, Norway, and many other countries.⁴

Weijer maintains, "The risks of daily life are familiar to us all. . . . Research interventions may be determined to be minimally risky because either the procedure is in fact encountered in daily life or it is sufficiently similar to those routinely encountered."⁵ He takes the second part of the definition to give "an example of such [everyday] risks." I disagree; I take the second part of the definition to be distinct and to set a further condition on research risk. In my view, this definition says that something has the probability and magnitude of a minimal risk of harm if it meets either or both parts. Something has a greater than minimal risk of harm if it meets neither. The second part of the definition seems to offer more guidance about what physical risks are minimal, since it directs us to ask if a risk is like that encountered in routine examinations. Little guidance is given about what constitutes a psychosocial risk, a worrying lapse since many confidential matters arise in routine examinations that would harm patients if generally known.⁶ In what follows, however, I shall not contest his premise that the second part of the

definition is an example of the former.

In contrast to Weijer and Freedman, Fuks and Weijer, I continue to question the clarity and utility of this definition that asserts everyday risk should guide assessments of minimal-risk research because of four unresolved moral issues: First, how should we establish and use thresholds regarding both the probability and magnitude of harm used to identify everyday risks? Second, given the different hazards in different countries and communities, what locale(s) should be used to assess everyday risks? Third, why should everyday risks of harm be regarded as relevant for determining that research risks are minimal? And fourth, if this is a useful and clear standard, why has there been sustained disagreement over whether common procedures should be viewed as daily or minimal risk, a minor increase over minimal risk, or greater?

What Thresholds Should Be Used?

The probability of something ranges between none and certain and magnitude of harms between trivial and catastrophic events. These are different continua since rare as well as common events may have either trivial or catastrophic harms. According to the regulations' definition of "minimal risk," we should guide moral judgments about what research risks of harm are minimal by consideration of the probability and magnitude of daily risks. One problem is how to set thresholds to mark those risks of harm that have the probability and magnitude of harm encountered in daily life. I do not view this as primarily a difficulty over quantification, as Weijer suggests. Rather, establishing a way to set thresholds is a complex moral or evaluative judgment about what probability is appropriately low, and what magnitude is appropriately trivial to constitute a morally and legally acceptable standard for judging whether some particular research project should be approved. The assessment is a

complicated balancing act since some extremely low risks of substantial harm might be approved in some circumstances, while high risks of moderate harm might not.

This moral and evaluative judgment about where to place thresholds is controversial. The Nuremberg Code forbids enrolling people in studies without their competent, voluntary, and informed consent and the Declaration of Helsinki forbids using them in nontherapeutic research. These theoretical stances, I have argued, are too restrictive.⁷ Yet they represent alternative approaches to assessing potential harms to subjects to the regulations we are discussing, and place the thresholds differently.

We need standards, in part, because personal or professional perceptions and interests may affect how people are inclined to place or use thresholds. People who are risk averse will probably place these cut-off points differently from those who are not. People fighting an epidemic or caught in a war zone have different perceptions of daily risks from those residing in healthy and peaceful regions.

What Locale Should Be Used?

The probability and magnitude of risks of harm varies in different places. In some locations daily risks are horrific. In war-torn countries many, sometimes most, young children perish, as starvation and death stalk their daily lives. In flooded areas, water-borne diseases constitute daily and life-threatening hazards, and some diseases, such as AIDS, constitute grave daily risks for whole populations.

Since everyday risks are not necessarily trivial or minimal, a moral judgment must be made about which group (refugees, firefighters, or librarians) in what community (peaceful or at war) should be used in making comparisons between everyday risks and minimal research risks. Interestingly, South Africa acknowledges this problem by amending its substantially similar definition of "minimal risk" in its research

guidelines by adding that the risk is no greater than everyday risks "in a stable society."⁸

I have suggested that one response to this problem is to discount the location by holding that the standard should be the risks any of us may be subject to, rather than some of us.⁹ Freedman, Fuks, and Weijer seem to agree with and elaborate on this suggestion.¹⁰ They acknowledge that some communities have such risky environments that high-risk studies could not be excluded, and that investigators might even seek them out. In response, they defend "intercultural ethics" in which the norms of all the cultures participating would have to be honored to conduct any cross-cultural research. I support this approach to solve this exceedingly difficult moral problem. The dangers of tying our understanding of risk to location and letting hazards be minimal for some, but not for the rest of us, opens the door to a variety of problems about discrimination and exploitation. Yet the solution is controversial and others might argue that it is reasonable to take local conditions or experiences of potential subjects into account in determining what sort of risks of harm are minimal for those subjects.

Why Should Everyday Risks Be Used to Assess Research Risk?

Some everyday hazards are trivial, and some catastrophic, some rare and some common, so what does everyday risk have to do with estimating that research risk is minimal? Death and starvation are everyday risks for some people in the world, but not an appropriate basis for assessing whether research risk is minimal. Others may regard burglary, muggings, rape, drive-by shootings, or battery to be daily risks. It seems easier to determine if developmental studies in which children name animals constitute a minimal risk than to compare the level of risk to hazards of daily life some or all of us encounter.

Weijer¹¹ and Freedman, Fuks and Weijer,¹² however, think the definition highlights the right

question that parents and IRB members should ask: Is the study sufficiently like the child's everyday experiences to merit approval? Parents, they write, when asked to give consent should reflect: "Are the risks sufficiently similar to those in my child's everyday life that I should allow this experience at this time?"¹³ IRBs, "acting in loco parentis, will need to debate whether the demarcated research intervention is similar to a common experience of this child, and whether the incremental research risks are similar to risks this child or others like him runs on a routine basis."¹⁴

Consideration of particular people's experiences is important, but not decisive. Some people, such as dying or disabled children, encounter horrible everyday experiences that could, if their particular everyday hazards are used, justify high-risk studies for them but not the rest of us. A minor increase in risk for them might be very different than for the rest of us. As noted, a variable standard introduces problems of fairness in assigning risks. In addition, agreement among parents, IRB members, investigators, and subjects does not show that their accord comes from making comparisons to the probability and magnitude of everyday harms some or all of us encounter. Their concurrence may mean that reasonable and informed people of good will often agree about what risks are acceptably low in particular studies for particular children.

Why Should We Tolerate So Much Ongoing Disagreement?

In his recent article, Weijer approvingly quotes Freedman, Fuks, and Weijer: "We are, by definition, each acquainted with them [minimal risks]; and, almost by definition, if we are unsure whether they belong within the set of common risks then they don't." For standards to be useful in settling controversies, there should be agreement about what they mean and how to use them. Studies and discussions, however, show long-standing and important disagree-

ment about what risks of harm constitute a "daily or minimal risk" or "minor increase over minimal risk" of harm for the purpose of assessing research. In 1981 Janofsky and Starfield found considerable differences among pediatric experts, in both treatment and research settings, about how to assess the risk of such procedures as venipuncture, arterial puncture, and gastric and intestinal intubation.¹⁵ An editorial in the *Journal of Pediatrics* concluded that this alarming variation shows that better standards of risk assessment in children's research need to be formulated.¹⁶

Recently, this lack of consensus and problems with regulatory guidance about what constituted a "daily or minimal risk" and "minor increase over minimal risk" within the research community surfaced in testimony before the National Bioethics Advisory Board (NBAC) recorded in "Regulatory Understanding of Minimal Risk."¹⁰ For example, there was substantive disagreement about how to assess the risks of a lumbar puncture done for research purposes on a pediatric population. Some argued that the risk was minimal, others said that it constituted a minor increase over minimal risk, and still others maintained that the risk was greater than this. They also disagreed about whether the risk of harm from this procedure is different from what is done in routine clinical examination. Members of NBAC agreed, however, that the definition of "minimal risk" was vague, and that the crucial upper limit that local boards can approve, "a minor increase over minimal risk," was even vaguer. Disagreements about how to assess psychosocial risks of harm are no less contentious. There have also been sustained disagreements about how to view multiple placebo injections.¹⁷ National Institutes of Health panelists, on a specially appointed review panel to evaluate a growth hormone study for idiopathic short stature, strongly disagreed about whether three placebo injections a week for many years should be viewed as daily or

minimal risk, a minor increase over minimal risk, or greater.¹⁸

Providing Clearer Guidance

Elsewhere, I have suggested ways that the guidance could be improved: (1) Clarify how to regard the nature and number of certain common procedures such as lumbar punctures or placebo injections.¹⁹ (2) Detailed examples could also serve as paradigms and spell out how to assess risks of harm, balance them with potential benefits, and set thresholds of acceptable risks. These might become fixed points for making some of these moral assessments about what studies should be approved for pediatric populations. (3) Regulatory guidance about how to address these four moral questions would further clarify the assessment of risk. (4) In the face of ongoing and sustained disagreements, clarify how our laws and traditions interact with research guidelines.

As over twenty years of debate shows, the assumption by Weijer and Freedman, Fuks and Weijer that a consensus exists regarding what paradigms to use in assessing minimal research risk and the crucial upper levels of justifiable risks of harm especially for children seems unwarranted. Whatever

agreement exists about what risks are minimal for the purpose of research may be the result of the practical wisdom of reasonable and informed people of good will. Layers of moral judgment generally protect subjects, but more likely from the good sense and moral character of parents, subjects, investigators, and IRB members, rather than help from the regulations' definitions of risk and its reliance on vague notions of "daily risk."

References

1. Weijer C. Thinking clearly about research risk: implications of the work of Benjamin Freedman. *IRB* 1999; 21(6): 1-5.
2. Freedman B, Fuks A, Weijer C. In loco parentis: minimal risk as an ethical threshold for research upon children. *Hastings Center Report* 1993; 23(2): 13-19. Characteristically, Freedman sent me a copy of this paper encouraging me to comment. I regret it took me so long that he cannot respond to me.
3. Council for International Organizations of Medical Science (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland, 1993.
4. Kopelman LM. Children as research subjects: a dilemma *Journal of Medicine and Philosophy* 2000; 25(6):745-64. Some of the points made here are also made in that article, or adapted from it.
5. See ref. 1, Weijer 1999:3.

6. See ref. 4, Kopelman 2000; and Kopelman L. Estimating risk in human research. *Clinical Research* 1981; 29: 1-8.
7. See ref. 4, Kopelman 2000.
8. "The MRC therefore defines negligible or less than minimal risk as equal to the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives of people in a stable society, or in the routine medical or psychological examination." *South African Medical Research Council. Guidelines on Ethics for Medical Research*, rev. ed. Tygerberg: MCR Corporate Communication Division, 1993.
9. See ref. 4, Kopelman 2000; ref. 6, Kopelman 1981.
10. See ref. 2, Freedman et al. 1993.
11. See ref. 1, Weijer 1999.
12. See ref. 2, Freedman et al. 1993.
13. See ref. 2, Freedman et al. 1993:16.
14. See ref. 2, Freedman et al. 1993:18.
15. Janofsky J, Starfield B. Assessment of risk and research on children. *Journal of Pediatrics* 1981; 98:842-6.
16. Lascari AD. Risk of research in children [editorial]. *Journal of Pediatrics* 1981; 98:759-60.
17. National Bioethics Advisory Commission. Regulatory understanding of minimal risk. Testimony before the Human Subject Subcommittee of the National Bioethics Advisory Commission Meetings, Arlington, Virginia, 8 January 1998. Available at <http://bioethics.gov/transcripts/index#jan98>.
18. See ref. 4, Kopelman 2000.
19. See ref. 4, Kopelman 2000.
20. See ref. 4, Kopelman 2000.

