



## Moral Solutions in Assessing Research Risk

by Paul B. Miller and Charles Weijer

Loretta Kopelman makes an important contribution to ongoing efforts to understand and elaborate on Benjamin Freedman's work in research ethics,<sup>1</sup> particularly for our understanding of the ethical

analysis of research risk. Through the course of the present paper, we wish to affirm Kopelman's emphasis on the "pivotal" status of minimal risk, while working towards a clarification of the nature of the disagreement between our respective interpretations of the meaning and function of this concept.

The concerns expressed in Kopelman's article are familiar.<sup>2</sup> She draws attention to problems with the concept of minimal risk

as it is currently defined in the Common Rule. Her suggestion that we merely defend minimal risk as articulated in the Common Rule is mistaken, however. While we believe that minimal risk provides a sound normative basis for the assessment of nontherapeutic research risk, we situate it within a comprehensive framework for the analysis of research risk, building on the work of Freedman and colleagues.<sup>3</sup> The integration of this comprehensive approach to the moral analysis of risk will require changes to current regulation.

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## A Comprehensive Framework for the Moral Analysis of Risk

As a consequence of misunderstanding of the place of minimal risk within the broader framework, there is a noticeable "lack of fit" between Kopelman's commentary and our original article. Nowhere is this discord more evident than where the commentary suggests that the minimal risk threshold sets "a foundation on which to assess potential harms and benefits in deciding if research is permissible." We believe that this statement misconstrues the role of the minimal risk threshold. The meaning of minimal risk, and its function in research review, becomes clear only when we understand the distinction between it and clinical equipoise, the ethical standard for therapeutic interventions.

Clinical research often involves both therapeutic and nontherapeutic procedures. Therapeutic procedures hold out the potential for medical benefit to the research subject. Nontherapeutic procedures do not; they are not administered with therapeutic warrant, but are undertaken solely in the interest of answering the scientific question. Accordingly, the IRB must evaluate therapeutic and nontherapeutic procedures separately.

With respect to therapeutic procedures, IRBs are indeed responsible for assessing and balancing potential harms and benefits in deciding if research is permissible. However, the ethical standard governing the assessment of risks related to therapeutic procedures is the requirement for clinical equipoise, *not* minimal risk. A state of clinical equipoise exists when the community of expert practitioners is uncertain as to the relative merits—i.e., the relative balance of benefits and harms—of standard *versus* experimental therapy.

Nontherapeutic procedures hold no prospect of benefit to individual subjects, and therefore a risk-benefit calculus is not appropriate. Rather, the IRB must ensure that the risks of such procedures are

(1) minimized, and (2) reasonable in relation to the knowledge to be gained. Thus nontherapeutic procedures are evaluated by a risk-knowledge, rather than a risk-benefit, calculus. Minimal risk is a threshold concept of allowable nontherapeutic risk applied only in certain situations. It functions either as a "sorting mechanism," directing the IRB's attention to riskier studies (e.g., 45 CFR 46.110(b)), or as a limit to allowable risk for research involving vulnerable populations (e.g., 45 CFR 46.406).

Related is our disagreement with the suggestion that the minimal risk threshold requires that IRBs only approve pediatric studies "having no more than a 'minor increase over minimal risk'."<sup>4</sup> This statement is misleading in suggesting that the minimal risk threshold forbids approval of research that poses serious therapeutic risk, such as cancer or HIV studies. Our comprehensive framework for the ethical analysis of risk sets no limit on the therapeutic risks to which children may be exposed, provided that a state of clinical equipoise exists. The threshold of a "minor increase over minimal risk" applies only to the nontherapeutic elements of a study.

Our view is supported not only by moral argument but also by an examination of the historical origins of minimal risk in the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. McCartney reports that the concept of minimal risk (the ensuing debate surrounding it, and the category of "minor increase over minimal risk") emerged from a feeling shared by "most Commissioners ... that they could approve research involving children even when not for their benefit as long as the risks presented by research were minimal."<sup>5</sup> Levine, a consultant to the National Commission, notes that "the National Commission never intended the minimal risk standard to be applied to interventions or procedures that hold out the prospect of direct benefit to the

individual subject. These are to be justified precisely as they are in medical practice."<sup>6</sup> The formulation of the minor increase over minimal risk category was to allow greater flexibility in IRB review of nontherapeutic procedures. It was not intended as a threshold limiting the risks of pediatric research generally.

## Flexibility Is a Virtue

Kopelman raises other questions regarding specification of risk thresholds, justice and the universalizability of equating everyday risk with acceptable risk, and the clarity of the minimal risk threshold as a category for the classification of common procedures.

The first "unresolved moral issue" she calls attention to is difficulties policymakers might encounter in establishing a threshold of acceptable risk based on a research subject's experience with "everyday" or "routine" risks in daily life. It might be difficult to compare risks of research and risks of everyday life meaningfully, given that in everyday life we engage in a broad array of activities that differ in regard to both the probability and magnitude of harm. Kopelman explains that:

The probability of something ranges between none and certain and magnitude of harms between trivial and catastrophic events. ... 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.<sup>7</sup>

The problem pointed to here is one primarily of specification. Given that risks in daily life can vary widely with respect to probability and magnitude, how can we as policymakers expect them to

provide a stable measure against which to judge the acceptability of research risk? Despite Kopelman's assertion that she does not advocate a quantitative over a qualitative approach to risk assessment, she does seem to suggest that what is lacking in the Common Rule definition of minimal risk is quantitative precision in relating the probability and magnitude of risks of research to those of everyday life.

The suggestion that there are difficulties encountered in setting a precise threshold of minimal risk complicates our thinking on this concept unnecessarily. Kopelman argues that "establishing thresholds is a complex moral or evaluative judgment about what probability is appropriately low, and what magnitude is appropriately trivial" and warns that "[t]he 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."<sup>8</sup>

The purported "complexity" of minimal risk lessens with the realization that it does not call for specification of levels of probability and magnitude of risks of daily life. Rather, flexibility was intentionally and appropriately built in to the Common Rule definition of minimal risk. Mandating specific numeric levels of probability and magnitude would have reduced the validity and utility of the concept. Kopelman grants this implicitly in stating that psychosocial risks and perceptions of risk vary significantly from one person to the next. Meaningful assessment of risk requires that IRB members evaluate on an individual basis all types of risk—physical, psychological, social, or economic—posed by participation in research. Inasmuch as the risk posed may vary from subject to subject and is difficult to quantify, it is hard to envision how minimal risk could be better specified. We believe that a more fully specified definition would serve only to complicate unnecessarily the assessment of risk by the IRB.

While most of the concerns Kopelman addresses explicitly re-

late to the definition of minimal risk, she also suggests that some difficulties could be alleviated by the provision of one or more lists of clinical and nonclinical procedures that are minimal risk:

guidance could be improved including by clarifying how to regard the nature and number of certain common procedures such as lumbar punctures or placebo injections. Detailed examples could 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.<sup>9</sup>

While "detailed examples" may have limited use, we would caution against reliance on such examples as "paradigms" for interpreting minimal risk. We believe that it would be a mistake to suppose that prima facie examples "spell out" for IRBs "how to assess harm." A meaningful interpretation of minimal risk, and attendant lists of prima facie minimal risk procedures, requires that the concept be contextualized within a framework for the moral analysis of risk.

Janofsky and Starfield's study of risk classification supports our call for caution. The lack of consensus within one narrowly defined group, expert pediatricians, as to the classification of research procedures highlights the ultimate futility of this approach to specifying minimal risk. The development of such lists depends on the opinion, and thus the value judgments, of experts in a variety of fields. Far from generating "fixed [i.e., absolute, value-free] points" of reference, lists of procedures reflect the values of those polled regarding the procedures. IRBs, therefore, must regard such lists of prima facie minimal risk procedures as a supplement to, rather than a substitute for, their own informed judgment.

Beyond problems associated with depending on such lists as a value-free resource, there are insuperable logistical problems in developing them. Both the original and the recently revised Department of Health and Human Services lists of prima facie minimally risky procedures apply *only* to research involving healthy adults.<sup>10</sup> If IRBs were to use lists as precedents to the extent Kopelman suggests, lists would have to be developed for all subpopulations of vulnerable groups. In the case of children, for instance, lists would have to be developed for children of different age groups. Given the requirement for commensurability, lists would then have to be developed for children of differing ages suffering from different diseases. The logistical challenges posed by the generation of lists of prima facie minimally risky procedures outweigh their usefulness.

The IRB's assessment of minimal risk does not require a quantitative comparison of the risks of everyday life and those of nontherapeutic elements of research. Given the complex nature of risk, and the particular circumstances of research subjects, neither quantitative measures nor lists are equal to the task of encompassing all that must be considered in the assessment of minimal risk. As we argue, the appropriate mode of reasoning is analogical. Acting *in loco parentis*, IRB members make moral judgments in the spirit and manner of the informed and scrupulous parent, considering the comparability of risks of research participation to risks of everyday activities of the subject. The effort to specify which clinical procedures or which everyday activities "count" universally as minimally risky distracts from what ought to be at issue in IRB deliberation on risk—namely, the protection of subjects from exposure to levels of nontherapeutic research risk greater than a minor increase over that which they unthinkingly assume in their everyday lives.

## Minimal Risk and Justice

Kopelman reserves special criticism for the possibility that the inherent flexibility of minimal risk may lead to injustice:

The probability and magnitude of risks [sic] of harm varies in different places. In some locations daily risks are horrific. ... [s]ince everyday risks are not necessarily minimal, a moral judgment must be made about which group ... in what community ... should be used in making comparisons between everyday risks and regarding minimal risks.

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.

As noted, a variable standard introduces problems of fairness in assigning risks.

Leaving the determination of minimal risk to the IRB's judgment, Kopelman argues, creates *regulatory justification* for injustice. Minimal risk seems to allow riskier nontherapeutic procedures to be done on those whose daily lives are already overburdened with hazard.

In the interests of allowing potentially beneficial research to continue, does the threshold err on the side of allowing too much, thereby compromising its correlative protective function? We suggest that such an interpretation is based on a narrow reading of minimal risk. Both as a moral concept and a regulatory threshold, minimal risk does not exist in a vacuum. It functions in conjunction with the fundamental principles of research ethics enunciated by the National Commission<sup>11</sup> and the regulatory protections derived therefrom.

These founding principles and regulation charge IRBs to promote

respect for subjects, protect them from harm, and ensure that the benefits *and* the burdens of research are fairly distributed. The National Commission sought to protect vulnerable populations from exploitation—i.e., uphold the principle of justice—in part through limiting the nontherapeutic risk to which they might be exposed. In their assessment of nontherapeutic risks of research involving children and other vulnerable groups (including non-U.S. citizens who participate in U.S.-funded research), IRBs must continue to ensure that risks are minimized and proportionate to the knowledge to be gained. Doing so does not mean, however, that IRBs must assess nontherapeutic risks faced by these subjects according to the standard of the risks of everyday life of healthy adult, middle class Americans.

To remain consistent with the moral and regulatory framework of which it is part, minimal risk cannot be used to justify the exploitation of vulnerable populations. However, it *does* provide a justification for allowing sick children and other vulnerable groups to be exposed to higher levels of nontherapeutic research risk than other populations. We have argued that this contextual flexibility in the threshold is consistent with the broader scope of parental decisionmaking for children. That is, the risks of nontherapeutic research are to be commensurate with those of the everyday life of the subject. Parents and their ill children are familiar with higher than average levels of risk in everyday life, and are thus in the best position to decide whether to assume comparable risks for the purposes of research that may benefit others in a like position.

In arguing for the specification of a universal standard of minimal risk, Kopelman mistakenly attributes to us the view that there is a need for such a standard in light of our commitment to an intercultural ethic of mutual respect. We do not favor a universal standard for international research. Indeed, we argue instead that an intercultural ethic demands a flexible in-

terpretation of minimal risk that formally recognizes the normativity of risks of daily life in differing communities.

On grounds of justice, researchers from a sponsor country may not engage in research in a host country unless a variety of conditions are fulfilled. The guidelines of the Council of International Organizations of Medical Science, for instance, specify that such research: cannot be "carried out reasonably" in the sponsor country; addresses "the health needs and priorities" of the host country; be undertaken with individuals' informed consent; and be reviewed by a committee whose membership includes representatives of the host country.<sup>12</sup> Over and above the U.S. moral and regulatory frameworks for the protection of human subjects, the CIOMS guidelines forbid exploitative targeting of persons from developing countries for risky research.

We do believe, however, that an intercultural ethic of mutual respect demands our recognition that riskier things can be done to people in countries in which people lead riskier lives by their own researchers. We need to acknowledge the moral validity of lives in other countries and cultures. The view that what is normative in the everyday life of most Americans ought to be normative universally is pure hegemony.

Justice does not require the establishment of an absolute threshold of minimal risk. Indeed, an intercultural ethic of respect for communities requires that we refrain from imposing Western standards of moral conduct. The flexibility of minimal risk is a virtue in this respect, insofar as built into the concept is an acknowledgment that the standards of everyday life in a community should guide the assessment of risks of research in that community

## Conclusion

Further work surely is required to become clearer yet on the meaning and function of the minimal risk threshold in IRB assessment



of domestic and cross-cultural research. Detailed consideration of the question of the normativity of risks of everyday life for the assessment of research risk is also required. We look forward to continued discussion and debate.

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**References**

1. Kopelman L. Moral problems assessing research risk. *IRB* 2000; 22(5):3-6.
2. See Kopelman L. Estimating risk in human research. *Clinical Research* 1981; 29: 1-8, and Kopelman L. When is risk minimal enough for children to be research subjects? In: Kopelman L, Moskop J, eds. *Children and Health Care: Moral and Social Issues*. Dordrecht: Kluwer Academic Press, 1989:xx-xx.
3. Weijer C. Thinking clearly about research risk: implications of the work of Benjamin Freedman. *IRB* 1999; 21: 1-5. See also, Freedman B. Equipoise and the ethics of clinical research. *New England Journal of Medicine* 1987; 317: 141-45; Freedman B, Fuks A, Weijer C. Delineating research and treatment: a systematic approach for the analysis of the ethics of clinical research. *Clinical Research* 1992; 40: 653-60; and 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.
4. See ref. 1, Kopelman 2000:xx.
5. McCartney J. Research on children: National Commission says "yes, if." *Hastings Center Report* 1978; 8(5): 26-31, 28.
6. Levine RJ. Research in emergency situations: the role of deferred consent. *JAMA* 1995; 273: 1300-3, 1301.
7. See ref. 1, Kopelman 2000:xx.
8. See ref. 1, Kopelman 2000:xx.
9. See ref. 1, Kopelman 2000:xx.
10. See revised list now in effect: Department of Health and Human Services. Categories of research that may be reviewed by the institutional review board (IRB) through an expedited review procedure. *Federal Register* 1998; November 9: 60664.
11. U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Conduct of Research Involving Human Subjects*. Washington, D.C.: Department of Health, Education, and Welfare, 1978.
12. Council of International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: CIOMS, 1993; Guideline 8.