In Loco Parentis

Minimal Risk as an Ethical Threshold for Research upon Children

by Benjamin Freedman, Abraham Fuks, and Charles Weijer

To what risks may children participating in research be subjected? Institutional review boards can stand surrogate for parents by filtering out studies whose risk is unacceptably high.

While respect for rights is the hallmark of a liberal society, responsibility toward vulnerable persons unable to care for themselves or even speak on their own behalf is the mark of a humane society. And within the broad field of social ethics, bioethics in particular must focus upon such responsibilities: to the very old and very young, those muted or rendered incoherent by illness. Yet delineating the nature of that responsibility has proven to be among the most vexing problems bioethics has faced.

Agreement in principle upon the touchstone of responsibility toward the incompetent is elusive. Should we act in their best interests, or as they would have directed us to act? More difficult still is the application of such a standard, as when we attempt to describe what is required by the best interests of a particular handicapped newborn. Most difficult, perhaps, is the application of a standard under conditions of risk and uncertainty, when our ethical calculus, ill-grounded as it is, is put to work on shifting and statistically ill-defined values.

The ethics of clinical research in children seems tailor-made for addressing these moral quandaries. Is it ever ethical to expose children to risks associated with research? If it is, what are the ethical limits to such risk? How can a specific threshold to research risk be formulated, justified, and applied? These questions have preoccupied pediatric researchers and others for many years. Recent revisions of United States regulations regarding research with human subjects and the formulation of a "common rule" applying to all federal departments involved with human research make it necessary to examine these questions.[1]

The new definition provided in the "common rule" 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 or psychological examinations or tests."[2] Finding that a research study poses only 'minimal risk' has some important procedural consequences for review. In this paper, though, we will focus upon another role: 'Minimal risk' is the concept used in American regulation to serve as an anchoring measure of allowable risk (or—the other side of the coin—relative safety) in clinical research. The critical threshold of risk that may not be surpassed (short of special federal approval) is in fact one level higher: 'minor increment over minimal risk.' However, since the rule offers no independent definition or specification of 'minor increment,' attention must first be focused upon its anchor, 'minimal risk.'

Similar measures may be found in other national guidelines concerning the ethics of human research as applied to children and other persons without the capacity to consent. Canada's Medical Research Council, for example, sets "the risks of everyday life" as the relevant measure, and the report concerning the ethics of research on children prepared by Great Britain's Institute for Medical Ethics employs the term 'negligible risk,' understood to be similar to 'minimal risk.'[3] Because the United States regulations are both the most familiar and most developed statements of the problem, they will serve as the focus for our discussion; however, our comments may well be applicable to these other national frameworks.

'Minimal risk' seems to raise more questions than it solves. This paper deals with a number of those questions: Do all forms of research upon children require the use of a threshold like 'minimal risk'? What is the meaning, use, and justification of 'minimal risk'? To what criticisms is the concept vulnerable, and what problems arise in its application? We will deal with these questions with the conviction that even if final answers remain elusive, clarification must be attempted. The many thousands of members of research ethics committees internationally that employ

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'minimal risk' or a similar concept must develop some shared understanding of what it means.

The Ubiquity of Research Risk

In any ethical consideration of research, the question of the allowable maximum of research risk must inevitably arise. Every activity poses some risks to its participants, and research is no exception to this rule. Risk, commonly expressed as the magnitude of some harm multiplied by the probability of its occurrence, can never be eliminated, because—to take one common philosophic interpretation of probability—the eradication of risk would require reducing the harms associated with an activity to zero in this world and in all other possible worlds.[4] William Clark has drawn a suggestive analogy between the European witch hunts of the sixteenth and seventeenth centuries and modern-day efforts to guarantee safety.[5] In each case, the accused is required to prove a negative—I am not a witch; I bear no risk—that no finite series of empirical observations can establish. Absolute safety can therefore never be guaranteed to participants in clinical research.

Ethics requires that clinical trials comparing two forms of treatment begin with an honest null hypothesis, a state of clinical equipoise—uncertainty in the expert clinical community concerning the comparative merits and disadvantages of each trial arm.[6] As current United States regulations put it, a trial comparing, for example, standard therapy with a nonvalidated intervention may only be approved if "the risk is justified by the anticipated benefit to the subjects" and "the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches."[7] When this condition is satisfied, some will feel that while one trial arm may involve more *uncertainty* than another, no arm is *riskier* than any other.

However, comparative trials raise their own problems of specific research risk. Once the trial's arms are established to be in clinical equipoise, a second stage of analyzing research risks proceeds. Now those interventions that have no therapeutic warrant, but that are required to answer the trial's scientific question, are separated from the treatment interventions. The risks associated with those interventions required purely for research purposes are tabulated and added separately. Their sum represents the incremental research risk of the study.[8]

Robert Levine, realistically reexamining the usual research interventions, has suggested that most often the concept of minimal risk could be replaced by a clearer threshold:

> It is of value to distinguish risk of physical or psychological injury from various phenomena for which more fitting terms are 'inconvenience,' 'discomfort,' 'embarrassment,' and so on; 'mere inconvenience' is a general term that may be used. . . . Research presenting mere inconvenience is characterized as presenting no greater risk of consequential injury to the subject than that inherent in his or her particular life situation. . . . The vast majority of research proposals present a burden that is more correctly described as mere inconvenience than as risk of physical or psychological harm. In general, prospective subjects are asked to give their time (e.g., to reside in a clinical research center, to be observed in a physiology laboratory, or to complete a questionnaire); often there is a request to draw some blood or to collect urine or feces. Although the withdrawal of venous blood may be momentarily painful and be followed by a bruise, no lasting physical harm is done."[9]

Is 'mere inconvenience' a better choice as a threshold? It more accurately reflects the consequences of participation in the run-of-the-mill protocol. Research subjects experience inconvenience—discomfort, annoyance, nuisance, and boredom—far more commonly than damage. However, 'inconvenience' shares some of the ambiguity of 'minimal risk,' in that both measures refer to the risks of everyday life (to be examined further below). More seriously, 'inconvenience' is a concept dealing with only a single variable: magnitude, the seriousness of resulting harm. As such, it cannot replace the concept of 'minimal risk,' which subsumes two variables: magnitude and likelihood of harm. For what if there is a potential for danger of much greater magnitude but minuscule likelihood? The language of 'inconvenience' makes it impossible for us to consider this prospect, which the ethics and law of clinical research must encompass.

Weiss v. Solomon et al., the first North American case to find that a research ethics committee had negligently approved a protocol, furnishes one example. In that case, the court found that the subject of a trial had died as a consequence of an anaphylactic reaction to fluorescein angiography, an investigation done purely for research purposes.[10] There had been no reports of fluorescein causing death by anaphylaxis at the time of Mr. Weiss's death; only a few such reports have emerged since.[11] In the overwhelming majority of cases, that is, the pure research intervention of fluorescein angiography poses no more than inconvenience—but not always. The same may be said of other common demarcated research interventions. Spending two days on a clinical research unit is no more than inconvenient—*unless* it results in a nosocomial infection like methicillin-resistant *Staph. aureus*. An antecubital venipuncture is 'merely inconvenient'—*unless* it results in an uncommon complication like cellulitis or venous thrombosis.[12] The more compendious concept of risk is needed to cover any magnitude of damage (ranging from nuisance to real damage), and any likelihood of any given magnitude.

The doctrine of informed consent to research constitutes one major response to the ethical challenge of research risks. Competent subjects with the capacity of understanding research risks and benefits, by consenting to serve as research subjects, voluntarily assume these risks. As the legal maxim states, *Volenti non fit injuria* (One who has agreed to an activity is not wronged by it). Conceivably, the same justification applies to research upon persons who have while competent executed a valid advance

directive permitting specified forms of research to be performed upon them when their competency should lapse. This stratagem, the research analogue to treatment's 'living will,' may in the future serve an important role in research upon Alzheimer's dementia.[13]

But no such solution is available on behalf of incompetent subjects who were never competent—most importantly, infants and small children but also those suffering from congenital intellectual handicaps. Unless safety is understood in a relative sense, permitting some small risk that falls below a specified threshold, these incompetent persons could never be permitted to participate in clinical research—a situation that would in the long run leave them 'therapeutic orphans,' and for that reason at even greater risk.

The Meaning and Use of 'Minimal Risk'

What does 'minimal risk' mean in the medical literature? How is it understood by clinical investigators? How is it defined within the regulations, and what role does it play in ethically evaluating research upon children? As we will see, a purely definitional approach, without reference to the ethical purpose underlying the threshold, is incapable of capturing anything significant by the term.

Which procedures are said in the medical literature to impose no more than minimal risk? Such highly invasive maneuvers as splenectomy, transthoracic enucleation of esophageal leiomyomas, and pancreatic biopsies are all described as "of minimal risk."[14] This characterization, on the surface so surprising, is nonetheless justifiable given the necessity for the procedure in the patient populations in question and the risks associated with alternative interventions. Clearly, the term cannot be defined without specifying a context: minimal risk to what end, from whose point of view, and under which situations? On a semantic level, 'minimal risk' is relational, context-dependent. To understand its meaning in the research context, we must examine that specific usage.

Even if we restrict the context to research interventions upon children, though, and even if we restrict our inquiry to investigators, significant disagreement remains. Janofsky and Starfield surveyed chairpersons of pediatric departments and directors of pediatric clinical research units in the United States to elicit their understanding of 'minimal risk,' 'minor increment over minimal risk,' and 'more than minor increment over minimal risk.'[15] (Recall that 'minor increment over minimal risk' is the critical threshold, determining whether a study could be approved by a local committee or would require approval by a special federal panel.) Respondents were asked to classify common research procedures as administered to pediatric subjects of different ages.

The results demonstrated serious disagreements among respondents: 14 percent thought tympanocentesis (puncturing of the ear drum) posed minimal risk or less, 46 percent classified this as a minor increment over minimal risk, and 40 percent thought it more than a minor increase. Expressed in practical terms, 40 percent thought research requiring tympanocentesis was impermissible, despite the importance of the research, without the approval of a federally authorized panel of ethics experts in addition to the approval of the parents. (With regard to a population of research subjects aged one to four years, respondents came close to the three-way mathematical maximum of dissension: 34% thought it minimally risky, 31% a minor increment, 35% more than a minor increment.) While these are extreme examples, substantial scatter across the categories was the rule rather than the exception throughout the study.

It does not seem, therefore, that 'minimal risk' or the other thresholds it anchors may be clarified by examination of sense or signification within the medical literature, nor by usage of the community of clinical investigators. There appears to be no natural or uniform understanding of 'minimal risk' upon which we can draw. If that is the case, we are left with only the definition of 'minimal risk' provided in the regulations: the risk of daily life or that encountered in routine physical or psychological examinations. Although other interpretations are possible,[16] this definition seems to set the risks of daily life as the baseline and the risks of routine examinations as an example of the risks of everyday life most similar to the kinds of interventions found in research studies—routine immunizations, developmental testing, and the obtaining of urine and blood specimens.[17] An intervention's satisfaction of the minimal risk standard can therefore be demonstrated in one of two ways: directly, by showing that it falls within the definition; or indirectly, by showing that it is relevantly similar to other interventions known to fall within the definition.

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But how is the definition itself to be interpreted? What is meant by 'the risks of everyday life'? As Kopelman notes, the risks of everyday life may be understood in several different ways; for example, it may refer to all the risks any person might encounter or to those that all of us encounter. She rightly rejects the first possibility. The fact that some people commonly face very high risks (parachuting, firefighting) could not justify allowing a similar level of risk in research upon children. The second charac-

terization is much more restrictive, constituting a lowest common denominator of risk. Kopelman criticizes this interpretation of the risks of everyday life as follows:

> This interpretation assumes that we know the kinds of risks we all encounter and their probability and magnitude. Neither is obvious. Most of us drive cars, walk across busy streets, and fly in airplanes. Are these the everyday risks the definition refers to? How do we determine what risks are encountered routinely by all of us and estimate the probability and magnitude of these risks?[18]

In the passage two distinct claims are made, one concerning the difficulty in *identifying* the risks of everyday life, the other, the difficulty in *quantifying* them. The first difficulty, though, is clearly exaggerated. While there will always be exceptions, within any given society daily life will present the bulk of its citizens with ordinary hazards at home, at work, at play, and in transit, crossing the street or taking a bath. It is not hard to identify this set of common social risks. We are, by definition, each acquainted with them; and, almost by definition, if we are unsure whether they belong within the set of common risks then they don't.

On quantification Kopelman seems on firmer ground. While we all ride in cars, few of us know the likelihood of our being in a fatal accident. And it is certainly true that IRBs or other research ethics bodies typically consider whether a given proposal is acceptable without recourse to actuarial charts of the risks of daily living.

Indeed, Kopelman could have posed a far more fundamental challenge to the concept. As noted above, the critical threshold for allowable research risk in children is not 'minimal risk' itself, but rather, 'a minor increase over minimal risk.' What meaning attaches to the qualification 'minor increase' that is not defined, specified, or characterized in any way within the regulations? If, as Kopelman believes, these thresholds are quantitative measures, verbal surrogates for numbers expressing the probability and magnitude of potential harms of everyday life, the question is unanswerable. This strongly suggests that an alternative, nonquantitative understanding of 'minimal risk' is intended. To understand that, we need to turn to the basic principles that underlie committee research review.

The Purpose of 'Minimal Risk'

A number of parties must concur in the judgment that a clinical study is ethically appropriate before that study will proceed. The first and probably most important decision-maker is the investigator, who must consider before developing a protocol whether the task may be ethically achieved, how risks may be minimized, how the study's goals and risks may be explained, and so forth. If the study is done upon competent persons, their consent represents another ethical decision node. If the subjects are young children the agreement of parents is required, as well as the assent of the child herself to the extent that she is capable of giving it.

What role does a research ethics committee play? The institution within which research proceeds, both in itself and as society's agent, has its own obligation to treat subjects in a trustworthy capacity. Research review by the ethics committee is a concrete expression of this institutional fiduciary responsibility. In addition, as investigators are sometimes overly enthusiastic or bold, committee review of the ethics of research serves in part as a fail-safe mechanism to curb inappropriate zeal. For example, in assessing any protocol, the IRB must determine that its risk-to-knowledge ratio is reasonable and that the scientific importance of the undertaking is proportional to the risks subjects will be undergoing. These issues should have been considered by the investigators; and usually they do that. Nonetheless, the research committee is charged not to take that for granted, to serve as a backup in case the investigator has not competently discharged his or her personal and professional obligation. Again, it is the inalienable obligation of the investigators properly to inform subjects prior to their participation in a trial. The IRB, in reviewing the study's consent form, serves as a fail-safe mechanism to ensure that the investigator's plan for informing subjects will satisfy ethical norms and the institution's own moral obligation to protect subjects.

The IRB plays the same backup role vis-à-vis parental (or guardian) approval of participation of a child (or other incompetent person) in research. Parents may be ignorant, apathetic, or merely inattentive. Cognizant of these and other possibilities, and of its own moral obligation to protect incompetent research subjects, the institution charges a review committee to act as surrogate for the scrupulous parent by filtering out those studies that would impose an unacceptable level of risk upon child participants. It is in this light that the threshold concept, 'minor increase over minimal risk,' needs to be understood. In applying this standard, the IRB is attempting to track those decisions that would be made by informed and scrupulous parents whose children are being invited to participate in research. This fail-safe measure does not ensure that parents will scrupulously evaluate studies; rather, it ensures that they will only have the opportunity to enroll a child in a study that could have passed such an evaluation.

Asking a parent to agree to the child's participation in research is asking for a decision for participation in a new situation, with new attendant risks. These decisions are not arrived at quantitatively, by calculating risks, but rather on a *categorical* basis. Consider another such choice. A child has been asked out to an overnight camping trip for the first time. The risks of the trip are not the risks of everyday life—it is a new experience. If the threshold of allowable risk never permitted anything other than the risks of everyday life, no new experiences could ever be enjoyed (something which itself in the not-very-long run would not be in the child's best interests). Rather, a mother asks herself, "Is the child ready for this? Should the child approach this by stages? *Are the risks sufficiently similar to those in my child's everyday life that I should allow this experience at this time?*" In discussions about whether to permit this involvement—with the mother resisting, and the child pressing—a certain logic may

be discerned. Appealing to consistency, the child will say that he has been permitted, and successfully undergone, situations relevantly and roughly similar, though not identical—while the parent will focus upon difference.

In other words, the parental decision to permit exposure to new risks is not itself governed by, but rather anchored to, the risks of everyday life. And this point is of course exactly mirrored in our understanding of the regulations, in which the upper threshold of research risk is not governed by, but anchored to, the concept of minimal risk. Almost by definition, exciting and important research ventures into the unknown. A prohibition on such research involvement would be to the long-term detriment of this child and other children, just as a prohibition on new experiences is harmful to children over the long term. Therefore, the limit is set as a 'minor increase over minimal risk.' This limit is not quantitative, but represents a categorical judgment that focuses upon the comparison of new experiences to those of everyday life. It is this form of discussion that needs to take place in research ethics committees considering the approval of research involving children.

Justifying and Applying the Threshold

Because children and their situations differ, a judgment anchored to the risks of everyday life, whether arrived at by parent or IRB, must be made relative to the child's actual situation. A diabetic child's everyday life includes pinprick blood tests, and additional such tests required by a study protocol represent much less of a variation in that child's daily life than in the life of a healthy child. This relativistic understanding of minimal risk, held by the National Commission for the Protection of Human Subjects (with the exception of Commissioner Turtle), is in fact the current interpretation of the regulations.

We should also point out that by choosing the risks of everyday life as an anchor to an acceptable level of research risk, less net added risk is imposed upon the child than might be thought. The risks of research are to a degree substitutive, rather than additive: research risks are undergone, but the risks of alternative activities are forgone. Normal, healthy subjects of research would otherwise be pursuing their normally risky daily lives; and ill subjects who are not enrolled in research studies may nonetheless receive treatments and diagnostic tests under the rubric of therapy that are similar to those they would have experienced in research. Furthermore, although in principle any given level of risk associated with an activity can be reduced, there is substantial empirical evidence that past a certain point individuals cease efforts at risk reduction, and the efforts of third parties to reduce risk yield severely diminishing returns. When cars have more safety features built in, for example, people seem to feel free to drive in a riskier fashion. Insurance companies have long since identified the problem under the phrase "moral hazard": property owners who are insured against damage or theft take fewer pains to avoid these contingencies.[19] People do differ in their propensity to trade off safety for other goods, but by specifying a threshold at or near the risks of everyday life we approximate a lowest common denominator of risk, the level at which most reasonable people feel 'safe enough' so that their choices can be made without considering the small risk repercussions.

The concept, 'risks of everyday life,' has normative as well as descriptive force, reflecting a level of risk that is not simply accepted but is deemed socially acceptable. Without defining the scope of parental authority and discretion within the law, therefore, we may be reasonably certain that the risks of everyday life fall within those bounds. There is, however, no precise legal analogue to this level. Questions of child abuse deal with risks and harms far above this threshold; so does the question of parental refusal of medical treatment for a child on religious grounds. In some ways, the closest analogy arises in disputes over child custody, which consider and weigh the risks of a child's transferring to a new school, being exposed to (or shielded from) church teachings, and so on.[20] But these cases, inevitably, are resolved on the relative basis of which parent is the better custodian rather than on the basis of whether parentally imposed risks fall beneath a threshold of acceptability.

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One last aspect of the 'risks of everyday life' should be discussed: its flexibility, in conformity to time and circumstance. Kopelman sees this as a serious drawback: "the risks to children living in Belfast and Edinburgh are different; but we would not want to have this automatically influence what sort of research we think would be 'not too risky' for them."[21] In our understanding developed above, the example is inapt—parental concern in Belfast may not be less than in Edinburgh—but the point that standards diverge across cultures is true.

However, this flexibility of the threshold is to our minds an advantage. Any society's notion of what demands on children are allowable changes over time. The routine labor expectations of children fifty years ago are considered exploitative now, and those made one hundred years ago would now be actionable child abuse. The same is true of exposure to risk. Given the huge historical and geographical differences among cultures as to the degree to which chil-

dren should be protected from risk or engaged in life's risky activities, only the most parochial would maintain that the currently prevailing view in Western Europe and North America is necessarily the one right approach. The ethical evaluation of research can and must insist upon the rigorous protection of subjects, but cannot in so doing lose all reference to common social norms. An ethics of research must be sufficiently flexible as to incorporate and accommodate cultural variance, as is done when 'the risks of everyday life' is used as a categorical anchor for research risk.

Intercultural variance does, however, raise a very distasteful possibility. A Western researcher, frustrated by restrictions upon his or her own research, might go shopping for a community whose children are sufficiently destitute and underprotected that even exposure to heinous risk falls within the expected daily routine. Exploiting their miserable conditions of life, this researcher would claim simply to be accommodating cultural differences.

This stratagem would be precluded by recognizing that research in these circumstances is governed not by cultural but by intercultural ethics. It follows from what we have said that because cultures differ in the degree of protection to which their children are entitled, a research project might be ethical in culture A and unethical in culture B. But when a researcher from culture B contemplates doing research upon children from culture A, the question is, Whose values should be controlling? Some students of intercultural research ethics have adopted a "both-and" approach: in cross-cultural research the norms of both groups A *and* B must be respected.[22] Such a requirement would eliminate, on ethical grounds, the prospect of a researcher's shopping for a useful risk pool.

The final question remaining is that of applying the standard. When is the aggregated risk of research interventions an increase above a minor increment over minimal risk? The status of many of the most common research interventions, for example, blood sampling, dietary restrictions, and other measures listed by the National Commission is easily settled: they are associated with routine physical examinations and so are of minimal risk. Some other interventions not on that list because not associated with the risks of everyday life of healthy persons are minor interventions common to the lives of all ill children within the relevant class. In accepting the principle of commensurate risks, it follows that the form, and perhaps also the sum, of research risk for ill children may exceed that imposed upon their healthy counterparts. The question, Is this research risk sufficiently similar to their daily experience? could not receive the same answer in two groups whose daily experience of risk is so different as the healthy and the ill. On the other hand, some interventions—for example, liver biopsies—are so risky and unfamiliar that no colorable case could be made on their behalf.[23]

What are the hard cases the threshold needs to address? One kind of problem is posed by the reiteration of minimally risky procedures for research purposes. One or two venipunctures are minimally risky; four, arguably so, but still not more than a minor increase over minimal risk. But what of five, ten, forty, or any number in between? Similarly, when testing a new treatment for meningitis it is acceptable to perform one lumbar puncture on a sick child to satisfy the protocol's scientific needs, but not five. Where is the break point? Another set of problems is posed by those procedures (arterial punctures performed upon healthy children, for example) that are qualitatively different from common procedures, although of low risk.

It is not to be expected that the threshold definition of minimal risk as the risk of everyday life will settle each of these questions in an unambiguous and nonarbitrary fashion. Neither this nor any other threshold definition is self-interpreting; each will require the exercise of judgment. But we can require that the threshold define the terms of the argument, the kinds of questions that will need to be posed in the committee's deliberations. This the threshold can do. The arguments will parallel those familiar to any parent considering allowing a child to undergo a new experience. The committee, 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 the risks this child or others like him runs on a routine basis. The debate takes place within a context recognizing that the committee owes a fiduciary duty to these subjects, and that this duty entails imposing upon a child no risks substantially above a socially defined minimum for any scientific end, however worthy.

If the above analysis is sound, it may shed light upon our broader responsibilities to children and other incompetent persons as well. All cases of medical intervention occur under conditions of relative uncertainty; because of patient variability, treatment is always an experiment in nature. And so, in clinical treatment as well as research, those concerned with the care of the patient—doctors, nurses, members of the institution's ethics committee, among others—may acknowledge their fiduciary responsibility to act *in loco parentis*. In doing so, we suggest, the same kinds of considerations we have raised for clinical research reappear. Risk is always present and seems more appropriately dealt with in categorical rather than quantitative fashion; the allowable limits of risk will always, ineluctably, rely upon a social consensus that varies over time and geographical setting. This consensus itself, fuzzy at the edges, is better at identifying those numerous and varied acts contrary to a person's best interests than at defining the one course of action dictated by them.

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20. Compare *Chauvin v. Chauvin*, 6 Reports of Family Law (3d) 403, [1987] (per Killeen, D.C.J., Ontario; withdrawal from French immersion school contrary to child's best interests); *Young v. Young*, 16 RFL (3d) 302, [1988] (per Scarth L.J.S.C., British Columbia; father's involving children in Jehovah's Witness activities at current level contrary to children's best interests); *Schulz v. Schulz*, 12 RFL: (3rd) 141, [1987] (per Prowse L.J.S.C., British Columbia; mother's involving children in fundamentalist church and enrolling them in church school in midyear contrary to their interest, custody should be granted to father); *Saunders v. Saunders*, 20 RFL (3d) 368, [1989] (per Wetmore Co. Ct. J., British Columbia; exposure of child to father's open homosexual relationship not in his interest, access of father should be modified).

21. Loretta Kopelman, "When Is the Risk Minimal Enough for Children to Be Research Subjects?" in *Children and Health Care: Moral and Social Issues*, ed. Loretta Kopelman and John Moskop (Dordrecht: Kluwer, 1989), p. 91.

22. Medical Research Council of Canada, *Guidelines on Research Involving Human Subjects*, p. 28; compare the international consensus statement printed in Medical Research Council of Canada, *Towards an International Ethic for Research with Human Beings*, Proceedings of the International Summit Conference on Bioethics, 5-10 April 1987 (Ottawa: Minister of Supply and Services, 1988), p. 64. Compare further Robert J. Levine, "Informed Consent: Some Challenges to the Universal Validity of the Western Model," *Law, Medicine & Health Care* 19 (1991): 207-13.

23. Levine, *Ethics and Regulation of Clinical Research*, p. 247.