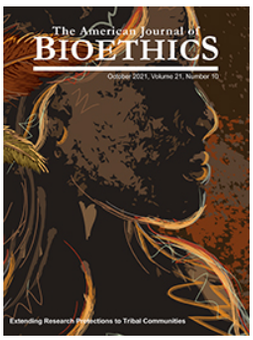

The American Journal of Bioethics

ISSN: 1526-5161 (Print) 1536-0075 (Online) Journal homepage: https://www.tandfonline.com/loi/uajb20

Determining Risk in Pediatric Research with No Prospect of Direct Benefit: Time for a National Consensus on the Interpretation of Federal Regulations

Celia B. Fisher , Susan Z. Kornetsky & Ernest D. Prentice

To cite this article: Celia B. Fisher , Susan Z. Kornetsky & Ernest D. Prentice (2007) Determining Risk in Pediatric Research with No Prospect of Direct Benefit: Time for a National Consensus on the Interpretation of Federal Regulations, The American Journal of Bioethics, 7:3, 5-10, DOI: 10.1080/15265160601171572

To link to this article: https://doi.org/10.1080/15265160601171572

Published online: 08 Mar 2007.

The American Journal of Bioethics, 7(3): 5–10, 2007

ISSN: 1526-5161 print / 1536-0075 online
DOI: 10.1080/15265160601171572

Target Article

Determining Risk in Pediatric Research with No Prospect of Direct Benefit: Time for a National Consensus on the Interpretation of Federal Regulations

Celia B. Fisher, Fordham University
Susan Z. Kornetsky, Children's Hospital, Boston
Ernest D. Prentice, University of Nebraska Medical Center

United States federal regulations for pediatric research with no prospect of direct benefit restrict institutional review board (IRB) approval to procedures presenting: 1) no more than "minimal risk" (§45CFR46.404); or 2) no more than a "minor increase over minimal risk" if the research is commensurate with the subjects' previous or expected experiences and intended to gain vitally important information about the child's disorder or condition (§45CFR46.406) (DHHS 2001). During the 25 years since their adoption, these regulations have helped IRBs balance subject protections with the pursuit of scientific knowledge to advance children's welfare. At the same time, inconsistency in IRB application of these regulations to pediatric protocols has been widespread, in part because of the ambiguity of the regulatory language. During the past decade, three federally-charged committees have addressed these ambiguities: 1) the National Human Research Protections Advisory Committee (NHRPAC) (Washington, DC), 2) the Institute of Medicine (IOM) Committee on the Ethical Conduct of Clinical Research Involving Children (Washington, DC); and 3) the United States Department of Health and Human Services Secretary's Advisory Committee for Human Research Protections (SACHRP) (Washington, DC). The committees have reached similar conclusions on interpretation of language within regulations §§45CFR46.404 and 406; these conclusions are remarkably consistent with recent international recommendations and those of the original National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1977) report from which current regulations are based. Drawing on the committees' public reports, this article identifies the ethical issues posed by ambiguities in regulatory language, summarizes the committees' deliberations, and calls for a national consensus on recommended criteria.

The history of federal regulations for pediatric research with no prospect of direct benefit has been driven by ethical tension between the responsibility to protect child subjects from research harms and the obligation to ensure that medical and behavioral science adequately address health and social issues unique to children as a class. Grounded in the moral justification and language of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research Report and Recommendations for Research Involving Children (1977), current regulations restrict institutional review board (IRB) approval for non-therapeutic pediatric research to procedures presenting: 1) no more than "minimal risk" (§45CFR46.404); or 2) no more than a "minor increase over minimal risk" if the research is commensurate with the subjects' previous or expected experiences and intended to gain vitally important information about the child's disorder or condition (§45CFR46.406) (Department of Health and Human Services 2001; National Commission 1977). In 2001, the United States Food and Drug Administration (FDA) included these provisions in its interim rule to provide additional safeguards for children (Department of Health and Human Services, Food and Drug Administration 2001). Over the past 25 years, regulations §§46.404 and 406 have helped IRBs ethically balance research protections and knowledge generation important to children's welfare. At the same time, there has been widespread inconsistency among different IRBs in applying regulations to pediatric protocols, in part because of the ambiguity of

Received 16 April 2006; Accepted 9 August 2006.
Address correspondence to Celia B. Fisher, PhD, Director Center for Ethics Education and Marie Ward Doty Professor of Psychology, Fordham University, 441 East Fordham Road, Dealy Hall, Bronx, NY 10458. E-mail: Fisher@Fordham.edu
Dr. Fisher and Ms. Kornetsky were members of the United States Department of Health and Human Services Secretary's Advisory Committee for Human Research Protections (SACHRP) and the Institute of Medicine Committee on Clinical Research Involving Children and co-chairs of the SACHRP Subcommittee on Research Involving Children. Ms. Kornetsky was a member of National Human Research Protections Advisory Committee. Dr. Prentice is Chair of SACHRP.
Disclaimer: The opinions expressed in this paper are solely those of the authors and do not represent the opinions of any committees on which the authors served.
Acknowledgements: We gratefully acknowledge the wisdom of members of the National Commission, NHRPAC, the Institute of Medicine Committee on Clinical Research Involving Children, SACHRP, and the SACHRP Subcommittee on Research Involving Children, from whom we have learned a great deal.

regulatory language (Janofsky and Starfield 1981; Shah et al. 2004). In the absence of a national consensus, IRB inconsistencies can result in perceived or actual inequities in subject protections for children across different regions of the country, underprotection of child participants with disorders or conditions, or exclusion of children from research that may yield knowledge that can help improve child health or alleviate childhood disorders.

During the past decade three federally-charged committees have addressed these ambiguities: the National Human Research Protections Advisory Committee (NHRPAC) (Washington, DC); the Institute of Medicine (IOM) Committee on the Ethical Conduct of Clinical Research Involving Children (Washington, DC); and the United States Department of Health and Human Services Secretary's Advisory Committee for Human Research Protections (SACHRP) (Washington, DC) (IOM 2004; NHRPAC 2001; SACHRP 2005). The committees have reached similar conclusions on interpretation of regulatory language within regulations §§45CFR46.404 and 406; these conclusions are remarkably consistent with those of the National Commission. Drawing on the committees' public reports, this article identifies the ethical issues posed by ambiguities in regulatory language, summarizes the committees' deliberations, and calls for a national consensus on recommended criteria.

§ 46.404 RESEARCH NOT INVOLVING GREATER THAN MINIMAL RISK

Regulation §46.404 permits IRB approval of pediatric research with no prospect of direct benefit if it does not involve greater than minimal risk and if the IRB finds adequate provisions are made for soliciting guardian permission and child assent. The "minimal risk" definition is thus a key concept for determining approval under §46.404 (Freedman, Fuks and Weijer 1993). However, no child-specific definition of minimal risk appears in federal regulations. Rather, IRBs must apply the general definition of minimal risk provided in subpart A of the regulations: "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" (§46.102(i)).

A Uniform Versus Relative Standard of Minimal Risk

Federal committees and IRBs have struggled over whether "minimal risk" when applied under regulation §46.404 should be measured against a *uniform* standard (the risks to which healthy children are typically exposed) or a *relative* standard (the type of risk to which the specific class of research subjects are typically exposed) (Kopelman 2004). The National Commission concluded that a uniform standard was preferable for pediatric research, recommending that minimal risk be indexed to the experiences of "healthy children" (National Commission 1977). Nonetheless, in response to public comment, the Preamble to the Final Rule articulated a relative standard describing minimal risk as "those risks encountered in the daily lives of the subjects of the research." Unfortunately, the final regulatory definition included neither the "healthy person" nor the "subjects of the research" language, resulting in the ongoing confusion about the regulation's intent.

NRPHAC, the IOM Committee, and SACHRP each concluded there were compelling reasons to adopt the National Commission's original uniform standard for research involving children. First, a relative standard for minimal risk in studies with no prospect of direct benefit unjustly permits children to be exposed to higher levels of risk simply because their daily lives are filled with greater risk than healthy children or those living in safe environments. Moreover, the relative risk argument that children with health problems or those living in high-risk environments will become research orphans under a uniform standard is simply incorrect (Freedman, Fuks and Weijer 1993; Wendler 2004). These children can participate in higher risk studies that: 1) offer the possibility of direct benefit §46.405; 2) are likely to yield generalizable knowledge about the child's disorder or condition §46.406; or 3) provide opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children §46.407 (Fisher and Kornetsky 2005). Finally, unlike adults, children need added protections under a minimal risk standard because typically they cannot provide fully informed consent.

Generally, over the past 25 years, national committees charged with evaluating federal protections for pediatric research have agreed that the definition of "minimal risk" in 45 CFR 46.102(i) when applied to research involving children should be interpreted as those risks encountered by normal healthy children living in safe environments in daily life or during the performance of routine physical or psychological examinations or tests (IOM 2004; National Commission 1977; NHRPAC 2001; SACHRP 2005). The committees have also concluded that a uniform minimal risk standard must be age-indexed to reflect the different daily and medical experiences of infants, children, and adolescents. Finally, each committee made clear that a uniform standard does not prevent IRBs from determining that in some cases, risks to which healthy children are routinely exposed (e.g., routine immunization or blood drawing procedures) may pose the likelihood of harms greater than minimal risk for less healthy children (e.g., children with hemophilia).

Risk Equivalence

Interpretation of specific procedures that meet the minimal risk criteria has also generated inconsistency in IRB review. A limited number of examples were provided by the National Commission and are included in the expedited review categories under regulation 45CFR46.110. However, some have argued that these efforts have inadvertently limited minimal risk approval because IRBs are reluctant to go beyond the specific examples. To broaden the range of exemplars, the IOM Committee and SACHRP identified the "well-child" pediatric visit and the pediatric mental health interview as reasonable benchmarks for determining

routine medical and psychological examinations or tests. However, many research procedures that can meet minimal risk criteria are not identical to those encountered in children's daily life, or routine medical or psychological examinations or tests. The national committees were unanimous in concluding that IRBs should be able to approve such procedures as minimal risk under regulation §46.404, if it can be determined the associated risks are equivalent to the types of experiences and risks encountered in the daily lives and routine examinations of similarly aged healthy children living in safe environments. Among the criteria identified for determining risk equivalence are: 1) the duration and frequency of the procedure; 2) the cumulative risk posed by a set of procedures that might individually be equivalent but cumulatively be greater in probability or magnitude of risk than those in daily life, or routine physical or psychological examinations; and 3) the degree to which any harms, if they do occur, are transient and reversible (IOM 2004; SACHRP 2005).

Risks of Daily Life

Identifying risks of daily life presents additional challenges. First, there have been few attempts to apply national statistics or conduct empirical studies to identify the magnitude and probability of risk in children's lives (Amler et al. 2003; Ernst 1999; Wendler et al. 2005). Second, even if IRBs could obtain statistics on the probability and magnitude of risk in the daily lives of children, the justification for applying an actuarial standard to the decision is based on the erroneous assumption that the risk–benefit balance for research and socially-allowable child experiences are morally equivalent. Some risks in the daily lives of healthy children living in safe environments (e.g., vehicular mortality, serious athletic injuries) are socially permissible because society judges these activities as important opportunities for children's growth and development. Society may not view these same risks (e.g., mortality, serious physical injury) as minimal when introduced solely for the purpose of producing generalizable knowledge that offers neither the probability of direct benefits to the individual child nor the promise of future benefits for children who share a disorder or condition with research participants (Marshall 2000).

Given the lack of empirical information on everyday risks and differences underlying normative judgments of socially-allowable risks for children, the moral justification for the daily life threshold may be weaker than the threshold associated with routine physical and psychological examinations (Kopelman 2004). In attempting to navigate the difficult risk assessment issues posed by the daily life standard, we concur with the Council for International Organizations of Medical Sciences (CIOMS) (Geneva, Switzerland) that IRBs should use the probability and magnitude of harm or discomfort posed by age-indexed routine medical or psychological examinations or tests as an upper limit of acceptable risk for daily-life-based minimal risk determinations (Council for International Organizations of Medical Sciences 2002).

§ 46.406 RESEARCH INVOLVING GREATER THAN MINIMAL RISK AND NO PROSPECT OF DIRECT BENEFIT TO INDIVIDUAL SUBJECTS

The National Commission (1977) concluded it was morally defensible to expose children to greater than minimal risk in research offering no prospect of direct benefit when knowledge gained is important to the future welfare of children with specific disorders or conditions and additional protections are established. Adopted as regulation §45CFR46.406, regulatory criteria for independent IRB approval of greater than minimal risk research involving children which offers no prospect of direct subject benefit include: 1) the increment in risk can be no more than a minor increase over minimal risk; 2) the experimental procedures are reasonably commensurate with those inherent in subjects' actual or expected medical, dental, psychological, social, or educational situations and are likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for its understanding or amelioration; and 3) assent and guardian permission procedures are adequate.

What is a "Minor" Increase Over Minimal Risk?

Quantifying a "minor" increase over minimal risk is difficult. First, across different types of risk there is no universal metric for judging "minor" increases in terms of either probability or magnitude of harm or discomfort. Second, the magnitude and probability of harm and discomfort posed by a specific research procedure is multiply determined by characteristics of the population (e.g., age, disorder or condition) and the competence of individuals performing the procedure. Because increases in harm or discomfort are both subjective and nonlinear, the National Commission may have arrived at the most practical solution when it left the determination of "minor" increase over minimal risk to the IRB (see Preamble to the Final Rule; DHHS 2001). At the same time, the Commission recommended IRB determinations include a common-sense estimation of the risk, relevant empirical information, and consideration of the investigator's experience and the subjects' situation. In keeping with the National Commission's recommendation, public deliberations by the more recent federally charged committees suggest that IRBs should require investigators to provide sufficient evidence that: 1) experimentally-induced pain, discomfort or stress must not be experienced as severe; 2) any potential harms will be transient and reversible (restricted to time or procedure or a short post-experimental period); 3) investigators are appropriately qualified to perform the procedures; and 4) the setting for procedures is appropriate.

Applying the "Commensurate" Criteria

Under regulation §46.406b, research presenting only a minor increase over minimal risk can only be approved if "the research intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental,

psychological, social, or educational situations." There has been considerable disagreement among IRBs over whether the term *commensurate* should be applied to determine acceptable level of risk or to ensure that parents/guardians and children will have an experiential reference for making an informed participation decision. The members of the National Commission made their intent clear: "The requirement of commensurability of experience should assist children who can assent to make a knowledgeable decision about their participation in research, based on some familiarity with the intervention or procedure and its effects" (National Commission 1977, 9). Each of the three recent federally-charged committees have concurred that IRBs should use the commensurate standard to help fortify parent/guardian permission and child assent protections and not to gauge the acceptable level of risk. In practical terms, the experimental procedures found to meet the "commensurate" criteria need only be reasonably similar, not identical, to subjects' actual or expected experiences, so that children and parents have a referent against which to evaluate the explanation of research risks provided during informed consent (IOM 2004; NHRPAC 2001; SACHRP 2005).

Defining "Condition"

The National Commission's majority statement argued that "foreseeable benefit to an identifiable class of children may justify a minor increment of risk to research subjects" (National Commission 1977, 125). As articulated in regulation §46.406c, the identifiable class of children must have a "disorder" or "condition" about which the research has the potential to yield generalizable knowledge of vital importance. IRBs are able to consistently determine whether subjects have a "disorder" through established physical and mental health diagnostic criteria. However, determining whether subjects have a "condition" is more difficult. The National Commission was clear that they intended the term *condition* to permit greater than minimal risk research participation of children who did not have a disease state, but for whom research without the prospect of direct benefit was necessary to develop methods of diagnosis, treatment and prevention of conditions that jeopardize the health of children, interfere with optimal development, or adversely affect well-being in later years.

All three recent national committees agreed with the National Commission's intent, but also noted that a definition of the term *condition* that is too broad (e.g., poverty, race or age) could be misused to justify exposing any group of children to higher levels of research risk. Each committee crafted language to help ensure equitable and nonexploitative application of the term. In general, the committees proposed that approval of a class of children as having a "condition" under regulation §46.406c should be based on a body of evidence indicating that the condition negatively affects children's health and well-being or increases their risk of developing a health problem in the future. Can research involving a cohort of healthy children be approved under regulation §46.406c? Based on these criteria, in some research contexts a protocol presenting a minor increase over minimal risk involving a cohort of healthy children could be approved. For example, healthy children might be judged to have a condition for a study on the immunogenicity of a potential vaccine for a common childhood disease (i.e., staphylococcus infection) or for a serious disease endemic to their living conditions (i.e., children living in areas where rates of childhood malaria are high). In contrast, healthy siblings of children with autism would not have a condition under regulation §46.406c if the protocol were aimed at including the healthy siblings simply as a comparison group to study the biochemistry of the siblings' illness.

Evaluating "Vital Importance"

IRB approval under regulation §46.406c must not only establish that a protocol holds the potential to yield generalizable knowledge about the child's disorder or condition, but that this knowledge is of vital importance for the understanding or amelioration of the subjects' disorder or condition. As with criteria for judging a "minor increase" there is no universal metric for determining whether knowledge is "vital" for the health and well-being of a particular population. The National Commission stated that "the research must hold out the promise of significant benefit in the future to children suffering from or at risk for the disorder or condition (including, possibly, the subjects themselves)" (National Commission 1977, 9). To help guard against spurious claims about the potential benefit of knowledge generated by a protocol presenting a minor increase over minimal risk, the more recent federally charged committees recommended IRBs require investigators to provide empirical evidence that the research design and scientific question addressed is likely to yield generalizable knowledge that would contribute to understanding the etiology, prevention, diagnosis, pathophysiology, amelioration, or treatment of the subjects' condition or disorder. In a practical sense, this means that the literature review and empirical rationale for studies that will expose children to greater than minimal risk must be sufficient to convince an IRB that knowledge derived from the study has a high probability of contributing to an understanding of the children's condition or disorder under investigation. As suggested by the National Commission this may require that an IRB seek advice of scientific consultation to assist in making this determination (National Commission 1977, 9).

TIME FOR A NATIONAL CONSENSUS

The value of federal regulations for the protections of children involved in research with no prospect of direct benefit is diluted when there is widespread variability and lack of consensus across multiple IRBs on applying minimal risk and minor increase over minimal risk standards. Differences among IRBs in determining the risk level of confidential surveys of adolescent sexual activity or the frequency of blood drawings are just some examples (Shah et al. 2004). Determination of risk rests on the confluence of quantitative estimates of risk probability

and magnitude of harm, estimations of participants' subjective experience of harm and discomfort, contextual estimates of investigator competence in performing procedures, and the importance of the research to the health and welfare of children. Consequently, determination of minimal risk and minor increases over minimal risk will always be somewhat imprecise and tied to moral and social values (Kopelman 2004). Nevertheless, during the past 25 years there has been remarkable consistency in the normative framework from which federally charged committees and international organizations have suggested these risk thresholds ought to be interpreted. Drawing on those committees' deliberations, we propose the time has come for a national IRB consensus on the following criteria for determining approvability under regulations §46.404 and §406:

1. The definition of minimal risk by regulation 45 CFR 46.102(i), when applied to Subpart D, should be interpreted as those age-indexed risks encountered by healthy children living in safe environments in daily life or during the performance of routine physical or psychological examinations or tests.
2. The magnitude and probability of risks encountered during a well-child medical visit and during the administration of standard psychological or psychiatric interviewing and standardized testing should be used as indices of minimal risk as well as the ceiling for minimal risk determinations based on the daily life criteria.
3. Duration, frequency, aggregated effects, transience and reversibility should be used as criteria for judging equivalence of experimentally exposed risk to the magnitude and probability of risk in daily life or routine medical or psychological examinations or tests and for determining whether the risks are no more than a minor increase over minimal risk.
4. In determining whether experimental procedures pose only a minor increase over minimal risk, IRBs should require investigators to provide sufficient evidence (empirical or clinical) that: 1) participants will not experience any experimentally-induced pain, discomfort, or stress that is more than a slight increase over the amount of severity of pain associated with a routine injection or other equivalent procedures; 2) any potential harms associated with the procedure will be transient and reversible; 3) team members administering the procedures are experienced and competent; and 4) the setting in which the procedures are administered is appropriate.
5. IRBs should only apply the commensurate criteria (regulation §46.406b) to determine whether guardians and/or child participants as a class have or are likely to have experiences similar to the experimental procedures that will assist understanding of information presented during guardian permission and child assent.
6. In determining whether a class of children have a condition under regulation §46.406(c), IRBs should interpret the term *condition* as referring to a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific or clinical evidence has shown to negatively affect children's health and well-being or to increase their risk of developing a health problem in the future.
7. Determination that a protocol that may expose children to greater than minimal risk is likely to yield information "of vital importance" (regulation §46.406c) should be based on an established body of scientific evidence and empirical rational sufficient to conclude that the study is likely to yield generalizable knowledge that could significantly contribute to the understanding or amelioration of the class of subjects' disorder or condition.

CONCLUSION

In 1993, Freedman, Fuks and Weijer asked "To what risks may children participating in research be subjected?" (p. 9). We believe 25 years of national debate and federally-charged committee deliberations has at least illuminated that question for pediatric research involving no prospect of direct benefit and certainly narrowed the range of disagreement among both researchers and ethicists. It is time to adopt the decisional rules consistently endorsed by national committees to achieve a fair and uniform IRB approval process that adequately protects child participants while ensuring that high-quality research aimed at understanding, preventing, and treating childhood disorders and conditions can continue to flourish.

REFERENCES

Amler, S. N., C. T. De Rosa, M. M. Williams-Johnson, D. E. Jones, R. W. Amler, and S. Wilbur. 2003. Risk analysis, uncertainty factors, and the susceptibilities of children. *Human & Ecological Risk Assessment* 9: 1701–1711.

Council for International Organizations of Medical Sciences. 2002. International Ethical Guidelines for Biomedical Research Involving Human Subjects [Commentary on Guideline 13]. Available at http://www.cioms.ch/guidelines_nov_2002_blurb.htm (accessed December 20, 2006).

DHHS (Department of Health and Human Services). 2001. Final regulations amending basic HHS policy for the protection of human research subjects. *Federal Register* 46: 8366.

DHHS, Food and Drug Administration, 21 CFR Parts 50 and 56, [Docket No. 00N-0074], RIN 0910-AC07, April 21, 2001, Interim Rule: Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products.

Ernst, M. 1999. PET in child psychiatry: The risks and benefits of studying normal healthy children. *Neuropsychopharmacological & Biological Psychiatry* 23: 561–570.

Fisher, C. B., and S. Z. Kornetsky. 2005. SACHRP recommendations for review of children's research requiring DHHS Secretary's approval. *IRB: Ethics & Human Research* 27: 1–7.

Freedman, B., A. Fuks, and C. Weijer. 1993. *In loco parentis*: Minimal risk as an ethical threshold for research upon children. *Hastings Center Report* 23(2): 13–19.

Institute of Medicine of the National Academy. 2004. *Ethical Conduct of Clinical Research Involving Children* eds. M.J. Field and R.E. Behrman Washington, DC: National Academies Press.

Janofsky, J., and B. Starfield. 1981. Assessment of risk in children on children. *Journal of Pediatrics* 98: 142–856.

Kopelman, L. 2004. Minimal risk as an international ethical standard in research. *Journal of Medicine & Philosophy* 29: 351–358.

Marshall, E. 2000. Enforcers halt NIH study called less risky than outdoor play. *Science* 290: 1281.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1977. *Report and recommendations: Research involving children.* Washington, DC: U.S. Government Printing Office.

National Human Research Protections Advisory Committee. 2001. *Children's Workgroup Report: April 2001 meeting*. Available at http://www.hhs.gov/ohrp/nhrpac/mtg04-01/childworkgroup4-5-01.pdf (accessed December 20, 2006).

Secretary's Advisory Committee for Human Research Protections. *April 18–19, 2005, Meeting presentations and reports*. Available at http://www.hhs.gov/ohrp/sachrp/mtgings/mtg04-05/present.htm (accessed December 20, 2006).

Shah, S., A. Whittle, B. Wilfond, G. Gensler, and D. Wendler. 2004. How do institutional review boards apply the federal risk and benefit standards for pediatric research? *Journal of the American Medical Association* 291: 476–482.

Wendler, D. 2004. Risk standards for pediatric research: Rethinking the *Grimes* ruling. *Kennedy Institute of Ethics Journal* 14: 187–198.

Wendler, D., L. Belsky, K. M. Thompson, and E.J. Emanuel. 2005. Quantifying the federal minimal risk standard: Implications for pediatric research without a prospect of direct benefit. *Journal of the American Medical Association* 294: 826–832.