How Do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Pediatric Research?

Seema Shah, BA
Amy Whittle, BA
Benjamin Wilfond, MD
Gary Gensler, MS
David Wendler, PhD

Context Federal regulations allow children in the United States to be enrolled in clinical research only when the institutional review board (IRB) determines that the risks are minimal or a minor increase over minimal, or that the research offers a prospect of direct benefit. Despite this reliance on IRBs, no data exist on how IRBs apply the risk and benefit categories for pediatric research.

Objective To determine how IRB chairpersons apply the federal risk and benefit categories for pediatric research.

Design, Setting, and Participants Telephone survey, conducted between May and August 2002 of 188 randomly selected chairpersons of IRBs in the Unites States. The survey consisted of 21 questions to assess the application of federal risk standards to research procedures, whether certain interventions offer a prospect of direct benefit to participating children, and the extent to which IRBs use the federal definition of minimal risk when categorizing the risks of research procedures in children.

Main Outcome Measures Responses regarding categorization of the risk level and direct benefits of pediatric research procedures.

Results A single blood draw was the only procedure categorized as minimal risk by a majority (152 or 81%) of the 188 respondents. An electromyogram was categorized as minimal or a minor increase over minimal risk by 100 (53%) and as more than a minor increase over minimal risk by 77 (41%). Allergy skin testing was categorized as minimal risk by 43 IRB chairpersons (23%), a minor increase over minimal risk by 81 (43%), and more than a minor increase over minimal risk by 51 (27%). Regarding benefits, 113 chairpersons (60%) considered added psychological counseling to be a direct benefit, while participant payment was considered a direct benefit by 10% (n=19).

Conclusions Application of the federal risk and benefit categories for pediatric research by IRB chairpersons is variable and sometimes contradicted by the available data on risks and the regulations themselves. To protect children from excessive risks while allowing appropriate research, IRB chairpersons need guidance on applying the federal risk and benefit categories and also need data on the risks children face in daily life and during routine physical or psychological tests.

JAMA. 2004;291:476-482 www.jama.com

PEDIATRICIANS OFTEN MUST treat children in the absence of sufficient data.[1] For example, approximately 70% of all medications do not include sufficient data for use in children.[2,3] To provide the necessary data and to ensure medical interventions are safe and effective for children, it is necessary to conduct clinical research with children.[4,5] Currently, more than 1900 clinical trials are approved for children in the United States.[6] Food and Drug Administration (FDA) requests have led to proposals to enroll another 38 000 children in clinical research.[7] One FDA request led to a series of studies, enrolling thousands of children, to establish a safe and effective dose of ibuprofen for infants.[8] Another FDA request led to studies assessing whether the combination of lopinavir and ritonavir, proven effective in adults, is safe and effective in children with human immunodeficiency virus infection.[8]

Ethical guidelines for pediatric research must balance the protection of individual children with the importance of allowing research needed to improve pediatric medicine.[9-13] Federal regulations[14,15] attempt to achieve this balance by empowering institutional review boards (IRBs) to approve pediatric research in 3 risk and benefit categories: (1) studies that offer participating children a prospect of direct benefit[16]; (2) studies that do not of-

See also pp 470 and 494.

Author Affiliations: Department of Clinical Bioethics (Mss Shah and Whittle and Drs Wilfond and Wendler) and Human Genome Research Institute (Dr Wilfond), National Institutes of Health, Bethesda, Md; and Emmes Corporation, Bethesda, Md (Mr Gensler). **Corresponding Author and Reprints**: David Wendler, PhD, National Institutes of Health, Bldg 10, Room 1C118, 10 Center Dr, Bethesda, MD 20892 (e-mail: dwendler@nih.gov).

Health Law and Ethics Section Editors: Lawrence O. Gostin, JD, Center for Law and the Public's Health at Georgetown University, Washington, DC, and the Johns Hopkins University, Baltimore, Md; Helene M. Cole, MD, Contributing Editor, *JAMA*.

fer a prospect of direct benefit but pose only minimal risk[17]; and (3) studies that do not offer a prospect of direct benefit and pose a minor increase over minimal risk.[18] The federal regulations prohibit IRBs from approving pediatric research that poses more than a minor increase over minimal risk and does not offer a prospect of direct benefit to the participating children.

The federal regulations define *minimal risk* as the risk of harm or discomfort "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[19] The regulations do not further specify the risks of daily life, nor do they define what constitutes a "direct" benefit or a "minor increase" over minimal risk. Consequently, whether children are enrolled in clinical research only when the risks are low or the research offers the potential for individual benefit depends on how IRBs apply the federal risk and benefit categories.

How do IRBs apply the federal risk and benefit categories in specific cases? Do IRBs apply the federal risk and benefit categories in ways that allow appropriate research, while protecting children from excessive risks? Or do IRBs apply these categories in ways that have the potential to expose children to excessively risky research and/or block valuable and appropriate research? The only empirical data on assessing the risks of pediatric research come from a study that interviewed department chairpersons, not IRB members, and was collected more than 20 years ago, prior to the adoption of federal regulations.[20] To provide empirical data on how IRBs apply the federal risk and benefit categories for pediatric research, we asked the chairpersons of 188 IRBs responsible for reviewing and approving pediatric research in the United States to categorize the risks and benefits of hypothetical pediatric studies.

METHODS

Respondents

We chose to contact chairpersons from 3 different types of IRBs. First, we sought IRBs that primarily review pediatric research identified through the National Association of Children's Hospitals and Related Institutions and the Association of Medical School Pediatric Department Chairpersons. Second, we sought independent IRBs from the Health Industry Manufacturers Association list (now called AdvaMed). Finally, we randomly selected IRBs on an Office for Human Research Protections IRB listing. We selected 154 IRBs from the National Association of Children's Hospitals and Related Institutions and the Association of Medical School Pediatric Department Chairpersons; and 37 IRBs from the Health Industry Manufacturers Association. Next, we randomly selected 71 (6.4%) of the 1113 IRBs from the list from the Office for Human Research Protections. We had a total of 262 potential respondents.

Potential respondents were contacted by telephone. Potential respondents were excluded if (1) his/her IRB did not review any pediatric research in calendar year 2000; (2) his/her IRB reviewed fewer than 10 studies in calendar year 2000, or; (3) the chairperson had less than 1 year of IRB experience. Four potential respondents reported that his/her IRB was no longer operating, while 34 potential respondents met at least 1 exclusion criterion. Of the remaining 224 eligible respondents, 12 declined to participate and 24 were unreachable. A total of 188 agreed to participate (a response rate of 84%). The IRB of the National Institute of Child Health and Human Development approved the survey.

Survey

We contacted respondents between May and August 2002 and asked 21 questions. These questions addressed (1) application of the federal risk standards to research procedures; (2) determination of whether certain interventions offer a prospect of direct benefit to the participating children; and (3) extent to which chairpersons use the federal definition of minimal risk when categorizing the risks of research procedures in children.

We first asked the chairpersons whether they were familiar with and followed the federal regulations for pediatric research. We then asked him/her to categorize 8 research procedures as "minimal risk," "a minor increase over minimal risk," or "more than a minor increase over minimal risk" when performed in healthy 11-year-olds for research purposes only. Respondents were asked to categorize the risk level of a single blood draw, as well as the risk level of a blood draw each week for 6 months. Respondents were also asked to categorize the risk level of lumbar puncture with conscious sedation in healthy children, the risk level of lumbar puncture without conscious sedation in healthy children, and the risk level of lumbar puncture without conscious sedation in ill 11-year-olds who had had numerous lumbar punctures. Because respondents were experienced IRB members and familiar with the regulations, no definition of minimal risk was provided for these questions.

Next, respondents were asked how much they rely on the following federal definition of minimal risk when categorizing research risks in children:

> The federal regulations define minimal risks as the risks ordinarily encountered in daily life. When determining whether a procedure poses minimal risks in children, would you say that you rely on this definition a great deal, a moderate amount, very little, or not at all?

Finally, to assess which interventions chairpersons regard as offering a prospect of direct benefit to participating children, we asked

- "In deciding whether a study qualifies as offering a prospect for direct benefit, would you take into account the fact that the children will be offered extra medical care independent of the research, such as free exams or medicines?"
- "Would you take into account the fact that the children will receive clinically indicated counseling from a psychologist that is independent of the research?"

Table 1. Characteristics of IRB Chairpersons Reviewing Pediatric Research

Characteristics	No. (%) of Chairpersons (N = 188)
Sex	
Female	41 (22)
Male	147 (78)
Age, y	
30-49	64 (34)
50-59	88 (47)
≥60	36 (19)
Physician*	118 (63)
Internal medicine	51 (27)
Surgery	7 (4)
Pediatrics	44 (23)
Other	17 (9)
Nonphysician	70 (37)
Lawyer	7 (4)
Nurse/midwife	7 (4)
Psychologist	11 (6)
Pharmacologist	11 (6)
Sociologist	5 (3)
Other	29 (15)
Years as IRB chair	
<1	28 (15)
1-2	45 (24)
3-5	51 (27)
6-10	38 (20)
11-15	13 (7)
>15	13 (7)
Years as an IRB member	
1-2	8 (4)
3-5	31 (16)
6-10	50 (27)
11-15	47 (25)
>15	52 (28)
IRB's institutional affiliation	
Academic general medical	92 (49)
Academic pediatric medical	26 (14)
Community general medical	17 (9)
Community pediatric medical	4 (2)
Independent	21 (11)
Government agency	6 (3)
Other	23 (12)

Abbreviation: IRB, institutional review board.
*Total sums to 119 rather than 118 because respondents could choose more than 1 specialty.

- "How about the fact that subjects will be paid for their participation?"

Statistical Analysis

Univariate characteristics of respondents and cross-tabulations of procedures and risks were calculated using SAS procedure FREQ. Univariate associations between respondent characteristics and their assessments of risks and benefits were calculated using SAS LOGISTIC. All analyses were performed using SAS statistical software (Version 8.0; SAS Institute Inc, Cary, NC).

RESULTS

The majority (78%) of respondents were male; 63% were physicians (TABLE 1). Eighty percent had 6 or more years of IRB experience; 49% reported being "very familiar" and 42% reported being "moderately familiar" with the federal regulations for pediatric research. Half of the respondents reported that his/her IRB was affiliated with an academic general medical center, and 14% reported that their IRBs were affiliated with an academic pediatric medical center.

Risk Assessments

A single 10-mL blood draw by venipuncture was the only procedure categorized as minimal risk by a majority (81%) of IRB chairpersons (TABLE 2). Electromyography was categorized as minimal or a minor increase over minimal risk by 53%, but as more than a minor increase over minimal risk, hence too risky for IRB approval without a prospect of direct benefit to participating children, by 41% of IRB chairpersons (Table 2). Allergy skin testing was categorized as minimal risk by 23%, a minor increase over minimal risk by 43%, and more than a minor increase over minimal risk, hence too risky for IRB approval without a prospect of direct benefit to participating children, by 27% of respondents. A single dose of an antibiotic that had a 1 in 100 000 chance of death, but no other adverse effects, was categorized as minimal risk by 7%, but more than a minor increase over minimal risk by a majority (59%) of chairpersons.

Significantly more IRB chairpersons categorized lumbar puncture without conscious sedation as minimal risk in ill children, who had numerous lumbar punctures in the past, compared with the same lumbar puncture in healthy children (6% vs 2%; Table 2). Finally, 62% reported that they rely on the federal definition of minimal risk a "great deal" when categorizing the risks of research procedures in children.

Assessments of Direct Benefits

The federal regulations allow IRBs to approve pediatric research that poses more than a minor increase over minimal risk only when it offers a prospect of "direct" benefit to participating children (BOX). Overall, 113 respondents (60%) considered added psychological counseling not necessary for research purposes to offer a prospect of direct benefit to the participating children. Added medical examinations and medicines not necessary for research purposes were considered to offer a prospect of direct benefit by 94 (51%). Even payment for participation was considered to offer a prospect of direct benefit to the participating children by 19 IRB chairpersons (10%).

Predictors of Responses

In univariate analysis, older IRB chairpersons were significantly more likely to categorize several procedures as "less" risky such as lumbar puncture with conscious sedation (odds ratio [OR], 4.57; 95% confidence interval [CI], 1.26-16.67; TABLE 3). Conversely, IRB chairpersons who reported relying on the federal definition of minimal risk were significantly more likely to categorize several procedures as "more" risky such as a blood draw (OR, 2.67; 95% CI, 1.19-6.00).

COMMENT

Institutional review boards are charged with the vital responsibility of protecting individual children, while allowing appropriate research needed to improve pediatric medical care. To provide data on how IRBs try to achieve this balance, we asked IRB chairpersons responsible for approving pediatric research in the United States to categorize the risks and benefits of hypothetical pediatric studies. The responses suggest that IRB chairpersons' application of the federal risk and benefit categories is variable and sometimes inconsistent with the federal regulations and actual risks to children. To ensure individual children are protected while also allowing important research to occur, IRBs need guidance on applying the federal risk and benefit categories and data on the risks of research procedures in children, as well as the risks children face in daily life.

The variation we found also raises the question of whether the federal risk and benefit categories for pediatric research need to be clarified or reassessed.

The federal regulations define *minimal risk* as the risk of harm or discomfort "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." Yet 70% of chairpersons categorized allergy skin testing as more than minimal risk, despite the fact that allergy skin testing is a routine physical test. Similarly, a single car trip across town during rush hour poses approximately a 1 in 10 000 risk of serious injury and approximately a 1 in 100 000 risk of death in children.[21] Research studies that pose a 1 in 100 000 risk of death are no more dangerous than riding in a car during rush hour, which is an ordinary activity of daily life. Nonetheless, 59% of IRB chairpersons categorized a pharmacokinetic study that poses a 1 in 100 000 risk of death, but no other adverse effects, as more than a minor increase over minimal risk. These assessments imply that a majority of chairpersons consider the risks of this study to be so much greater than the risks of daily life that it cannot be approved by an IRB. To ensure IRBs are in a position to protect children in pediatric research trials without blocking appropriate pediatric research based on mistaken risk assessments, data are needed on the risks of research procedures and the risks children face in daily life.

These findings reveal substantial variability in IRB chairpersons' assessments of the risks of research procedures in children. Overall, 27% of IRB chairpersons categorized allergy skin testing as too risky for IRB approval without a prospect of direct benefit to the participating children, while 66% deemed such testing safe enough for IRB approval without a prospect of direct benefit. Similarly, 59% would prohibit a pharmacokinetic study with a 1 in 100 000 risk of death as excessively risky, yet 37% would permit such a study as posing minimal risk or a minor increase over minimal risk. While 19% of chairpersons consider a confidential survey of sexual behavior to be too risky for IRB approval, 73% deemed it approvable by an IRB.

Are these variations problematic? Wide variations in the use of surgical procedures were reported 30 years ago.[22,23] While "unable to state which utilization rates are 'normal,'" such variations raise concerns because they are traceable to arbitrary factors, such as "differences in beliefs among physicians [and] the supply of general surgeons," not to differences in medical indications.[22]

The variation in IRB chairpersons' categorization of the risks of research procedures in children seems similarly unjustified. How can 37% of IRB chairpersons determine that the risks of a pharmacokinetic study are similar to the risks children face in daily life, while 59% determine that the same risks significantly exceed the risks children face in daily life? This level of variation raises concern that some IRBs may be mistakenly categorizing risky procedures as only minimal risk in children and other IRBs may be prohibiting research that may only pose minimal risk based on the mistaken assumption that the procedures pose serious risks to children.

These data do not determine whether the risks of specific research procedures in fact are similar to or exceed the risks children face in daily life. Hence, these data do not determine which risk assessments are mistaken in each case. However, the importance of protecting children from excessive risks, while allowing appropriate research, suggests that both mistakes are ethically troubling, and need to be addressed.

The variation in IRB chairpersons' risk assessments of pediatric research may be caused by a lack of data, especially for nonphysical risks. For example, the variation in chairpersons' categorization of the risks of allergy skin

Table 2. Categorization of Risk by IRB Chairpersons of Common Research Procedures Performed in Healthy 11-Year-Olds (N = 188)*

Procedure	No. (%) of Chairpersons Who Categorized Risk		
	Minimal Risk	Minor Increase Over Minimal Risk	More Than a Minor Increase Over Minimal Risk
Blood draw (10 mL)	152 (81)	32 (17)	2 (1)
Magnetic resonance imaging (no sedation)	90 (48)	66 (35)	17 (9)
Confidential survey of sexual activity	83 (44)	55 (29)	36 (19)
Allergy skin testing	43 (23)	81 (43)	51 (27)
Blood drawn for 6 mo (10 mL/wk)	28 (15)	96 (51)	60 (32)
Electromyography	17 (9)	83 (44)	77 (41)
Pharmacokinetic study (risk of death: 1/100 000)	13 (7)	56 (30)	111 (59)
Initial pediatric testing of drug found safe in 500 adults	9 (5)	43 (23)	122 (65)
Lumbar puncture with conscious sedation in healthy children	6 (3)	23 (12)	154 (82)
Lumbar puncture without conscious sedation in healthy children	4 (2)	30 (16)	147 (78)
Lumbar puncture without conscious sedation in ill children	11 (6)†	60 (32)	105 (56)

Abbreviation: IRB, institutional review board.
*Because respondents could answer "Don't know," percentages may not add up to 100%.
†Significantly more chairpersons categorized lumbar puncture without conscious sedation in ill children as minimal risk compared with lumbar puncture without conscious sedation in healthy children ($P = .03$; McNemar test).

Box. Federal Risk and Benefit Categories for Pediatric Research

Prospect of Direct Benefit	No Prospect of Direct Benefit
Minimal Risk*	Minimal Risk*
Approvable by an institutional review board (IRB) provided[17]: • Parental permission† • Child's assent‡	Approvable by an IRB provided[17]: • Parental permission† • Child's assent‡
Minor Increase Over Minimal Risk	Minor Increase Over Minimal Risk
Approvable by an IRB provided[16]: • Risks are "justified" by the anticipated benefit • Risk-to-benefit profile is at least as favorable as the available alternatives • Parental permission† • Child's assent‡	Approvable by an IRB provided[18]: • Intervention is reasonably commensurate with subjects' actual or expected experience(s) • Intervention is likely to yield generalizable knowledge about subjects' disorder or condition • Parental permission† • Child's assent‡
More Than a Minor Increase Over Minimal Risk	More Than a Minor Increase Over Minimal Risk
Approvable by an IRB provided[16]: • Risks are "justified" by the anticipated benefit • Risk-to-benefit profile is at least as favorable as the available alternatives • Parental permission† • Child's assent‡	Not approvable by an IRB§

*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]).
†Permission of 1 parent is sufficient for minimal risk and prospect of direct benefit research; permission of both parents is required in all other cases, if both are reasonably available. Parental permission may be waived if the IRB judges that it is not a "reasonable requirement to protect the subjects" (§46.408 [c]).
‡May be waived if the IRB judges that the children are not capable of providing assent, or the "research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research" (§46.408 [a]).
§May be approved by the Secretary of the Department of Health and Human Services after consultation with a panel of experts and public review and comment, if the research offers a "reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children" (§46.407).

testing may result from uncertainty over whether allergy skin testing poses more than a minimal risk of anxiety in children. To ensure that the risk assessments made by IRB chairpersons are based on all the risks to children, it will be important to conduct research to systematically assess the risks of research procedures in children, including any psychological risks or risks of discomfort. Until such data are collected, IRBs should not speculate on what risks research procedures pose to children. Instead, IRBs should consult with those who have experience, especially in research settings, with the procedures in children.

The variation in risk assessments may be caused by the ambiguity of the terms *minimal* and *minor* increase over minimal, which are used to define the federal risk categories for pediatric research. The federal regulations attempt to address the ambiguity of "minimal" risk by providing an objective standard for assessing minimal risks, namely, the risks of daily life. However, the federal regulations do not provide a corresponding standard for what constitutes a "minor" increase over minimal risk.

When assessing whether research participation offers children sufficient individual benefit to justify the risks, the federal regulations direct IRBs to consider only "direct" benefits to pediatric participants. According to the IRB guidebook, "Direct payments or other forms of remuneration offered to potential subjects as an incentive or reward for participation should not be considered a 'benefit' to be gained from research."[24] Similarly, most commentators argue that IRBs should count as "direct" only medical benefits from research procedures, not any benefits from added services that are unnecessary for research purposes.[25] In contrast, 10% of IRB chairpersons considered payment to offer a prospect of direct benefit and 60% considered added psychological counseling not needed for research purposes to offer a prospect of direct benefit.

This conflict between current guidance and assessments made by IRB chairpersons highlights the need to clarify which benefits to participating children can justify the research risks they face. Current guidance seems to assume that there are compelling ethical or practical reasons why the benefits of added interventions, such as

Table 3. Predictors of Chairpersons' Application of the Federal Risk and Benefit Standards*

Predictor and Procedure	Effect	OR (95% CI)
Chairperson's age >60 y†	More likely to put procedure in lower risk category	
Blood draw (10 mL)		5.88 (1.26-27.03)
Blood draw for 6 mo (10 mL/wk)		3.42 (1.02-11.49)
Lumbar puncture with conscious sedation		4.57 (1.26-16.67)
Electromyography		5.56 (1.11-27.78)
Relies on federal definition of minimal risk a great deal‡	More likely to put procedure in higher risk category	
Blood draw (10 mL)		2.67 (1.19-6.00)
Electromyography		2.17 (1.10-4.27)
Survey of sexual activity		2.85 (1.23-6.60)
Chair of an independent IRB§	More likely to consider a direct benefit	
Payment		3.57 (1.13-11.29)

Abbreviations: IRB, institutional review board; CI, confidence interval; OR, odds ratio.
*Nonsignificant predictors: respondent's years of IRB experience; the total number of studies reviewed by respondent's IRB per year; the number of pediatric studies reviewed by respondent's IRB per year; the IRB's affiliation; respondent's profession; respondent's sex; and the presence of a pediatrician on the respondent's IRB.
†Compared with chairpersons younger than 50 years.
‡Compared with chairpersons who rely on the federal definition of minimal risk "very little" or "not at all."
§Compared with chairpersons of IRBs affiliated with a particular institution.

added counseling, should never be allowed to justify research risks to children. If this assumption is correct, the present data suggest that IRBs may sometimes be allowing children to be exposed to research risks without an appropriate potential for individual benefit. Conversely, if the benefits of added interventions sometimes can justify research risks in children, existing guidance may need to be revised.

Finally, we found that IRB chairpersons are significantly more likely to categorize a lumbar puncture without conscious sedation as minimal risk when performed in ill children who had had numerous lumbar punctures compared with the same lumbar puncture performed in healthy children. This finding suggests that some chairpersons may be applying the minimal risk standard based on the risks in the daily lives of specific groups of children. This interpretation conflicts with the general consensus that, to minimize the potential for exploitation, the "minimal" risk standard should be interpreted as referring to the risks in the daily lives of "typical" children: "Minimal risk should be defined as the probability and magnitude of harms that are normally encountered in the daily life of the general population."[26,27]

To minimize the potential for exploitation of specific groups of children, it may be important to specify in the regulations the extent to which the minimal risk standard should be based on the risks in the daily lives of typical children. Similarly, the federal regulations instruct IRBs to take into account the risks faced by ill children in particular when reviewing research that poses more than minimal risk without a prospect of direct benefit.[18] Future research should consider whether the importance of minimizing the potential for exploitation of specific groups of children implies that this reference to the risks faced by ill children should be deleted.

Our study has several limitations. We surveyed IRB chairpersons, whose views may not reflect the actual determinations made by their entire committees during convened meetings. In addition, IRBs may rely on specific committee members to apply the federal risk and benefit standards. Our survey did not allow respondents to consult these individuals, although respondents could respond "don't know" to each question.

The federal risk and benefit categories for pediatric research are based on ethical standards concerning the appropriate balance between protecting individual children and allowing important pediatric research. However, IRB chairpersons' application of the federal risk and benefit categories to hypothetical pediatric research studies is variable and sometimes inconsistent with the federal regulations and the available data. These findings suggest that to ensure this vital balance is achieved in practice, IRBs need guidance on how to apply the federal risk and benefit categories and data on the risks children face from research procedures and in daily life.

Author Contributions: As principal investigator, Dr Wendler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Shah, Wilfond, Wendler.
Acquisition of data: Shah, Whittle, Wendler.
Analysis and interpretation of data: Shah, Whittle, Wilfond, Gensler, Wendler.
Drafting of the manuscript: Shah, Wendler.
Critical revision of the manuscript for important intellectual content: Shah, Whittle, Wilfond, Gensler, Wendler.
Statistical expertise: Gensler.
Administrative, technical, or material support: Shah, Whittle, Wendler.
Study supervision: Shah, Wendler.
Funding/Support: This article was completed as part of the authors' official duties as employees of the National Institutes of Health, with the exception of Gary Gensler, who completed his work as a contractor to the Department of Clinical Bioethics, National Institutes of Health.
Disclaimer: The opinions expressed are the authors' own. They do not reflect any position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.
Acknowledgment: We thank Christine Grady, Ezekiel Emanuel, and Connie Ulrich for their helpful suggestions on previous versions of the manuscript.

REFERENCES

1. American Academy of Pediatrics. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Available at: http//:www.aap.org/policy/00655.html. Accessibility verified December 29, 2003.
2. Center for Drug Evaluation and Research and US Food and Drug Administration. *Offices of Drug Evalu-*

ation Statistical Report. Rockville, Md: US Dept of Health and Human Services; 1989. Publication 89-233530.
3. Steinbrook R. Testing medications in children. *N Engl J Med.* 2002;347:1462-1470.
4. §505A of the Food and Drug Administration Modernization Act of 1997. Available at: http://www.fda.gov/opacom/7modact.html. Accessibility verified December 29, 2003.
5. NIH policy and guidelines on the inclusion of children as participants in research involving human subjects. Available at: http://www.nih.gov/grants/guide/notice-files/not98-024.html. Accessibility verified December 29, 2003.
6. Clinical Trials Web site. Available at: http://clinicaltrials.gov/ct/gui. Accessibility verified December 29, 2003.
7. Food and Drug Administration and the Center for Drug Evaluation and Research. Pediatric drug development. Available at: http://www.fda.gov/cder/pediatric. Accessibility verified December 29, 2003.
8. Food and Drug Administration. Pediatric Exclusivity Provision: January 2001 status report to Congress. Available at: http://www.fda.gov/cder/pediatric/reportcong01.pdf. Accessibility verified December 29, 2003.
9. Bartholome W. Ethics of non-therapeutic clinical research on children. In: *Appendix to Report Recommendations: Research Involving Children.* Washington, DC: US Government Printing office; 1977:3.1-3.22.
10. Ackerman TF. Moral duties of parents and non-therapeutic clinical research procedures involving children. *Bioethics Q.* 1980;2:94-111.
11. Brock DW. Ethical issues in exposing children to risks in research. In: Grodin MA, Glantz LH, eds. *Children as Research Subjects: Science, Ethics and Law.* New York, NY: Oxford University Press; 1994:81-101.
12. Glantz LH. Research with children. *Am J Law Med.* 1998;24:213-244.
13. Freedman B, Fuks A, Weijer C. *In loco parentis*: minimal risk as an ethical threshold for research upon children. *Hastings Cent Rep.* 1993;23:13-19.
14. Department of Health and Human Services. 45 CFR §46. Revised June 18, 1991.
15. Food and Drug Administration. 21 CFR §50.53.
16. Department of Health and Human Services. 45 CFR §46.405. Revised June 18, 1991.
17. Department of Health and Human Services. 45 CFR §46.404. Revised June 18, 1991.
18. Department of Health and Human Services. 45 CFR §46.406. Revised June 18, 1991.
19. Department of Health and Human Services. 45 CFR §46.102(i). Revised June 18, 1991.
20. Janofsky J, Starfield B. Assessment of risk in research on children. *J Pediatr.* 1981;98:842-846.
21. Forum on Child and Family Statistics. America's children: key national indicators of child well-being 2001. Available at: http://www.childstats.gov/order.asp#AC00. Accessibility verified December 29, 2003.
22. Wennberg J, Gittelsohn A. Small area variations in health care delivery. *Science.* 1973;182:1102-1108.
23. Bunker JP, Wennberg JE. Operation rates, mortality statistics and the quality of life. *N Engl J Med.* 1973;289:1249-1251.
24. Office for the Protection from Research Risks. *Protecting Human Research Subjects: Institutional Review Board Guidebook.* Washington, DC: US Government Printing Office; 1993.
25. King NM. Defining and describing benefit appropriately in clinical trials. *J Law Med Ethics.* 2000;28:332-343.
26. National Bioethics Advisory Commission. Ethical and policy issues in research involving human participants. Available at: http://www.georgetown.edu/research/nrcbl/nbac/human/overvol1.pdf. Accessibility verified December 29, 2003.
27. Kopelman LM. Children as research subjects: a dilemma. *J Med Philos.* 2000;25:745-764.

> Knowledge is, indeed, that which, next to virtue, truly and essentially raises one man above another.
> —Joseph Addison (1672-1719)