Published in final edited form as:
IRB. 2008 ; 30(5): 1–7.

Knowledge of Regulations Governing Pediatric Research:

A Pilot Study

Annemarie Stroustrup,
is Fellow, Division of Newborn Medicine, Kravis Children's Hospital, Mount Sinai Medical Center, New York, NY

Susan Kornetsky, and
is Director, Clinical Research Compliance, Children's Hospital Boston, Boston, MA

Steven Joffe
is Assistant Professor of Pediatrics, Children's Hospital Boston, and Dana-Farber Cancer Institute, Boston, MA

Agrowing awareness of the paucity of evidence for most treatments in pediatric medicine[1] has led to a rapid increase in the number of clinical trials involving children.[2] This means that some Institutional Review Boards (IRBs) are increasingly called upon to review pediatric research protocols. Because children's cognitive, psychological, and social immaturity limits their ability to understand and make decisions about participation in clinical research, federal regulations governing research with children require IRBs to implement additional protections beyond those afforded to adults who are recruited to participate in clinical research. Moreover, because children generally lack legal standing to authorize their own participation in research through the mechanism of informed consent, IRBs must ensure that regulatory requirements for proxy permission and child assent—as well as for upper limits on the acceptable degree of research-related risk—are met.[3] Application of these extra protections to specific studies is complicated by the heterogeneity of children who might participate in pediatric research.[4] Given these factors, review and oversight of pediatric research is a specialized area of IRB practice.[5]

Several studies of IRB practices reveal inconsistency among IRBs when applying regulations governing clinical research, including specific provisions governing research with children.[6] Although this inconsistency is likely due in part to legitimate differences in interpreting regulatory requirements and ethical standards,[7] it might also stem from some IRB members' lack of necessary expertise regarding pediatric research ethics and regulations.[8] In its 2004 report, Ethical Conduct of Clinical Research Involving Children, the Institute of Medicine (IOM) highlighted the need to educate IRB members about regulatory requirements and ethical standards for conducting research with children.[9]

In this pilot study, we assessed knowledge of pediatric research regulations among IRB members who review protocols involving children. We also evaluated members' training and experience regarding the practice and oversight of pediatric research. To our knowledge, this study represents the first attempt to evaluate IRB members' knowledge of these important topics.

Disclosure
Susan Kornetsky serves as a site visitor for the Association for the Accreditation of Human Research Protection Programs (AAHRPP), for which she is paid on a per diem basis. She also receives financial compensation to teach seminars for IRB members (IRB 101) and administrators (IRB Administrator 101) on behalf of Public Responsibility in Medicine and Research (PRIM&R).

Study Methods

Using the member list of the National Association of Children's Hospitals and Related Institutions (NACHRI),[10] we identified institutions within the United States likely to conduct research involving children. We focused on centers providing comprehensive pediatric care. Shriner's hospitals, rehabilitation centers, and disease-specific specialty hospitals were excluded from our sample. We also excluded institutions located outside the United States, as these operate under different regulatory requirements.

One hundred fifty-six institutions met criteria for inclusion in this study. We randomly selected 12 institutions from this list for our pilot study group. We contacted IRB officials at these centers and asked them to provide contact information for all active members of their institution's IRB. Five centers reporting a total of 72 members (range 8-20 per IRB) agreed to participate.

For four of the institutions, we mailed the study packet directly to all active IRB members. At the request of the fifth institution, we sent all study packets to the IRB administrator, who distributed them to members. The study packet contained a cover letter, an anonymous questionnaire, a separate coded postcard to notify us that the respondent had returned the questionnaire or preferred not to participate, and a return envelope. It was not possible to link questionnaires to individual respondents or to their institutions. Upon receipt of the postcard indicating return of the questionnaire, respondents were entered into a drawing for a gift certificate to a local restaurant. Four weeks after the initial mailing, we mailed a second questionnaire to IRB members from whom we had not received a response postcard. Seventy-two individuals were contacted. One survey recipient who reported not being an IRB member was excluded. After two mailings, 58% (41 out of 71) of eligible IRB members returned their questionnaires.

Our pilot study sought to assess two fundamental constructs: 1) self-reported preparedness for the tasks involved in IRB review, both overall and specifically with respect to pediatric protocols, and 2) knowledge of pediatric research regulations. The 12-question preparedness section asked respondents "How prepared do you consider yourself to be when performing each of the following IRB member tasks?" Responses were on a five-point ordinal scale, ranging from "not prepared" to "very well prepared," and included a "not applicable" response option.

The five-question knowledge section of the survey assessed understanding of federal regulations governing pediatric clinical research (e.g., those related to risk categorization, parental permission, and participant assent). We designed questions based on the regulatory requirements governing research with children (45 CFR 46, Subpart D),[11] the IOM report,[12] and Kornetsky et al.'s Study Guide for Institutional Review Board Management and Function.[13] Questions were multiple-choice format, with one best answer, and included a "not sure" response option. Instructions accompanying the knowledge items asked respondents to answer the questions without the use of reference materials.

Additional items asked about respondents' professional backgrounds, their previous experience with conduct and review of clinical research, the structure and workload of their IRBs, and the general and pediatric-specific education regarding IRB review that they had received.

Prior to distribution, a threemember panel of experts on pediatric research oversight reviewed a draft questionnaire. We also pilottested the draft questionnaire with five individuals of varying professional backgrounds who are IRB members at the Dana-Farber Cancer Institute

(DFCI). We revised or omitted questions that the panel review and pilot test showed to be confusing or ambiguous.

We calculated a knowledge score for each respondent by assigning one point for each best answer selected. *A priori* sample size calculations indicated that 40 respondents would allow estimation of the mean knowledge score within ± 0.32 standard deviations with 95% confidence.

We calculated an overall self-assessment score by averaging responses to the 12 questions regarding preparedness for elements of protocol review, and then we normalized the average to a 0-100 point scale. Similarly, we calculated a "pediatric-specific" self-assessment score by averaging the responses to the subset of seven questions regarding preparedness for elements of pediatric protocol review, then we normalized the average to a 0-100 point scale.

In bivariate analyses, we tested potential correlates of dependent variables (i.e., knowledge score, overall self-assessment score, and pediatric-specific self-assessment score) using Wilcoxon rank-sum tests, Kruskal-Wallis tests, or Spearman rank correlation coefficients as appropriate to the data. We considered associations to be potentially significant if two-sided p was less than 0.05. Because we viewed the analyses as exploratory, we did not adjust for multiple comparisons. Statistical analyses were performed using Stata 8 for Windows (Stata Corp., College Station, Texas).

The study was approved by the DFCI IRB, which waived the requirement for documentation of informed consent.

IRB Knowledge

Respondent Characteristics

Table 1 shows that most respondents were affiliated with the medical center their IRB served. Approximately half reported professional experience related to child health or development. Almost all had at least one year of experience as an IRB member; almost half had at least five years experience. Six respondents (15%) were currently serving as IRB chairs. Respondents reported exposure to a variety of training methods, with computer- and lecture-based methods being most common. Most (78%) reported receiving ongoing training, and most (68%) had received specific training in review of pediatric research.

Preparedness for Protocol Review

Levels of self-reported preparedness to perform tasks involved in reviewing research protocols were high (Figure 1). The median self-assessment score was 79 (interquartile range [IQR] 71-85); the median pediatric-specific self-assessment score was 75 (IQR 64-93). Internal consistency reliabilities of the overall self-assessment and pediatric-specific self-assessment scales were high (Cronbach's $\alpha = 0.93$ and 0.92, respectively). Respondents felt least prepared to evaluate the need for a child's assent (66% responding "well prepared" or "very well prepared") and to determine whether the research involved a minor increase over minimal risk (68% responding "well prepared" or "very well prepared").

Several facets of experience and training correlated with self-reported preparedness for IRB tasks (Table 2). Overall, IRB chairs considered themselves better prepared than did other members, although this difference was not apparent when asking specifically about review of pediatric protocols. Respondents who received ongoing training in IRB review and those who had received specific training in the review of pediatric protocols considered themselves better prepared than did other respondents. Respondents who attended at least 12 IRB meetings annually considered themselves better prepared than did those who attended fewer meetings.

Knowledge of Pediatric Research Regulations

The median knowledge score was one (IQR 0.5-2, range 0-4). Ten respondents (25%) did not select the best answer for any question. For individual questions, 8-40% of respondents selected the best answer (Table 3; an appendix presenting comprehensive results is available online at http://www.thehastingscenter.org/Publications/IRB/Default.aspx).

Respondent characteristics associated with increased knowledge are shown in Table 4. IRB chairs were more knowledgeable than other members ($p = 0.04$), respondents who had received lecture-based training were more knowledgeable than those who had not received such training ($p = 0.02$), and respondents who had received pediatric-specific training were more knowledgeable than those who had not ($p = 0.04$). Other characteristics, including affiliated/unaffiliated status, prior professional experience in child health, prior experience as a clinical investigator, years of IRB service, number of protocols reviewed, number of IRB meetings attended per year, percent of protocols reviewed that enrolled primarily children, and receipt of ongoing education regarding IRB review were not statistically associated with knowledge of regulations governing pediatric research review.

There was no significant correlation between knowledge score and either overall self-assessment score (Spearman's $\rho = 0.26$, $p = 0.11$) or pediatric-specific self-assessment score ($\rho = 0.14$, $p = 0.39$).

Discussion

IRB review of research involving children requires careful attention to regulations governing pediatric research. According to the IOM, however, "no systematic documentation exists on the extent to which IRB members understand and fulfill their responsibilities in reviewing studies that include children."[14] We therefore evaluated self-reported preparedness for clinical research review, both in general and with respect to pediatric protocols, among IRB members at institutions that self-identify as children's hospitals or related institutions. We also assessed members' knowledge of federal regulations governing research with children. Despite high levels of self-reported preparedness, our data suggest limited knowledge of regulatory requirements specific to pediatric research.

Problems with knowledge of regulations governing pediatric research may partly explain the consistent heterogeneity in IRB review of research involving children.[15] In a survey of IRB chairs, Shah et al. observed marked variability in assessments of risk level of various procedures (i.e., minimal risk, minor increase over minimal risk)—a determination that plays a critical role in IRBs' decisions regarding the approvability of pediatric research protocols.[16] In a different analysis based on the same survey, Whittle et al.[17] noted that IRBs differ markedly in the standards used to determine whether child assent is required and in their attitudes towards payment to research participants or their parents. Kimberly et al.[18] recently reported substantial variation among IRBs at hospitals participating in three multicenter trials regarding the requirement for and documentation of assent as well as the presence, amount, and form of payment for participation. Smith Rogers et al.[19] found similar variability in risk assessment and assent requirements among 11 IRBs reviewing an identical study involving adolescents. Finally, Mammel et al.[20] found variability among IRB chairs in their willingness to waive the requirement for parental permission for both observational and intervention research involving adolescents. Other studies in the adult context show striking heterogeneity in IRBs' handling of common multicenter protocols.[21] As the IOM notes, this variability in IRB decisions may have legitimate causes—including limited data on the risks of research procedures, lack of precision in the regulations, and reasonable disagreement among reviewers about interpretation of regulations—as well as less justifiable causes, such as inadequate reviewer education.[22]

Whether this heterogeneity fosters inadequate protection or impedes ethical scientific inquiry is unknown.

We emphasize the pilot nature of this study and note that it has several limitations. First, though the development of the survey involved expert review and cognitive pilot testing, the potential for ambiguity in questions or response options remains. Furthermore, as noted previously, the regulations are themselves often imprecise and subject to interpretation. "Incorrect" responses to some survey questions could therefore indicate defensible alternative interpretations of the regulations, rather than lack of knowledge. For example, the regulations leave room for judgment about what role IRBs should play in determining the capability of individual children to provide assent. IRB members' views on this issue may have influenced their responses to the question about when children are considered capable of assent. Second, because respondents were asked to complete the knowledge questions without the use of reference materials, our results may underestimate their performance during actual research reviews when reference materials are presumably available. Third, the study's small size, limited number of participating institutions, and exploratory nature indicate that the findings should be viewed as preliminary and in need of confirmation. Finally, the imperfect individual and institutional response rates raise the possibility that the generalizability of the results may be affected by response bias at both levels. Though selected at random from the NACHRI list, the IRBs that agreed to participate in this survey may not be representative of all IRBs at NACHRI institutions. Participating IRBs served children's hospitals in the eastern (one), midwestern (three), and western (one) United States. Nonparticipating institutions were also geographically diverse, representing the eastern (three), midwestern (one), and western (three) United States. The participating IRBs tended to have fewer members (mean 14, standard deviation [SD 5] versus mean 28 [SD 15]) and to serve smaller pediatric institutions and services (mean 130 [SD 62] versus 177 [SD 82] pediatric beds) than the seven nonparticipating IRBs. Two participating IRBs were at freestanding children's hospitals, while three were at children's hospitals that are part of larger hospitals, or "hospitals within hospitals." Among nonparticipating IRBs, three served freestanding children's hospitals, while four served hospitals within hospitals.

Given the small size of the survey and the multiple tests of association performed, our results could also be affected by false negative or false positive tests of association between IRB members' knowledge and their individual characteristics. In addition, the anonymous design of the survey, used to maximize individual and IRB willingness to participate, precludes our ability to investigate differences between IRBs or to control for clustering within IRBs. For all these reasons, a larger, more comprehensive survey of IRB members' knowledge that preserves links to institutions is urgently needed.

Finally, at a conceptual level, our study presupposes that all IRB members who review studies involving children should be knowledgeable about regulations governing pediatric research. This view receives support from the IOM, which concluded that "To be effective, IRB members should understand the ethics and history of research with humans, the current structure and funding of research projects, and the regulatory structure of research, including local laws."[23] An alternative model might view knowledge of regulations as the province of a specialized subset of IRB members, or even just of the chair along with committee staff. If such a model were adopted, the roles of IRB members who are not responsible for knowledge of regulations should be clarified. Nonetheless, our study raises the concern that there may be inadequate understanding of pediatric research regulations among IRB members at institutions that conduct research with children. Additional studies to corroborate these findings and to identify modifiable factors at the individual or institutional level that are associated with IRB members' knowledge are needed. If confirmed, our results suggest a pressing need for education of IRB members in the specialized task of reviewing pediatric research protocols.

Acknowledgments

We thank Jeffrey Botkin, E. Francis Cook, Celia Fisher, Alan Fleischman, and Tina Gelsomino for their invaluable advice and assistance with study and survey development and execution.

This work was supported by funding from the Alexandra J. Miliotis Pediatric Oncology Research Fund and the Harvard-MIT Division of Health Sciences and Technology. Dr. Joffe received support from the National Cancer Institute (K01 CA096872).

Appendix

Appendix

Complete Knowledge Questionnaire

Question		*Response Options*	*Number (%) Selecting Answer*
Which statement regarding parental permission for a child's involvement in IRB-approved research is correct?	Best	Permission of both parents, if they are reasonably available, is required for research that lacks the prospect for direct benefit and involves a minor increment over minimal risk.	3 (8%)
	Alternatives	Parental permission is always required before a child can participate in clinical research.	28 (74%)
		Parental permission may be waived whenever the research poses no greater than minimal risk to the child.	0 (0%)
		Permission of both parents, if they are reasonably available, is required for research that offers the prospect of direct benefit to the child but carries substantial risks.	6 (16%)
		Not sure	1 (2%)
According to the regulations, children are considered capable of assent when:	Best	The IRB determines that they are capable of assent on the basis of age, maturity and psychological state.	11 (27%)
		They are at least seven years of age and of normal cognitive ability.	9 (22%)
	Alternatives	They are at least twelve years of age and of normal cognitive ability.	10 (24%)
		Their parents determine that they are capable of assent on the basis of age, maturity and psychological state.	6 (15%)
		Not sure	5 (12%)
Federal regulations define the concept of "minimal risk" as situations where:	Best	The anticipated risks of participating in the research are not greater than those ordinarily encountered in daily life.	16 (40%)
		The anticipated risks of participating in the research are not greater than those ordinarily encountered during the course of the subjects' medical care.	9 (22%)
	Alternatives	The anticipated risks of participating in the research are only slightly greater than those ordinarily encountered in daily life.	4 (10%)
		The anticipated risks of participating in the research are only slightly greater than those ordinarily encountered during the course of the subjects' medical care.	11 (28%)
		Not sure	0 (0%)
Which statement about child assent is correct?	Best	An IRB may waive the requirement for assent if the research offers benefits to the child that are unavailable outside the research.	11 (28%)

Question		*Response Options*	*Number (%) Selecting Answer*
Which statement regarding the ability of an IRB to approve pediatric research is correct?	Alternatives	An investigator can assume that a child has assented to research participation as long as the child does not voice an objection.	1 (2%)
		An investigator can assume that a child has assented to research participation as long as the child does not voice an objection, provided that the parent agrees with this assessment.	8 (20%)
		Assent can be waived if the parent thinks that the purpose of the research is sufficiently important.	6 (15%)
		Not sure	14 (35%)
	Best	An IRB can approve a protocol that presents a minor increase over minimal risk if it determines that the research is likely to yield generalizable information about the subject's disorder or condition.	12 (30%)
		To approve a protocol that presents greater than minimal risk, the IRB must determine that the research offers the prospect of direct benefit to the child.	13 (33%)
	Alternatives	An IRB must refer all protocols enrolling children that present greater than minimal risk and no prospect of direct benefit to the child to the Department of Health and Human Services.	2 (5%)
		An IRB can approve a protocol that presents a minor increase over minimal risk only if it also offers the prospect of direct benefit to the child.	8 (20%)
		Not sure	5 (12%)

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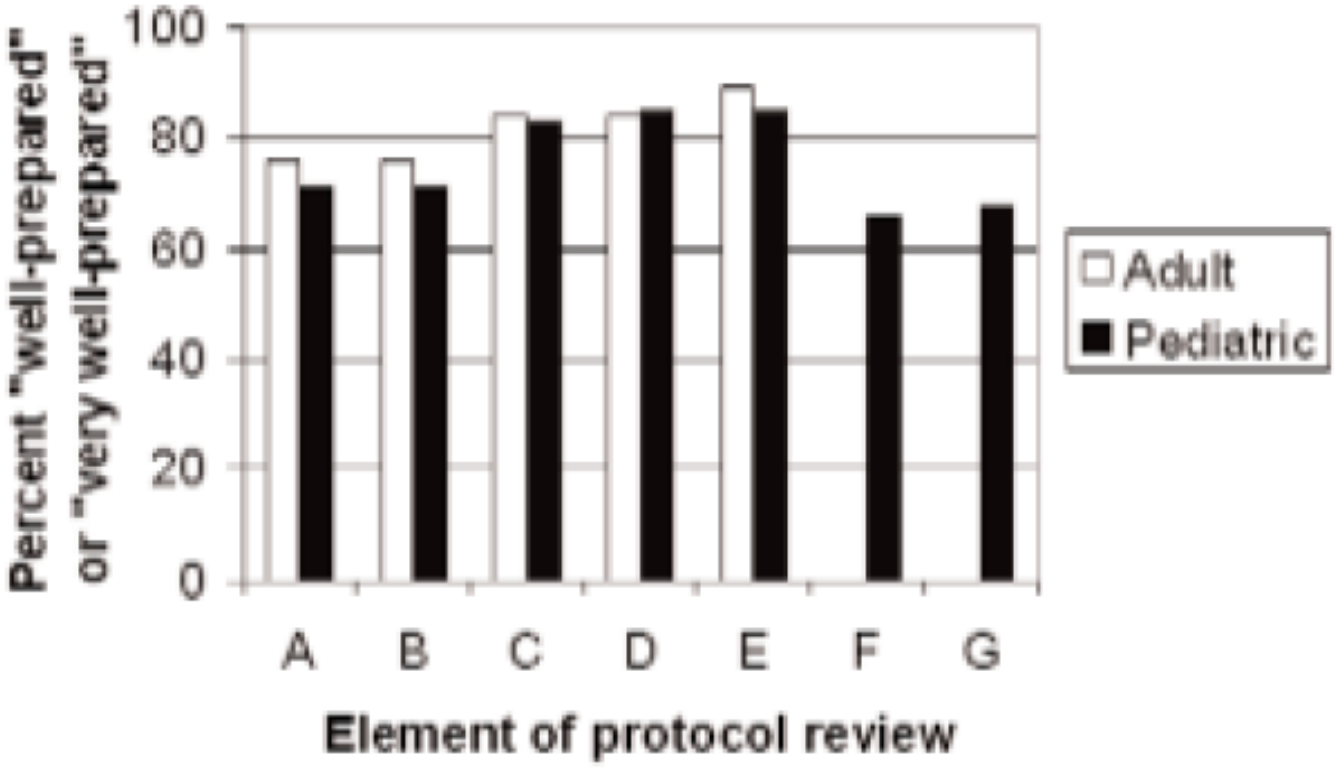

Figure 1. Respondent Preparedness for Adult vs. Pediatric Protocol Review

Table 1

Characteristics of Survey Respondents (N = 41)

Characteristic	*Number*	*Percent*
Affiliated with the medical center (other than membership on IRB)		
Yes*	24	59%
No†	17	41%
IRB chair		
Yes	6	15%
No	35	85%
Professional experience in child health or development		
Yes	21	51%
No	20	49%
Duration of IRB membership		
<1 year	3	7%
1-4 years	19	46%
5 years	19	46%
Current or prior involvement as an investigator or research study staff		
Principal investigator	6	15%
Coinvestigator or other study staff	9	22%
None	26	63%
Number of new protocols undergoing full-committee review each year		
25-49	13	32%
50-99	20	49%
100-299	5	12%
Not sure	3	7%
Number of IRB meetings attended each year		
6-11	30	73%
12 or more	11	27%
Percent of protocols reviewed by the IRB that enroll primarily children		
≤10%	4	10%
11-24%	8	20%
25-49%	13	32%
50% or more	13	32%

Characteristic	*Number*	*Percent*
Not sure	3	7%
Initial training received[‡]		
Computer-based tutorial	23	56%
Paper-based tutorial	9	22%
Video tutorial	7	17%
Lecture, workshop, or in-person tutorial	21	51%
Other	6	15%
No training	8	20%
Receipt of ongoing training		
Yes	31	78%
No	9	23%
Prior training in review of pediatric protocols		
Yes	28	68%
No	13	32%

[*] Includes six physicians, four nurses, one social worker, five pharmacists, one statistician, two administrators, one chaplain, one lawyer, one therapist, one risk manager, one vendor, and one volunteer.

[†] Includes six physicians, one lawyer, five community members, one ethicist, two retired physicians, and one retired nurse.

[‡] Respondents could identify more than one type of training.

Table 2

Correlates of Self-Reported Preparedness for Overall and Pediatric-Specific Protocol Review

Item[*]	*Preparedness for Protocol Review*			
	Overall		*Pediatric-Specific*	
	Median (Interquartile Range)	*p-value*	*Median (Interquartile Range)*	*p-value*
IRB chair				
Yes	89 (83-100)	0.05	84 (71-100)	0.35
No	77 (63-85)		75 (64-93)	
Receives ongoing IRB training				
Yes	83 (75-92)	0.01	79 (71-96)	0.02
No	61 (54-73)		64 (50-75)	
Receives training in pediatric research review				
Yes	83 (77-100)	0.02	86 (75-100)	0.03
No	75 (61-84)		73 (63-88)	
Number of IRB meetings attended per year				
6-11	75 (61-83)	0.02	73 (64-89)	0.06
12 or more	85 (83-98)		86 (79-96)	

[*] Status as affiliated/unaffiliated member, prior professional experience in child health or development, prior experience as a principal investigator or other study staff, years of IRB experience, number of protocols reviewed per year, percent of protocols reviewed that are primarily pediatric, and type of initial training received were unassociated with self-reported preparedness for overall and pediatric-specific protocol review.

Table 3

Knowledge of Federal Regulations Regarding Review of Pediatric Clinical Research

Question	*Best Answer*[*]	*Number (Percent) Selecting Best Answer*
Which statement regarding parental permission for a child's involvement in IRB-approved research is correct?	Permission of both parents, if they are reasonably available, is required for research that lacks the prospect for direct benefit and involves a minor increment over minimal risk.	3 (8%)
According to the regulations, children are considered capable of assent when:	The IRB determines that they are capable of assent on the basis of age, maturity, and psychological state.	11 (27%)
Federal regulations define the concept of "minimal risk" as situations where:	The anticipated risks of participating in the research are not greater than those ordinarily encountered in daily life.	16 (40%)
Which statement about child assent is correct?	An IRB may waive the requirement for assent if the research offers benefits to the child that are unavailable outside the research.	11 (28%)
Which statement regarding the ability of an IRB to approve pediatric research is correct?	An IRB can approve a protocol that presents a minor increase over minimal risk if it determines that the research is likely to yield generalizable information about the subject's disorder or condition.	12 (30%)

[*] A table that includes all response options is provided in the appendix (online at http://www.thehastingscenter.org/Publications/IRB/Default.aspx).

IRB. Author manuscript; available in PMC 2009 April 29.

Table 4

Correlates of Knowledge Score

Item	*Knowledge Score Median (Interquartile Range)* *	*p-value*
IRB chair		
Yes	2.25 (1-3)	0.04
No	1 (0-2)	
Received lecture- or seminar-based training to prepare for IRB position		
Yes	1 (1-2.75)	0.02
No	1 (0-2)	
Received training specific to pediatric review process		
Yes	2 (1-2.5)	0.04
No	1 (0-2)	

* Knowledge score was unrelated to status as an affiliated vs. unaffiliated IRB member, prior professional experience in child health, or development; prior participation in a protocol as a principal investigator, coinvestigator, or study staff; years of IRB service; number of protocols reviewed by the respondent's IRB; percent of protocols reviewed by the respondent's IRB that are primarily pediatric; or receipt of ongoing education regarding IRB review.