

Perception of risk associated with asthma research procedures among adolescents, parents, and pediatricians

Robert D. Annett, PhD,^a Janet L. Brody, PhD,^b David G. Scherer, PhD,^c and Elizabeth A. Perket, MD^a *Albuquerque, NM, and Eugene, Ore*

Background: Little empirical data exist about how adolescents with asthma, their parents, and pediatricians view the risks and benefits associated with asthma clinical research.

Objective: Two studies examined similarities and differences in the perception of risks and benefits associated with asthma research.

Methods: In study I questionnaires were completed by adolescents with asthma and parents at the end of an audio and written presentation of a hypothetical research vignette. In study II adolescents with asthma, their parents, and pediatricians rated the risks and benefits associated with discreet asthma research procedures.

Results: In study I adolescents and parents made distinctions in riskiness among the asthma research procedures ($P < .001$ and $P < .001$, respectively). With the exception of venipuncture, rank orders of risk ratings among procedures were similar for both groups. In study II significant differences in risk and benefit ratings for individual procedures were found among respondent groups, including experimental medication, placebo, and venipuncture. Overall, asthma research procedures were viewed as more beneficial than risky ($P < .001$).

Conclusion: Participants generally viewed asthma research procedures as more beneficial than risky. Overall, the relative risk rankings among all respondents were similar. However, there were between-group difference in ratings of risk associated with venipuncture and experimental medication. Parents and adolescents rated the benefit of placebo significantly higher than did pediatricians. (*J Allergy Clin Immunol* 2004;114:1138-45.)

Key words: Bioethics, risk-benefit evaluation

Abbreviations used

FDA: US Food and Drug Administration

IRB: Institutional review boards

MANOVA: Multivariate analysis of variance

The concept of research risk is not well defined by federal regulations and guidelines. Physical considerations have dominated the conceptual thinking about risk, and other potential risk domains, such as psychological, economic, or social aspects, have not received equal attention.¹ Research with adults has suggested there are differences in research risk evaluation between investigators and their participants,^{2,3} with concern and some evidence that adolescents evaluate research risk differently from adults.^{4,5} The formal definition of minimal risk in biomedical research is "risks ordinarily encountered in daily life."⁶ Although there are examples of minimal-risk research, the definition is again vague,⁷ with local institutional review boards (IRBs) given the ultimate responsibility for interpretation, resulting in substantial disagreement, confusion, and variability in the application of federal guidelines.¹ The *IRB Guidebook* provides several benchmark examples of minimal research procedures, including venipuncture.⁸

Unlike risk assessment, benefit associated with research participation has lacked clear benchmarks. Benefit can be framed in terms of benefits to the individual for participation in a research study, as the benefit to society, or both. Unfortunately, there is a lack of empiric data to guide investigators or IRBs in conceptualizing how research participants understand benefits. Qualitative research has suggested that information on perception of benefits is strongly desired by IRB members because appraisal of benefits is critical to the ethical judgment of the risk-benefit balance within studies.⁹

Thus there is a lack of clarity surrounding the definition and interpretation of risks and benefits in child research, with little attention paid to the implications of differences in risk and benefit perceptions between adolescents and adults. Hence the purpose of the following studies was to evaluate the differences and similarities in perceptions of risks and benefits among adolescents with asthma, their parents, and pediatricians to clarify factors that might

From ^athe University of New Mexico Health Sciences Center, Albuquerque; ^bthe Oregon Research Institute, Eugene; and ^cthe University of New Mexico College of Education.

Supported by the Department of Health and Human Services, National Heart, Lung, and Blood Institute (NHLBI-RO1-HL64677).

Received for publication May 26, 2004; revised July 11, 2004; accepted for publication July 28, 2004.

Reprint requests: Robert D. Annett, PhD, Department of Pediatrics, MSC-10-5590, 1 University of New Mexico, Albuquerque, NM, 87131-0001. E-mail: rdannett@unm.edu.

0091-6749/\$30.00

© 2004 American Academy of Allergy, Asthma and Immunology
doi:10.1016/j.jaci.2004.07.058

TABLE I. Demographic characteristics of adolescent and parent participants in Study I (n = 19) and Study II (n = 36)

	Study I, n (%)	Study II, n (%)
Relationship with adolescent		
Parent	17 (89.5)	34 (94.4)
Other	2 (10.6)	2 (5.6)
Child ethnicity		
White	6 (31.6)	15 (41.7)
Hispanic	8 (42.1)	13 (36.1)
Other (American Indian and mixed)	4 (21.1)	8 (22.2)
Missing	1 (5.3)	
Highest parental educational level		
High school diploma	8 (42.1)	8 (22.2)
Associates-vocational degree	5 (26.3)	9 (24.0)
Bachelors or graduate degree	5 (26.4)	16 (34.5)
Missing	1 (5.3)	3 (8.3)
Yearly household income		
<\$20,000	2 (10.5)	9 (25.0)
\$20,001-\$40,000	7 (36.8)	8 (22.2)
\$40,001-\$60,000	4 (21.1)	3 (8.3)
>\$60,001	5 (26.3)	16 (44.4)
Missing	1 (5.3)	

result in differing opinions about research participation. In the first study our objective was to gain an understanding of how risks associated with asthma research procedures were evaluated within a research consent form describing a hypothetical clinical trial for a new asthma medication. In the second study we sought to verify and expand the findings on a separate sample by including comparison ratings from pediatricians and presenting only descriptions of research procedures.

STUDY I

This study compared willingness to participate and perceptions of research risk between adolescents with asthma and their parents as they evaluated a vignette of a hypothetical research consent form. The vignette, based on an actual 5-year multisite pediatric asthma clinical trial, described a randomized medication trial in which adolescent participants would receive either an experimental medication, with some unknown risks and side effects, or continue taking their current medication (see Table E1 in the Journal's Online Repository at www.mosby.com/jaci). The vignette included all of the procedures performed in the actual trial on which the hypothetical consent form was based. The descriptions within the vignette included all of the elements required for fully informed consent and were written at a 5th-grade reading level (see Table E1 in the Journal's Online Repository). The health sciences center human research review committee reviewed and approved the informed consent-assent form for this study before data collection began. Adolescents with an established diagnosis of asthma and their parents were recruited for this study. Written informed consent-assent was obtained

TABLE II. Asthma characteristics of adolescent participants in Study I (n = 19) and Study II (n = 36)

	Study I, n (%)	Study II, n (%)
Years since diagnosis of asthma		
<2	2 (10.5)	4 (11.1)
2-5	3 (15.8)	13 (36.1)
>5	14 (73.7)	19 (52.8)
Physician office and emergency department visits in past year		
<6	11 (57.9)	29 (80.6)
6-12	2 (10.5)	5 (13.9)
>12	6 (31.6)	2 (5.6)
In the past 4 weeks, has your child had:*		
coughing at night that has awakened him-her?	6 (31.6)	20 (55.6)
coughing early in the morning?	6 (31.6)	25 (69.4)
coughing after physical activity?	13 (68.4)	29 (80.0)

*Values in parentheses are percent responding yes.

from parents-adolescents, and adolescents received a gift certificate for their participation.

Procedures

The procedures used in Study I have been previously described.⁵ Briefly, informed consent-assent was obtained from parents and adolescents before initiation of study procedures. Each parent-adolescent dyad sat together and listened to an audiotaped reading of the vignette while following along with a written copy. The vignette was in the format of an actual research consent form written to a 5th-grade reading level. The vignette described the purpose, procedures, and anticipated risks and benefits of the hypothetical study, as well as standard consent form information, such as participant rights and options. At the conclusion of the vignette presentation, parents and adolescents independently completed questionnaires that asked about their willingness to participate and about their perceptions of risk associated with the 11 hypothetical study procedures by using a 7-point Likert scale.

Results

Participants were 19 adolescent-parent dyads that are a subset of participants in a larger study of informed consent and assent. Adolescents ranged in age from 11 to 17 years, with a mean age of 13 years (SD = 1.73 years). There were 6 female and 13 male adolescent participants. Table I presents additional demographic information on the participants.

For the adolescents participating in this study, 89% had been given a diagnosis of asthma for at least 2 years. Sixty-three percent of the participants reported using asthma medications several times per day. During the past year, all adolescents had used asthma medications at some time; 95% reported cough-wheeze precipitated by specific activities or objects (eg, pets), 84% reported seasonal cough-wheeze, and 79% reported experiencing severe-recurrent episodes of shortness of breath (Table II). Four

TABLE III. Study I: mean (SD) and *P* values for pairwise comparisons of risk (venipuncture vs asthma research procedures; adolescents vs parents)

	Adolescents*	Parents†
Methacholine	3.89 (1.9)	4.95 (1.8)§
Taking new medicine	3.47 (1.5)	4.32 (1.7)§
Allergy skin testing	2.89 (1.4)	3.37 (2.0)§
Wrist radiograph	1.94 (1.4)	3.16 (1.5)§
Tanner staging	2.11 (1.3)	2.21 (1.6)
Spirometry	1.82 (1.2)	2.00 (1.9)
Venipuncture	2.84 (1.8)	1.84 (1.2)
Psychological tests	1.40 (0.7)‡	1.63 (1.0)
Height-weight measurements	1.21 (0.4)‡	1.00 (0.0)
Blood pressure measurement	1.32 (0.7)‡	1.00 (0.0)
Heart auscultation	1.11 (0.3)‡	1.00 (0.0)

1 = Not at all risky, 7 = extremely risky.

*Multivariate *F* value for adolescents = 10.94, *P* < .001.†Multivariate *F* value for parents = 10.24, *P* < .001.‡Significantly different from adolescent's rating of venipuncture, *P* ≤ .005.§Significantly different from parent's rating of venipuncture, *P* ≤ .005.

(21%) of the parents and 5 (26%) of the adolescents had participated in a research study before this experience, and all of these previous research experiences had been with asthma studies.

The list of asthma research procedures ordered by parent ratings of riskiness is presented in Table III. Distinctions between the risks associated with a variety of research procedures were analyzed with a multivariate analysis of variance (MANOVA) by using SPSS 11.0 for the Macintosh (SPSS, Chicago, Ill). There was a significant effect for the overall rating of riskiness among the asthma research procedures (*P* < .001), although no interaction effect between respondent (adolescent and parent) and risk rating was observed. The within-subject MANOVA indicated that both adolescents and parents made distinctions about riskiness among the asthma research procedures (*P* < .001 and *P* < .001, respectively).

Pairwise comparisons with multivariate analysis were used to explore the relationship between the procedures to better understand these differences. Because venipuncture has traditionally been viewed as a minimal-risk procedure, the list of procedures in Table III was compared with ratings of venipuncture. A Bonferroni correction *P* value of .005 was used for the identification of significant findings to control for the 10 planned comparisons. From an adolescent's perspective, venipuncture was considered no different in risk to methacholine challenge testing, taking a new medicine, allergy-skin testing, a wrist radiograph, Tanner staging, and spirometry. Adolescents rated the other 4 procedures as being significantly less risky than venipuncture (all *P* ≤ .005). By contrast, parents rated methacholine challenge testing, taking new medicine, allergy-skin testing, and wrist radiography as more risky than venipuncture. The remaining procedures were rated by parents as no different in risk from venipuncture.

Parents and adolescents agreed on their rank orders of the 3 most risky procedures. These were methacholine challenge, taking new medicine, and allergy skin testing, al-

though parents gave higher overall risk ratings to all 3 of these procedures. Venipuncture ranked fourth in risk according to adolescents, whereas parents ranked it seventh. With this notable exception, parents and adolescents demonstrated agreement on their risk rankings of all asthma procedures.

STUDY II

A second investigation focused only on evaluations of asthma research procedures, expanding the prior study by incorporating additional procedures, providing more detailed descriptions, and adding a pediatrician comparison group. Medications were differentiated to compare US Food and Drug Administration (FDA)-approved medication to both investigational medication and placebo. The sputum induction procedure was also added. Table E1 in the Journal's Online Repository presents the actual content information for each procedure. Participants were asked to rate the risks and benefits associated with each asthma research procedure. A separate sample of adolescents with asthma and their parents was recruited, along with a comparison sample of university-based pediatricians.

Procedures

Consent and assent procedures for this study were reviewed and approved by the health sciences center human research review committee. Adolescent and parent participants were approached about this study while waiting for a scheduled medical appointment at a pediatric pulmonary clinic. For those agreeing to participate, a separate appointment was made to conduct the research at an office located outside the medical clinic. Informed consent-assent was obtained from parents and adolescents before initiation of study procedures. Parents and adolescents together completed questionnaires about demographic information and asthma history. The family members were then taken to separate rooms, where each participated in a semistructured interview with a research assistant. The Asthma Procedures Questionnaire was administered as follows: A description of each study procedure was read aloud, and then participants were asked to rate the risks and benefits associated with each procedure on a 7-point Likert scale. Pediatricians were mailed the Asthma Procedures Questionnaire and a short demographic questionnaire including questions about their work with children with asthma in the clinic setting, the pediatrician's research experience, and the level of risk associated with the pediatrician's research studies (ie, minimal risk and above-minimal risk). A reminder card was sent to each pediatrician after a 2-week interval to optimize the return rate. Adolescents and parents received compensation for their participation, and physicians received a token gift for their participation.

The Asthma Procedures Questionnaire was developed specifically for the current study and contained a brief description of 10 procedures that were simply described at a 5th-grade reading level (See Table E1 in the Journal's

Online Repository). All participants were asked to read along with the description of each procedure and consider what effect the procedure would have on them before answering 5 questions with a 7-point Likert scale (“not at all” to “extremely”). Two of the questions were used for analysis (eg, “How risky is a blood draw?” “How beneficial is a blood draw?”). In an attempt to help participants personalize their responses, specific instructions for each participant group included unique wording. With the adolescent version of this questionnaire, participants were asked to base their response on what effect they believed the procedure would have on them personally. For parents, the instructions asked that procedures be rated on the basis of what effect the parent believed the procedure would have for their adolescent. In the pediatrician version participants were asked to make ratings on the basis of what effect they believed the procedure would have on their child patients with asthma.

Results

Participants included 36 adolescent-parent dyads recruited specifically for this study from a pediatric pulmonary center at a tertiary children’s hospital. Adolescents ranged in age from 11 to 17 years (mean, 13.17 years; SD, 1.75 years), and parent age ranged from 30 to 60 years (mean, 43.19 years; SD, 7.04 years). All adolescents had a confirmed diagnosis of asthma. Demographic information about these participants is presented in Table I, and characteristics of participant’s asthma are presented in Table II. Statistical comparison of demographic characteristics and illness severity variables yielded no significant differences between the samples in Study I and Study II.

Sixty-seven percent of adolescents and 61% of parents had no previous research participation. Parents reported their adolescent with asthma typically missed 4 days of school in the past year (median), with a maximum of 70 days missed. Adolescent participants had relatively few visits to the emergency department (83% had no visits) and few hospitalizations (95% had none) in the past year. In the 4 weeks before participation in this study, 44% of participants reported no awakenings because of nocturnal asthma symptoms, whereas 6% reported awakenings every night. Asthma symptom frequency was reported as twice a week or less in 53% of participants, with daily asthma symptoms in 25% of participants. In the 12 months preceding study participation, the modal number of times adolescents had completed spirometry was 2 (range, 0-8), with a mode of zero for other asthma research procedures (eg, methacholine challenge testing and skin testing).

Faculty pediatricians within a university children’s hospital ($n = 74$) were approached through a mail survey to participate in this study, with 44 responding (59.5% response rate). The pediatricians ranged in age from 34 to 70 years (mean, 46.73 years; SD, 8.57 years). Female physicians comprised 57% of the sample. Self-reported ethnic identification was 68% white, 16% Hispanic, and 14% Asian, with 2% indicating “other.”

The majority of these pediatricians identified themselves as working in a group practice (95.5%), with

approximately 25% of clinical activity involving adolescents aged 11 to 17 years and 10% of their practice treating children with asthma. Of their child patients with asthma, pediatricians reported 50% with mild asthma and 28% with moderate asthma. Sixty-eight percent of the pediatricians have been actively involved in research, although they spend only 10% of their work week directly involved in research. When asked to report the number of patients they have referred to research studies, 9% indicated they had referred no one, 20% indicated they had referred between 1 and 10 patients, and 5% indicated they had referred more than 20 patients to research studies. For those pediatricians involved in research activities, 75% (median) described their research as minimal risk.

Overview of analysis plan. Several sets of analyses were performed on the data collected for Study II. These involved assessment of within-group differences on risk and benefit ratings, comparisons of risk and benefit ratings across respondent groups, and an overall comparison of perceived risk versus benefit of the asthma procedures. For each set of analyses, a Bonferroni corrected P value of .005 was used for the identification of significant findings. Power analysis determined the sample size was sufficient to detect moderate to large effects (.39 or larger) at 90% probability for both the risk and benefit analyses.

Risk ratings. A repeated-measures MANOVA revealed a main effect for risk ($P < .001$) and a significant interaction between group membership and risk rating ($P < .001$). Closer examination found the 3 participant groups made distinctions among the perceived risks of the asthma research procedures (adolescents, $P < .001$; parents, $P < .001$; pediatricians, $P < .001$); that is, each participant group identified differences in risk among the asthma research procedures. The significant interaction effect demonstrates that participant groups were also distinct from one another on ratings of riskiness. Previous research experience had no effect on risk ratings. To examine each group’s perception of risk associated with the procedures, pairwise comparisons between procedures were explored.

Adolescent, parent, and pediatrician ratings of risk associated with the 10 asthma research procedures appear in Fig 1. By using venipuncture as the standard minimal-risk procedure for pairwise comparisons, adolescents rated 2 procedures (taking an experimental medicine and methacholine challenge testing) as greater in risk than venipuncture and 2 procedures (psychological testing and spirometry) as less risky than venipuncture. By contrast, parents rated 6 of the procedures as greater in risk than venipuncture. Pediatricians rated 5 procedures as greater in risk than venipuncture (experimental medicine, methacholine challenge testing, FDA-approved medicine, placebo, and allergy-skin testing) and 2 procedures (psychological testing and spirometry) as less risky than venipuncture.

Comparisons of adolescent, parent, and pediatrician risk ratings. A comparison of composite risk scores created by summing the risk ratings across all procedures for each participant was not significantly different across

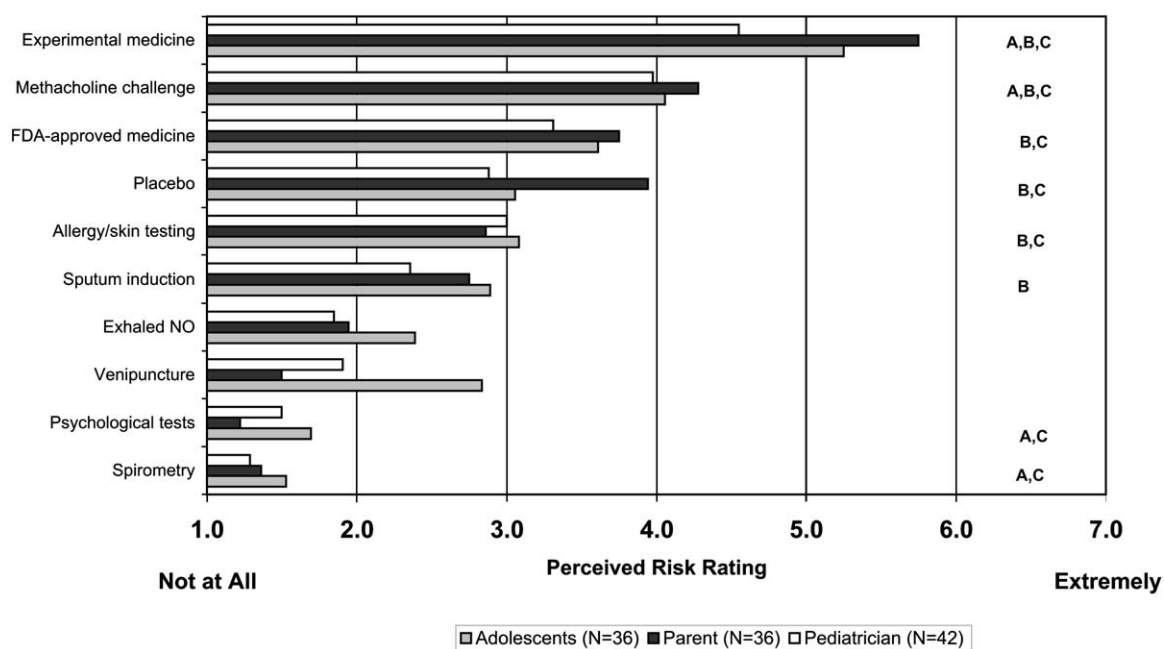


FIG 1. Study I: Mean risk ratings associated with asthma research procedures. Repeated-measures MANOVA: Adolescents: $F(9, 27) = 14.56$, $P < .001$ Parents: $F(9, 27) = 53.69$, $P < .001$ Pediatricians: $F(9, 32) = 52.88$, $P < .001$ P values for pairwise comparisons of risk of venipuncture with research procedures by group (adolescents, parents, and pediatricians). A, Adolescent: rating is significantly different from venipuncture ($P < .005$); B, Parent: rating is significantly different from venipuncture ($P < .005$); C, Pediatrician: rating is significantly different from venipuncture ($P < .005$).

the 3 groups of participants ($P = .10$), suggesting that overall ratings of risk did not differ across the groups. Comparisons of adolescent, parent, and pediatrician ratings of risk associated with individual procedures were subsequently examined. Taking an experimental medication was rated as the most risky procedure by all 3 groups. However, there was also a highly significant difference in the risk rating for experimental medicine between parents and pediatricians ($P < .001$), with parents rating this risk significantly greater. Adolescent mean ratings for the risk associated with taking experimental medicine fell in between pediatricians' and parents' ratings and were not significantly different from the ratings of either group. Adolescents rated venipuncture as significantly more risky than did parents ($P < .001$) and pediatricians ($P < .005$).

Benefit ratings. Participants were also asked to rate their perception of benefit associated with the same set of 10 procedures (Fig 2). By using repeated measures MANOVA, overall differences in benefit ratings were observed ($P < .001$), as was a significant interaction between benefit and group membership ($P < .001$). Further analyses revealed that parents and pediatricians made significant distinctions among the benefits associated with research procedures (parents, $P < .001$; pediatricians, $P < .001$). Parents' ratings of the benefit of asthma research procedures were consistently higher than ratings made by adolescents and pediatricians.

Comparisons of adolescent, parent, and pediatrician benefit ratings. When the responses of adolescents,

parents, and pediatricians were compared on each of the benefits, 5 items exhibited between-group differences: venipuncture ($P < .001$), spirometry ($P < .001$), exhaled nitric oxide ($P < .01$), taking placebo ($P < .001$), and psychological testing ($P < .01$). These between-group differences were subsequently examined with the Tukey Honestly Significant Difference (HSD) test for post-hoc comparisons. Parents considered venipuncture more beneficial than did either adolescents or pediatricians ($P < .05$ and $P < .001$, respectively). Both parents and pediatricians reported a high degree of benefit for spirometry, with both groups rating this procedure as significantly higher in benefit than did adolescents ($P < .001$ and $P < .001$, respectively). For exhaled nitric oxide, parents rated this as a more beneficial procedure than did adolescents ($P < .01$) or pediatricians ($P < .01$). Adolescent and parent ratings for the benefit of taking a placebo were significantly higher than the ratings made by pediatricians ($P < .001$ and $P < .01$, respectively). Finally, psychological testing was viewed as most beneficial by parents, who rated this as more beneficial than adolescents ($P < .01$).

Risk versus benefit ratings. Average risk and benefit scores were developed from ratings of the 3 participant groups. In this manner we were able to compare a global measure of risk ($M = 2.86$; $SD = 0.84$) with a global measure of benefit ($M = 4.59$; $SD = 1.04$), with results from a t test indicating that participants generally viewed asthma research procedures as more beneficial than risky ($P < .001$). Comparing Figs 1 and 2 suggests that

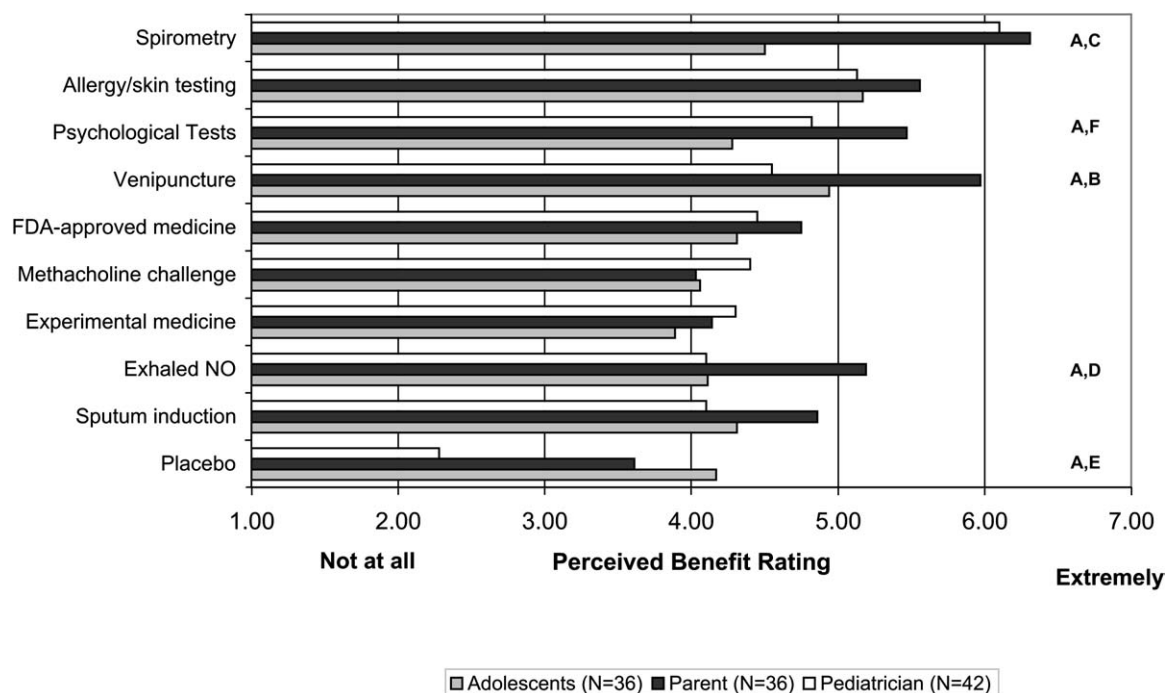


FIG 2. Study II: Mean benefit ratings associated with asthma research procedures. *P* values for 1-way ANOVA for each benefit rating among groups (adolescents, parents, and pediatricians). *A*, *P* < .001. Multiple comparisons for each asthma research procedure with the Tukey HSD test for post-hoc comparisons: *B*, Venipuncture: Parents > adolescents-pediatricians Parents > adolescents, *P* < .05 Parents > pediatricians, *P* < .001 *C*, Spirometry: Parents > adolescents-pediatricians Parents > adolescents, *P* < .001 Parents > pediatricians, *P* < .001 *D*, Exhaled nitric oxide (NO): Parents > adolescents-pediatricians Parents > adolescents, *P* < .01 Parents > pediatricians, *P* < .01 *E*, Placebo: Adolescents-parents > pediatricians Adolescents > pediatricians, *P* < .001 Parents > pediatricians, *P* < .01 *F*, Psychological tests: Parents > adolescents Parents > adolescents, *P* < .01 Parents = pediatricians and adolescents = pediatricians.

participants made distinctions between procedures when asked to evaluate the risk versus benefit. Across the 3 groups, a comparable amount of benefit and risk was associated with methacholine challenge testing and taking placebo. Seven of the 10 procedures were consistently rated as being more beneficial than risky by each group: venipuncture (*P* < .001), spirometry (*P* < .001), allergy skin testing (*P* < .001), exhaled nitric oxide (*P* < .001), sputum induction (*P* < .001), taking FDA-approved medicine (*P* < .001), and psychological testing (*P* < .001). Taking experimental medicine was rated as significantly more risky than beneficial by adolescents and parents (*P* < .001), whereas pediatricians indicated no difference between the risk and benefit of taking an experimental medication.

DISCUSSION

These 2 studies represent one of the first attempts to empirically evaluate perceptions of risks and benefits associated with standard pediatric asthma research procedures. The findings provide important new insights on similarities and differences in viewpoints among adolescents, parents, and pediatricians in ratings of risks and

benefits associated with these procedures. Using 2 different presentation formats, we compared evaluations of the risks and benefits associated with asthma research procedures within each respondent group. We further compared differences in ratings between respondents to determine important differences in viewpoints.

Evaluation of risk

Study I and Study II addressed questions of perceptions of relative risk among the various procedures. Not surprisingly, all respondents differentiated among the asthma research procedures. To both limit the number of analyses conducted and provide conceptually useful findings, we chose to benchmark the individual risk ratings by comparing each rating with that of venipuncture, which is a standard minimal-risk procedure. Adolescents' mean risk rating for venipuncture was similar in both studies. However, the comparative analyses differed. In Study I venipuncture was rated similarly to more common above-minimal-risk procedures, such as experimental medicine and methacholine challenge, whereas in Study II comparisons venipuncture was rated as significantly different from both minimal-risk and above-minimal-risk procedures. These differences appear to be the result of greater power in Study II because of a larger sample size and

higher risk ratings for experimental medicine in Study II, rather than because of differences in venipuncture ratings across the 2 studies. Both adolescents and parents rated the risk of experimental medicine much higher in Study II. This is likely due to differences in wording. Although the potential for unknown risks was described in both studies, Study I referred to the testing of a “new medicine,” whereas Study II used the term “experimental medicine.” Study II further emphasized distinctions between FDA-approved and experimental medicine. One interpretation of this finding is that variations in descriptive language might have a potentially powerful effect on influencing perceptions of risk for both parents and adolescents.

With the notable exception of venipuncture, parents and adolescents demonstrated significant agreement in their relative rankings of risk across Study I procedures. Adolescents' ratings for the risk of venipuncture were significantly greater than those of parents and pediatricians in Study II. The adolescents' ratings for venipuncture were not excessive; rather, the difference appears to be a function of extremely low ratings by parents and pediatricians. Adolescents might be more focused on the potential discomfort of the procedure when asked about their perception of risk.^{10,11} It is unknown whether the differences in venipuncture ratings would translate to an unwillingness to participate in research. However, these findings identify an important area of potential disagreement between parents, pediatricians, and adolescents concerning risk ratings. They further suggest the need for IRBs to attend to adolescents' discomfort with the procedure and carefully scrutinize the inclusion of venipuncture in research studies, especially when multiple blood draws are proposed.

In another important difference of opinion on risk, Study II findings revealed that parents' ratings on the risk of experimental medication were significantly higher than pediatrician's ratings. The mean parent rating was a very high 5.75 (SD, 1.32) out of a possible score of 7 compared with the pediatrician mean of 4.50 (SD, 1.10). It is reasonable to assume that perceptions of risk are likely to influence the decisions to participate in clinical research. That parents appear sensitive to potential risk might reflect a natural focus on protecting children from harm. Moreover, pediatricians' breadth of education, training, and prior experience with the asthma procedures and research likely influences their assessments of risk in general, promoting a greater level of trust that research procedures are safe. This finding further emphasizes that investigators can expect parents to possess an increased level of concern over the use of experimental medication and will need to give careful attention to their descriptions of the procedure and safety precautions to facilitate enrollment into asthma clinical trials.

Evaluations of benefit

Parents provided the highest benefit ratings for almost all of the procedures, with adolescents and pediatricians tending to be more similar in their ratings. In one notable

exception, however, both parents and adolescents rated the benefit of taking a placebo as significantly greater than did pediatricians. The finding suggests a lack of understanding surrounding the purpose of using a placebo and might reflect a lack of appreciation for the scientific purpose of the study or a misunderstanding that not all aspects of a medication protocol can expect to benefit a participant. This overestimation of the benefits of placebo has significant implications for informed consent and deserves more thorough evaluation.

It was also surprising that adolescents' rating of the benefit of spirometry was substantially lower than that of both parents and physicians, especially because it is central to the diagnosis and management of the disease and all participants had prior experience with the procedure. One interpretation of this finding is that adolescents do not fully appreciate the connection between medical procedures, diagnosis, and treatment, suggesting that pediatricians and asthma clinical researchers might want to spend more time educating their patients about the purpose of the procedure. On a more global level, adolescents' benefit ratings across all the asthma procedures demonstrated the least variability. Significant between-group differences in benefit ratings reflected variability in parent and pediatrician ratings across procedures rather than adolescents' ratings, implying that adolescents might be unclear about how to evaluate benefits generally.

Limitations

Several salient features of the 2 studies require acknowledgement. Prior experience with asthma research procedures might have an effect on their interpretation, perceived riskiness, or discomfort.^{12,13} Our samples were relatively research naive and had little experience with some of the procedures (eg, methacholine challenge testing). Individuals with more experience might have responded differently. In addition, neither of the studies examined influential aspects of a consent process, such as a participant's prior relationship with an investigator, or features of the consent process, such as a participant's opportunity to have a dialogue with an investigator. These components of the consent process might affect the perceptions that adolescents and parents have regarding the risks and benefits associated with asthma clinical research and thereby affect the decision-making process.

Conclusions

When physicians invite parents and adolescents to participate in pediatric asthma research, they are responsible for ensuring that participants have a full appreciation for the risks and benefits of the study. Moreover, families might expect physicians to provide advice on the basis of their experience and expert knowledge. Previous research has suggested that miscommunication might arise between adolescents and physicians when the probability of risk is described.¹⁴⁻¹⁶ One factor contributing to the miscommunication might be a lack of appreciation for some differences in risk perceptions among parents, adolescents, and

physicians. Awareness of differences in perspective on risk and benefit, especially for the procedures of venipuncture, experimental medication, and placebo, and attention to clarifying the purpose and probable risks and benefits of these procedures during the consent process will help ensure that parents and adolescents do not overestimate either the risks or benefits associated with asthma research procedures. Beyond the differences in perspectives on individual procedures described above, there was substantial agreement among all respondents concerning the relative rankings of risk associated with many of these procedures. These relative rankings of risks and benefits provide some of the first empiric guidance to IRBs and national agencies seeking to establish a uniform categorization of risk for research procedures, as well as some preliminary information for evaluating risk/benefit ratios associated with research protocols.

We wish to thank Jess Irwin, Melody Pearson-Bish, Mandy Perryman, and staff and patients from the Pediatric Pulmonary Center at the Children's Hospital of New Mexico for their time invested in these studies.

REFERENCES

1. Weijer C. The ethical analysis of risk. *J Law Med Ethics* 2000;28:344-61.
2. Michaels TF, Oetting ER. The informed consent dilemma: an empirical approach. *J Social Psych* 1979;109:223-30.
3. Sullivan DS, Dieker TE. Subject-experimenter perceptions of ethical issues in human research. *Am Psychol* 1973;28:587-91.
4. Kodish E. Informed consent for pediatric research: is it really possible? *J Pediatr* 2003;142:90-8.
5. Brody JL, Scherer DG, Annett RD, Pearson-Bish M. Voluntary assent in biomedical research with adolescents: a comparison of parent and adolescent views. *Ethics Behav* 2003;13:75-91.
6. Department of Health and Human Services, Code of Federal Regulations, Title 45, Part 46. Protection of human subjects (OPRR Reports). Washington, DC: US Government Printing Office; 1994.
7. Freedman B, Fuks A, Weijer C. In loco parentis. Minimal risk as an ethical threshold for research upon children. *Hastings Center Report* 1993;23:13-9.
8. Office for Human Research Protections (2001). IRB guidebook. Chapter VI: Special classes of subjects. Available at: http://ohrp.osophs.dhhs.gov/irb/irb_guidebook.htm.
9. Churchill LR, Nelson DK, Henderson GE, King NMP, Davis AM, Leahey E, et al. Assessing benefits in clinical research: why diversity in benefit assessment can be risky. *IRB: Ethics Hum Res* 2003;25:1-8.
10. Lander J, Fowler-Kerry S, Oberle S. Children's venipuncture pain: influence of technical factors. *J Pain Symptom Manage* 1992;7:343-9.
11. Fradet C, McGrath PJ, Kay J, Adams S, Luke B. A prospective survey of reactions to blood tests by children and adolescents. *Pain* 1990;40:53-60.
12. Goodenough B, Thomas W, Champion GD, Perrott D, Taplin JE, von Baeyer CL, et al. Unraveling age effects and sex differences in needle pain: ratings of sensory intensity and unpleasantness of venipuncture pain by children and their parents. *Pain* 1999;80:179-90.
13. Kolk AMM, van Hoof R, Fiedeldij Dop MJC. Preparing children for venipuncture: the effect of an integrated intervention on distress before and during venipuncture. *Child Care Health Dev* 2000;26:251-60.
14. Abramovitch R, Freedman JL, Henry K, Van Brunschot M. Children's capacity to agree to psychological research: knowledge of risks and benefits and voluntariness. *Ethics Behav* 1995;5:25-48.
15. Cohn LD, Schydlowerm M, Foley J, Copeland RL. Adolescents' misinterpretation of health risk probability expressions. *Pediatrics* 1995;95:713-6.
16. Fogas BS, Oosterheld JR, Shader RI. A retrospective study of children's perceptions of participation as clinical research subjects in a minimal risk study. *J Dev Behav Pediatr* 2001;22:211-6.