FINANCIAL COMPENSATION TO ADOLESCENTS FOR PARTICIPATION IN BIOMEDICAL RESEARCH: ADOLESCENT AND PARENT PERSPECTIVES IN SEVEN STUDIES

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Objective To examine the impact of financial compensation on pediatric asthma research participation decision-making and determine whether perceptions of fair compensation differed for parents and adolescents, lower and higher income participants, and compensation-informed and uninformed participants in minimal and above minimal risk research.

Study design Adolescents (n = 36) with asthma and their parents reviewed 7 pediatric asthma research protocols, decided whether they would choose to participate, and provided estimates of “fair” compensation for their participation. Chi-square, analysis of variance, and analysis of covariance were used to determine the affects of compensation on participation and whether various respondents differed in the perceptions of fair compensation.

Results Financial compensation did not affect participation decisions. Estimates of fair compensation were lower for adolescents, lower income respondents, and participants who were naïve about potential compensation. Fair compensation estimates were higher than actual compensation for minimal risk studies and lower for above minimal risk studies.

Conclusions Financial compensation may be a minor consideration in pediatric research participation decision-making. Still, differences in how pediatric researchers and their prospective participants judge fair compensation create the potential for undue influence. Pediatric researchers should use caution when determining a reasonable financial compensation for research participation. (J Pediatr 2005;146:552-8)

Research ethicists have questioned the influence of financial compensation for research volunteers. Some have contemplated whether people with fewer economic resources may be exploited, whether financial compensation may lead prospective participants to overlook potential risks in favor of financial gain, and whether financial compensation undermines altruistic motives. Others assert that research participation imposes costs on participants, that monetary payments are offers that expand options, not threats that coerce, and that research participation is analogous to unskilled labor, consequently compensation should approximate minimum wage.

Financial compensation to children and adolescents for research participation is even more problematic. Children and adolescents may be more susceptible to the allure of any monetary gain for research participation, and even minimum wage-based payments may result in large sums of money being offered to children and adolescents for compensation. Small amounts of money may be sufficient to induce children and adolescents to overlook research risks, and the promise of monetary gain may deter children and adolescents from withdrawing from participation when they believe they are compelled to continue to receive their “pay.” Finally, child and adolescent research participation requires surrogate decision-making by parents, which may lead to conflict and undue influence to assent or consent when parents and children or adolescents disagree about research participation.

Although researchers doubt that financial compensation is a compelling factor in research participation decision-making, this has not been empirically tested. In this report, we present findings from a larger study of adolescent assent, in which we examined the

TSDS Transformed standardized difference scores

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perspectives of adolescents with asthma and their parents about what constitutes “fair” compensation for participation in a variety of pediatric asthma research studies. We hypothesized that knowing financial compensation will be provided would affect participation decisions and that people who would choose to participate may seek more or less compensation than people who would not. We also hypothesized that adolescents would deem fair compensation to be less than parents, that low-income families would estimate fair compensation to be less than higher income families, that respondents naïve about research compensation would provide estimates of fair compensation less than respondents who were told what to expect, and that estimates of fair compensation in above minimal risk studies would be higher than in minimal risk studies.

METHODS

This study, including its assent and consent procedures, was reviewed and approved by the University of New Mexico Health Sciences Center Human Research Review Committee. Child and parent participants were recruited from a children’s hospital pediatric pulmonary outpatient clinic that serves as the statewide referral center for children with asthma. For those agreeing to participate, a separate appointment was made to conduct the research at an office located outside the medical clinic. Two families indicating early interest later declined to participate in the study.

Development of Stimulus Materials

Nine pediatric asthma protocols were selected from a sample of 37 consent forms obtained from pediatric asthma researchers in the United States and England and used in publicly and privately funded studies conducted during the 1990s and 2000. Studies were identified via a Medline literature review, and consent forms were requested from those for whom contact information was available and by contacting prominent asthma researchers known to the authors. Specific attempts were made to obtain consent forms from studies that involved varied designs and procedural elements.

A representative sample of the protocols for this study was selected by a panel of 8 physicians, clinical pharmacists, and psychologists recognized as having expertise in ethics, pediatric asthma research, or both. The panel unanimously rated 5 of the 9 studies as minimal-risk research and 4 as above minimal risk. Although institutional review boards vary in how minimal and above minimal risk is defined, the value of our panel’s distinctions lies in its having distinguished between those studies that involve higher risk from those that involve less risk. Similarly, both parent and adolescent respondents rated the minimal risk studies as having less risk than the above minimal risk studies.25 Data were collected from all 9 studies, but 2 studies were dropped from the analyses reported here because they lacked any financial compensation. The remaining studies involved the use of typical asthma research procedures, including medication trials comparing standard medications with a placebo control (Table 1).

Vignettes were developed from each of the selected protocols and were presented to adolescents and parents in a standardized written format. An informative study title was followed by a brief statement of the reason for the study, study procedures in bullet format, and a description of study incentives. Study procedures were described in detail in a separate part of our study and included explanation of the potential risks involved in undergoing a procedure. Medication trials included a description of the medications and any known risks or adverse effects. Participation requirements were summarized after a presentation of all information in the research vignette. The vignettes remained faithful to the original research protocol, although information provided was formatted differently, and in some cases, procedure descriptions were more detailed than in the original consent form.

Measures

Measures included a 15-item Demographic Questionnaire and a 33-item Asthma History Questionnaire developed from the Guidelines for the Diagnosis and Management of Asthma and included items pertaining to current asthma medications, experiences with various asthma-related procedures, and prior participation in asthma research. The Asthma Research Procedures Questionnaire assessed the participant’s evaluation of the risks and benefits associated with 11 asthma research procedures, the results of which are presented elsewhere.27 A 12-item Asthma Vignette Questionnaire evaluated participant responses to each of the 7 study vignettes. Ten Likert scaled questions assessed participants’ perceptions of study risks, benefits, discomforts, and burdens, their willingness to participate, and to what extent a parent or child’s opinion would influence their decision. One yes/no question asked participants to decide whether they would choose to participate in the study. Finally, each participant indicated what they believed to be fair compensation for participating in the hypothetical study (“In your opinion, what amount of money is fair compensation for a person participating in this study?”) This paper reports on the subset of this data about participants’ estimates of fair compensation.

Procedures

Adolescents and parents met together with a research assistant to review and sign informed assent and consent documents. Parents completed the demographic form, and the parent and adolescent together completed the Asthma History Questionnaire. Parents and adolescents were then separated and presented with the study vignettes. Presentation orders of the vignettes were altered with a standard Latin square design. Half of the participants were told the actual amount of money offered for participation in each study (“told” condition); the other half were informed only that they would be “fairly compensated” for their time, effort, and expenses incurred (“not told” condition). After hearing each vignette, responses were obtained for the Asthma Vignette Questionnaire. After completing the study, each parent and adolescent participant received $25.
Chi-square analyses were used to determine whether participants who were told the amount of financial compensation would choose to participate more or less often than those who were kept naïve. The alpha level was set at .007 via a Bonferoni adjustment to minimize the potential for type I error. Analysis of variance was used to determine whether respondents who would decline participation in a study estimated fair compensation differently than those who indicated they would participate. Again, the alpha level was adjusted to minimize the potential for type I error.

Several steps were required to transform the estimates of fair compensation into a dependent variable that could be used to examine the differences among study participants and across the 7 research protocols. For each participant, a difference score was calculated, subtracting the actual amount of compensation from the expected amount of compensation (Table II). To ensure consistent comparisons across vignettes, standardized difference scores were calculated by dividing respondents’ difference scores for each vignette by the SD for difference scores associated with that vignette. These standardized difference scores were then weighted by 2 and transformed into base 10 logarithms to correct distorting skew in the data caused by statistical outlying responses, yielding transformed standardized difference scores (TSDS) used as the dependent variable in subsequent analyses.

A mixed effect analysis of covariance with an alpha level of .05 was used to evaluate our 4 independent hypotheses. Interaction effects were included in our statistical model to control for any statistical influence they may have on main effects, but in the absence of hypotheses on interaction effects, we did not use these tests of significance.

### Table I. Summary description of research protocols and procedures

<table>
<thead>
<tr>
<th>Protocol descriptions</th>
<th>Required procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimal-risk studies</strong></td>
<td></td>
</tr>
<tr>
<td>Can some medicine make it harder to learn?</td>
<td>Random assignment to 1 of 2 “over-the-counter” medicines (diphenhydramine or loratadine) or placebo; allergy skin testing; psychological testing</td>
</tr>
<tr>
<td>What are the characteristics of adolescents with mild to severe asthma?</td>
<td>Eight clinic visits including physical examination, spirometry, and asthma symptom/treatment questionnaires at each visit; 1 blood test</td>
</tr>
<tr>
<td>Can a HRCT help in studying asthma?</td>
<td>Spirometry test; HRCT x-ray</td>
</tr>
<tr>
<td>How much cortisol and nitric oxide do I have in my body</td>
<td>Twenty-four hour urine collection; 1 spirometry test; 3 peak flow measures; nitric oxide levels measured every 4 hours</td>
</tr>
<tr>
<td><strong>Above minimal risk studies</strong></td>
<td></td>
</tr>
<tr>
<td>Which of these medicines works better?</td>
<td>Medication change every 4 weeks; 3 overnight hospital stays; 8 spirometry tests; 8 Nitric Oxide measures; 6 — 24hr urine collections</td>
</tr>
<tr>
<td>How often should asthma medicine be taken?</td>
<td>Random assignment to treatment; medical history; 12 physical examinations; 12 spirometry tests; 7 methacholine challenge tests; 1 allergy skin test; 1 electrocardiogram; 1 quality of life questionnaire; 7 urine pregnancy tests</td>
</tr>
<tr>
<td>How effective are these treatments for asthma over time?</td>
<td>Random assignment to treatment; 6 comprehensive physical examinations; 2 allergy skin tests; 6 Tanner Staging examinations; 6 spirometry tests; 2 blood draws; 5 psychological tests; 6 methacholine challenge tests; 2 neuropsychological tests; 6 bone density measurements</td>
</tr>
</tbody>
</table>

HRCT=High Resolution Computer Tomography; FDA=US Food and Drug Administration.
Results

Participants

Participants in this study included 36 adolescents with asthma and their parents or guardians; 68 (94%) of the adolescents’ parents or guardians were parents, the remainder were identified as grandparents. Most parents were mothers (65%); the remainder were identified as fathers. The 4 grandparents were equally split between men and women. The mean age of parents was 43.2 years (SD, 7.04; range, 30-60 years). Twenty-two (61%) of the 36 adolescents were male. The adolescent mean age was 13.2 years (SD, 1.75; range, 11-17 years). The ethnic constitution of our sample mirrored the population in the Southwest United States and consisted of whites (43.4%), Hispanics (40.3%), Blacks (2.8%), Asians (5.6%), and other/mixed ethnicity (8.3%). One adolescent participant responded to only 2 of the 7 protocols and was dropped from subsequent analyses. One parent participant declined to provide estimates of fair compensation and consequently was dropped from the subsequent analyses. Two adolescents provided 3 facetious estimates of fair compensation ($20,000, $25,000, and $30,000) for 2 of the above minimal risk studies. These 3 responses were also dropped from further analyses.

Participation Analyses

Our chi-square analyses revealed that a difference in willingness to participate on the basis of knowing the compensation amount existed in only 1 vignette (the minimal risk, Can some medicines make it harder to learn? vignette; \( \chi^2 = 10.3; P = .002 \)). In this vignette, respondents who were not told the financial compensation were more likely to indicate they would decline participation in this study, whereas the participants who were told what to expect were more inclined to participate. There were no significant findings for the analysis of variance that tested whether those who declined to participate estimated fair compensation differently than those inclined to participate.

Financial Compensation Analysis

Because respondents with prior research experience might have a better ability to estimate actual compensation than those with no prior experience, we examined the effect of previous research experience on the TSDS. Respondents were split into dichotomous groups, those with and those without previous research experience (66.7% of adolescents and 61.1% of parents had no previous experience). Adolescents with previous research experience expected more compensation for their participation (\( P < .045 \)). Because an adolescent’s prior research experience had a significant effect on standardized compensation scores, we opted to include this variable as a covariate in all subsequent analyses (Table III).

Adolescents in our sample designated fair compensation values (mean TSDS, .236; SE, .016) that were significantly lower than those designated by parents (mean TSDS, .301; SE, .015). Families with an annual income of $40,000 or less per year also provided estimates of fair compensation (mean TSDS, .227; SE, .019) that were significantly less than families with an annual income >$40,000 per year (mean TSDS, .318; SE, .019). Respondents who were not told what they would receive for financial compensation estimated fair compensation (mean TSDS, .331; SE, .020) significantly lower than those respondents who were told what to expect (mean TSDS, .214; SE, .020). Within-subject analyses revealed that, contrary to our hypothesis, the TSDS for minimal-risk studies (mean TSDS, .236; SE, .016) were greater than the TSDS for above-minimal risk studies (mean TSDS, .236; SE, .016). That is, estimates of fair compensation exceeded the actual compensation more often in minimal-risk studies than in above minimal risk studies.

### Table II. Means and standard deviations for difference between actual compensation and estimates of “fair” compensation in dollars

<table>
<thead>
<tr>
<th>Vignette title (actual compensation)</th>
<th>Adolescents</th>
<th>Parents</th>
<th>Lower income (&lt;$40,000)</th>
<th>Higher income (&gt;=$40,000)</th>
<th>Not told actual compensation</th>
<th>Told actual compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimal risk studies</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Learn ($550)</td>
<td>-205/224.9</td>
<td>-118/321.5</td>
<td>-253/240.4</td>
<td>-84/288.5</td>
<td>-316/304.0</td>
<td>-15/144.8</td>
</tr>
<tr>
<td>Characteristics ($105)</td>
<td>116/229.8</td>
<td>72/141.2</td>
<td>67/189.8</td>
<td>116/191.0</td>
<td>110/244.9</td>
<td>78/120.7</td>
</tr>
<tr>
<td>HRCT ($35)</td>
<td>6/29.3</td>
<td>8/27.3</td>
<td>2/26.1</td>
<td>11/29.4</td>
<td>12/35.4</td>
<td>3/18.5</td>
</tr>
<tr>
<td>Cortisol and NO ($100)</td>
<td>11/63.0</td>
<td>120/209.0</td>
<td>18/84.8</td>
<td>105/199.5</td>
<td>52/134.2</td>
<td>78/186.8</td>
</tr>
<tr>
<td><strong>Above minimal risk studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicines ($300)</td>
<td>-23/205.7</td>
<td>291/681.9</td>
<td>-37/222.3</td>
<td>278/651.9</td>
<td>100/580.3</td>
<td>166/471.6</td>
</tr>
<tr>
<td>How often ($1000)</td>
<td>-453/415.7</td>
<td>-401/390.6</td>
<td>-506/417.0</td>
<td>-358/379.0</td>
<td>-719/261.1</td>
<td>-143/295.3</td>
</tr>
<tr>
<td>How effective ($400)</td>
<td>502/1723.8</td>
<td>971/2066.1</td>
<td>260/911.2</td>
<td>1149/2390.3</td>
<td>845/2456.8</td>
<td>648/1214.4</td>
</tr>
</tbody>
</table>

NO = nitric oxide.
DISCUSSION

United States and Canadian regulations reflect concern about undue influence, but permit financial compensation for participation in research studies. \(^{15}\) In contrast, the European Union prohibits providing children and adolescents with financial compensation for research participation. Practices on financial compensation for pediatric asthma research differ considerably. The 37 consent forms reviewed for this study used no compensation (7-15 studies), a small gift certificate (1 study), or financial compensation ranging from $20 to $2400 (21 studies). Most of the consent forms solicited for this study did not indicate the time commitment required for completion of the study, making it difficult to calculate financial compensation on an hourly basis. However, interpolating from the studies that did offer an expectation of time involvement, we calculated “best-guess” estimates of hourly compensation and found widely varied hourly rates of compensation (all studies: mean, $32.05/hour; range, $2.65-$100.00/hour; 7 studies used in these analyses: mean, $18.76/hour; range, $2.78-$50.00/hour).

Financial compensation is only one consideration among a complex variety of factors that adolescents and their parents use to decide about research participation. For example, human immunodeficiency virus-positive and -negative adolescent research participants revealed that financial compensation was a relatively minor factor in their decisions to participate in research, compared with the importance of their relationship with research personnel. \(^{28}\) This may also be true in most studies on pediatric asthma. In only 1 study of the 7 we analyzed did knowing the amount of financial compensation make a difference in choosing to participate. Nor did we detect any differences in the estimates of fair compensation between participants who would enroll in a study versus those who would not. Our study was not designed to detect the extent to which financial compensation may constrain autonomous decision-making, but it appears that the actual compensation in our selected studies was not perceived to be irresistible or coercive in nature. However, this issue continues to warrant special attention for studies that offer large sums of financial compensation. Our results suggest that when concerns exist that financial compensation may unduly influence participation decisions, pediatric researchers could opt to inform potential participants that financial compensation will be provided, but choose to not indicate the exact amount, without discouraging enrollment.

The pediatric asthma studies we sampled revealed important differences in what prospective participants estimate to be fair compensation. Adolescents’ estimates were significantly less than those of parents. Lower income respondents estimated fair compensation as significantly lower than respondents from higher incomes families. The compensation-naïve participants in our study indicated fair compensation values that were significantly lower than the amounts stated by participants who were told what to expect.
Also, our participants responded differently to minimal risk studies versus above minimal risk studies. When financial compensation exceeds the value prospective participants place on their involvement, the potential exists that financial compensation will become a more salient and complicating factor in their participation deliberations and may inhibit altruistic and intrinsic motivations that enhance enrollment and retention. This may not be particularly troublesome for minimal risk studies in which the amount of financial compensation is fairly modest and the risks of participation are negligible, but may be problematic in above minimal risk studies that tend to offer substantial compensation for research participation.

Several cautions must accompany the interpretation of these data. Although our sample was ethnically diverse, it may not be representative of research participants in other parts of the United States. The adolescents in our sample were young. Older adolescents may place an entirely different value on research participation. Prospective participants might respond differently to actual research participation decisions than they did to our hypothetical research decisions. Although our effect sizes were in some cases quite robust (told versus not told, lower versus higher income), in other cases the effect sizes were modest (parent versus adolescent). Also, the participants in this study received a small stipend for their participation, and it’s possible this affected our “told” versus “not told” analysis. Further research is needed to clarify the ability to generalize these findings to pediatric research.

In the meantime, the most central questions we continue to face are clarifying the circumstances under which offering financial compensation is ethically appropriate and determining how to calculate financial compensation in a variety of contexts that is both respectful of participants and facilitates research participation without compromising authentic decision-making. Cognitive psychologists assert that people use different heuristics for determining value.29 In some circumstances, value rises as the scope of what is being evaluated increases. Providing more money for longer periods of effort is an example of this type of “valuation by calculation” that theoretically has no upper limit. However, people often use “valuation by feeling” or affective valuation, particularly in situations that evoke strong emotional responses, which is relatively unaffected by scope and results in an upper limit on the value placed on a stimulus. The differences found in how our respondents perceived “fair” compensation may be caused by using these different heuristics. For example, pediatric researchers may be more inclined to assign a financial compensation amount on the basis of calculation and scope of what participants are being asked to do, whereas many prospective participants may estimate appropriate financial compensation on the basis of emotion. These different formulas used for determining the value placed on research participation may result in researchers “calculating” a financial compensation figure that may exceed what participants “feel” is fair.

Pediatric researchers must engage in a thoughtful analysis of how financial compensation may affect potential research participants and use prudence in determining that amount. Because of the variability in pediatric research and the current lack of consensus on appropriate compensation amounts, institutional review boards may need to empirically evaluate community standards on appropriate compensation for studies involving children and adolescents. Creating a more uniform and empirically based process for determining financial compensation will minimize the potential for coercion in the decision-making process and strengthen the ethical grounding of pediatric research.

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50 Years Ago in The Journal of Pediatrics

**MORQUIO’S DISEASE**


In 1955, clinical findings and radiographs were the only methods used for classifying skeletal dysplasias. Consensus was usually reached with classical radiographs. Unfortunately, then, as today, too many children with dysplasias had subtle or atypical findings that delayed or obscured a diagnosis. Such was the dilemma faced by Dr Lipschutz at Hahnemann Hospital in Philadelphia when confronted with a 15-month-old boy and his 7-year-old sister. Both children had with marked kyphoscoliosis, generalized hypotonia, severe developmental delays, and normal eyes during their second year of life. Both had abnormal radiograph findings, with flattened and wedge-shaped thoracic and lumbar vertebrae and flattened acetabular cavities. Their long bones were less severely involved. Lipschutz relentlessly pursued a diagnosis. He showed the radiographs to 5 prominent pediatric radiologists, 3 of whom felt that the features were diagnostic of Morquio’s disease. The other 2 had entirely different opinions.

Today, the diagnosis of Morquio’s disease, also know as mucopolysaccharidosis type IV (MPS IV types A and B), and of other lysosomal enzyme disorders is usually more straightforward. Symptoms in children affected with MPS IV usually present in the second year of life, with mild coarse facies, hearing loss, mild hepatomegaly, inguinal hernias, and normal intellect. Characteristic radiographic findings include platyspondyly, kyphoscoliosis, coxa valga, odontoid hypoplasia, and cervical subluxation that can cause cervical myelopathy. Increased urinary excretion of 2 glycosaminoglycans (keratin and chondroitin 6-sulfate) and deficient enzyme activity of either N-acetylgalactosamine-6-sulfatase in type A and of Beta-galactosidase in type B confirm the diagnosis. Mutational analysis is available. Although lysosomal replacement enzyme therapy is not yet available for MPS IV, multispecialty management improves the quality of life and minimizes complications.

Why do we, as Lipschutz did in 1955, try so hard to confirm a diagnosis? It is not only of academic interest. It is critical for parents to pursue the best and most experienced care for their child with a rare disorder, to consider their reproductive options, and to network with other families. Because both of these children were profoundly delayed, had normal eyes, and neither had evidence of cervical subluxation, I doubt that they had Morquio’s disease. Although Lipschutz may have never achieved a final diagnosis, it was his pursuit of a diagnosis that was remarkable and, I suspect, most appreciated by his colleagues and fellow caregivers.

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