Higher-Hazard, No Benefit Research Involving Children: Parental Perspectives

WHAT’S KNOWN ON THIS SUBJECT: Higher-hazard, no-benefit research involving children may be approved by local institutional review boards only when the protocol enrolls children with the medical condition under study. The ethics of this distinction have been debated, but parental opinions have not been explored.

WHAT THIS STUDY ADDS: We found that parental opinions support federal regulations. We discuss parental motivations for and against research participation and the extent to which enrolling a child in higher-hazard, no-benefit research reflects appropriate surrogate decision-making.

abstract

OBJECTIVES: US regulations allow local institutional review boards to approve greater than minimal risk, no-benefit research when the research enrolls children with the condition under study but not when it enrolls healthy children. We aim to describe the opinions of parents regarding higher-hazard, no-benefit research.

METHODS: Quantitative and qualitative interviews with parents of children without heart disease or chronic medical conditions (no heart disease [noHD], n = 30), children with fully correctable heart disease (FCHD, n = 30), and children with life-altering heart disease (LAHD, n = 30).

RESULTS: Parents of children with heart disease endorse higher-hazard, no-benefit heart disease research more strongly than noHD parents. Eight of 30 noHD parents, 19 of 30 FCHD parents, and 26 of 30 LAHD parents reported willingness to enroll their children in a heart disease research study involving an otherwise unnecessary chest radiograph (P < .01). There was no difference among groups in willingness to enroll their children in a similar study focused on childhood cancer. Twenty-two of 30 FCHD and 30 of 30 LAHD parents reported that parents have a responsibility to enroll their children in medical research to help future children with heart disease. Twenty-one of 30 noHD parents, 29 of 30 FCHD parents, and 30 of 30 LAHD parents feel able to evaluate the risks of medical research (P = .01).

CONCLUSIONS: Parental opinions regarding higher-hazard, no-benefit research align with federal regulations. Parental willingness to enroll their children in higher-hazard, no-benefit research is driven in part by a sense of obligation to a community of families affected by childhood heart disease. Pediatrics 2013;132:e1302–e1309

AUTHORS: Tanya Sachdeva, MD,a and Marilyn C. Morris, MD, MPHb

aDepartment of Pediatrics, Children’s Hospital of New York, and bDepartment of Pediatrics, Columbia University, New York, New York

KEY WORDS: research ethics, higher-hazard no-benefit research, best-interest standard


Dr Morris conceptualized and designed the study, drafted the initial manuscript, and codrafted the manuscript; Dr Sachdeva performed data collection, carried out the initial analyses, and codrafted the manuscript; and both authors approved the final manuscript as submitted.


doi:10.1542/peds.2013-1700

Accepted for publication Aug 20, 2013

Address correspondence to Marilyn Morris, MD, MPH, Department of Pediatrics, Children’s Hospital of New York, 3559 Broadway, CHN 10-24, New York, NY 10032. mcm2113@columbia.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2013 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
Children are widely recognized as a vulnerable population deserving of additional protections from research risk.1–3 Of particular concern is exposure of children to risk when there is no balancing prospect for benefit. In this discussion, we focus on nontherapeutic research, research in which the participant does not stand to benefit. Competent adults are routinely allowed to volunteer for nontherapeutic research that carries real risk, but regulations about the involvement of children in nontherapeutic research are more nuanced.

The Code of Federal Regulations (CFR) describes 4 categories of research involving children (Table 1).5 Research that poses minimal risk and research in which the risks are justified by the prospect of direct benefit may be reviewed and approved without significant controversy. More controversial is the category of research that poses risk without the prospect for benefit. Loretta Kopelman terms this type of research “higher-hazard, no-benefit research,”4 and we adopt this term here.

Federal regulations allow local institutional review boards (IRBs) to approve higher-hazard, no-benefit research only under those circumstances listed under 45 CFR, Section 46.406, termed “category 406” (Table 1). Of particular interest for this discussion is the provision that “The intervention or procedure is likely to yield generalizable knowledge which is of vital importance for the understanding or amelioration of the subjects’ disorder or condition” (emphasis added). Similar protocols involving healthy children or children with unrelated conditions require approval from the Department of Health and Human Services. Restated, there is a higher standard for the review and approval of higher-hazard, no-benefit research when it involves healthy children than when it involves sick children.

To be locally approvable, higher-hazard, no-benefit research must also be found to pose only a “minor increase over minimal risk,” and the research must involve only procedures that are “reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.” The proper interpretation of each of these restrictions is controversial6,6 but beyond the scope of this work. Nonetheless, the term “higher-hazard research” should be interpreted in light of the provision that the research must pose only a minor increment above minimal risk. Although the term “minor increment” is open to interpretation, it does preclude the conduct of significantly risky research under category 406.

The provisions that allow higher-hazard, no-benefit research involving sick but not healthy children have been controversial from their inception. These regulations grew directly from a 1977 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research report,7 but the regulatory distinction between participation of children with and without a medical condition was not unanimously supported even among the members of the commission.8

Regulations about higher-hazard, no-benefit research involving children must be examined on 2 levels. First, one must question whether higher-hazard, no-benefit research involving children is ever ethically permissible. Surrogate decision-making on behalf of children is generally predicated on the “best-interest standard,” which dictates that decisions on behalf of children should be made so as to promote the highest net benefit for these individuals.9,10 It can be argued that the best-interest

### Table 1 Summary Description of the Types of Research That Can Be Funded by the Department of Health and Human Services Under the 45 CFR 46

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 404</td>
<td>Research not involving greater than minimal risk</td>
</tr>
<tr>
<td>Category 405</td>
<td>Research involving greater than minimal risk but leading to the prospect of direct benefit to individual subjects, and the risk is justified by the anticipated benefit to the subjects</td>
</tr>
<tr>
<td>Category 406</td>
<td>DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; (c) the intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding or amelioration of the subjects’ disorder or condition; and (d) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in 46.408.</td>
</tr>
<tr>
<td>Category 407</td>
<td>Research not otherwise approvable that presents an opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children (requires specific DHHS approval)</td>
</tr>
</tbody>
</table>

DHHS, Department of Health and Human Services.

*US academic medical centers typically operate with a Federalwide Assurance, in which case these categories apply to all research within the institution.
standard should preclude enrolling any children in higher-hazard, no-benefit research. Paul Ramsey writes: “A parent’s decisive concern is for the care and protection of the child. . . . No parent is morally competent to consent that his child shall be submitted to hazardous or other experiments having no diagnostic or therapeutic significance for the child.”11 We recognize the legitimacy of this position, although we do not share it. The debate has received extensive attention in the research ethics literature.12–16 and we will not attempt to review it here. We focus instead on the distinction allowing children with a medical disorder or condition, but not healthy children, to be enrolled in such research after local IRB review. To engage this question is to accept the premise that the value of advancing medical science sometimes justifies exposing children to a low level of risk, even with no prospect for direct benefit.

Opponents of limiting higher-hazard, no-benefit research to children with the medical condition or disorder under study point to the double standard inherent in the regulations.8,17 Anna Iltis questions rhetorically: “Do healthy children require greater protection before being used to help sick children, while sick children can be used with less scrutiny to help other similarly sick children?”18 Others argue that children with a medical disorder or condition should receive more, rather than less, regulatory protection from research risks. Sick people in general are susceptible to pressure from treating physicians,19 and parents of children with a disorder or condition may be more vulnerable to coercion than parents of healthy children.8,20

Defenses of the regulatory distinction have also been made. The philosopher Hans Jonas argues that the ideal of informed consent to research participation is more likely to be achieved when the potential subject identifies closely with the goals of the research. Jonas writes in reference to nontherapeutic research that “patients should be experimented upon, if at all, only with reference to their disease” (italics in original).19 Robert Redmon writes: “One may very well say to himself that although this disease was killing him, he would try to prevent it from killing others by being a research subject.”13 The senior author of this work has argued that families of children with significant medical conditions have an interest in advancing knowledge about these conditions and that this interest justifies the exposure of their children to low-level risk.21

In this work, we seek to describe the opinions of parents regarding higher hazard, no-benefit research and to determine the extent to which these parental opinions align with current regulations. We conducted a series of quantitative and qualitative interviews with parents of hospitalized children, focusing particularly on whether and how the views of parents of children with chronic medical conditions differ from the views of parents of children without chronic medical conditions. We hypothesized the following: (1) parents of children with significant medical conditions are more willing to enroll their children in medical research about their child’s condition than are parents of children without that medical condition, and (2) this willingness is based in part on a desire to advance the interests of a perceived community of families of children affected by similar conditions.

METHODS

This IRB-approved study was conducted at a 191-bed, quaternary care children’s hospital. Data were collected between January and September 2012. This study was limited to English-speaking parents or guardians who had a child admitted to the hospital.

Exploratory Interviews

We conducted exploratory interviews of 3 parents of children with and 3 parents of children without chronic medical conditions to develop a preliminary overview of parental perspectives regarding higher-hazard, no-benefit research and to ensure that relevant domains were identified. Interviews were audio-recorded then transcribed by a professional medical transcriptionist. Major themes identified included the following: limited familiarity with medical research, concerns about research risk, desire to advance medical knowledge, and parental desire to advance knowledge of their own child’s disease.

Survey

Participants in the survey portion of the study were chosen on the basis of their membership in 1 of 3 groups: parents of children with no heart disease and no chronic medical conditions (no Heart Disease, noHD), parents of children with fully correctable heart disease (FCHD), and parents of children with life-altering heart disease (LAHD). All interviews were conducted by a single interviewer.

We designed the survey tool based on a priori hypotheses and on content analysis of the exploratory interview transcripts. Validity testing (reviewing the surveys with parents before initiation of the study to ensure consistent interpretation of items) led to minor clarifications.

To control for bias introduced by question order, 2 versions of the survey were created, differing only in the order of 2 sets of questions. The randomized sets of items included the order in which 2 similar hypothetical research studies were presented, and the order in which parents were asked about their degree of comfort in refusing
research participation when approached by their own physician or a physician they did not know.

**Statistical Analysis**

Interview transcripts and qualitative survey responses were organized and relevant themes were established based on the content analysis of the transcripts and on the prospectively defined research questions. Detailed definitions of each theme were established before categorization. Two investigators independently categorized the qualitative responses and any nonconcordant categorizations were resolved to the satisfaction of both. Categorical data were analyzed by using $\chi^2$ or Fisher exact tests where appropriate. Continuous data were compared by using Student’s t test or Wilcoxon rank-sum where appropriate.

**RESULTS**

Ninety parents completed the verbal survey. Demographics of the participating parents and their hospitalized children are summarized in Table 2 and medical diagnoses in Table 3.

Each parent was asked to consider 2 hypothetical research studies, each involving 1 otherwise unnecessary chest radiograph. One study was described as helping doctors learn more about early diagnosis of childhood cancer and the other as helping doctors learn more about early diagnosis of childhood heart disease. Parents were asked whether they thought the study should be allowed to take place (definitely or probably yes), with no significant differences between groups. Twenty-four of 30 noHD, 30 of 30 FCHD, and 30 of 30 LAHD parents reported that the heart disease study detection should be allowed to take place ($P = .001$). Ten of 30 noHD, 13 of 30 FCHD, and 16 of 30 LAHD parents reported willingness to enroll their own children in the cancer study ($P = .30$). 8 of 30 noHD, 19 of 30 FCHD, and 26 of 30 LAHD parents reported willingness to enroll their own children in the heart disease study ($P < .01$ FCHD vs noHD and LAHD vs noHD.)

To evaluate the impact of question order, we analyzed responses in which parents reported that they would want their child to participate in only 1 of the 2 studies discussed. When the study involving cancer research was introduced first (Survey A), 13 parents about the same 2 studies in the reverse order (Survey B).

Eighty-one of 90 parents reported that the cancer detection study should be allowed to take place (definitely or probably yes), with no significant differences between groups. Twenty-four of 30 noHD, 30 of 30 FCHD, and 30 of 30 LAHD parents reported that the heart disease study detection should be allowed to take place ($P = .001$). Ten of 30 noHD, 13 of 30 FCHD, and 16 of 30 LAHD parents reported willingness to enroll their own children in the cancer study ($P = .30$). 8 of 30 noHD, 19 of 30 FCHD, and 26 of 30 LAHD parents reported willingness to enroll their own children in the heart disease study ($P < .01$ FCHD vs noHD and LAHD vs noHD.)

To evaluate the impact of question order, we analyzed responses in which parents reported that they would want their child to participate in only 1 of the 2 studies discussed. When the study involving cancer research was introduced first (Survey A), 13 parents
provided discordant responses. The 1 parent (noHD) who responded yes to the cancer study but no to the heart disease study referenced having a cousin with childhood cancer. Six FCHD parents and 6 LAHD parents first said no to the cancer study then said yes to the heart disease study. When the heart disease study was introduced first (Survey B), 6 parents (all LAHD) provided discordant responses; all said yes to the heart disease study, then said no to the cancer study. One of these parents expressed some discomfort about replying no to the cancer study: “I feel guilty saying no to this study, but honestly the first one is more important to me.” Of note, 4 parents who said yes to the cancer study after having said yes to the heart disease study spontaneously commented that they may not have agreed to the cancer study if they had not just agreed to the heart disease study (“Well, I said yes to the other one, so I guess I should say yes to this one, too”; Table 4). Therefore, the number of HD parents who replied yes to the cancer study is likely higher than it would be if the cancer study were proposed in isolation. Parental responses to which (if any) specific no-benefit procedures they would approve for their child to help advance knowledge about pediatric heart disease are presented in Table 5.

Table 6 summarizes parental responses indicating why they would or would not want their child to participate in the higher-hazard, no-benefit studies described. The following themes were identified among positive respondents: altruism, the low degree of risk, and desire of the child to participate (assent). Negative respondents cited not wanting extra tests and risks. During the course of the survey, 5 parents of children with noHD and 3 parents of children with FCHD used the specific phrase “no reason” as an explanation for not wanting their child to participate: for example, “It doesn’t seem right to do a test for no reason.”

LAHD parents and FCHD parents perceived themselves as more able to evaluate research risk than noHD parents. Twenty-one of 30 noHD parents, 29 of 30 FCHD parents, and 30 of 30 LAHD parents agreed or strongly agreed with the following: “I feel that I can evaluate the risks of medical research studies and make an informed decision about whether my child should participate” (noHD vs LAHD, P = .004; noHD vs FCHD, P = .015).

To assess whether parents of children with significant medical conditions may be particularly vulnerable to disproportionate influence from their children’s physicians, we asked parents whether they would feel comfortable refusing study participation when asked by a physician they had never met and also asked whether they would be comfortable refusing participation when asked by their child’s regular doctor. Twenty-nine of 30 noHD parents reported they would feel comfortable saying no to a physician they did not know, and 28 of 30 reported they would feel comfortable saying no to their own physician. Corresponding proportions for FCHD parents were 28 of 30 vs 30 of 30 and for LAHD parents were 30 of 30 vs 26 of 30 (P = .77 between groups for own physician; P = .16 between groups for physician they did not know). The order of these 2 items was randomized, but we did not detect any significant impact of question order.

Twenty-five of 30 LAHD parents and 2 of 30 FCHD parents agreed somewhat or agreed strongly with the statement: “I feel like I am part of a community of parents whose children have heart disease” (P < .0001); 26 described the community as a support network (“We share info, experiences, support.”), and 11 parents referred to the community as a source of information (“A lot of our kids have the same kinds of complications”). Twenty-one of these 27 parents responded that this feeling of community affects their willingness to enroll their children in nontherapeutic research (“Medical research could help our community” and “When I think about all the parents who are like me, of course I would want to help them.”) LAHD parents were more likely than noHD or FCHD parents to report that parents have a responsibility to enroll their children in medical research (Table 7).

### Table 4 Impact of Question Order on Parental Interest in Enrolling Their Children in Hypothetical Studies

<table>
<thead>
<tr>
<th></th>
<th>Survey A Study Regarding Cancer Presented First</th>
<th>Survey B Study Regarding Heart Disease Presented First</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Discordant Responses</td>
<td>Yes to Cancer Only</td>
</tr>
<tr>
<td>noHD</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>FCHD</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>LAHD</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Only discordant responses are included (parents replied yes to one study and no to the other).
TABLE 5  Number of Parents Who Responded Probably or Definitely Yes When Asked If They Would Give Permission for the Following Tests to Be Done in a No-Benefit Research Study to Help Doctors Learn More About Caring for Children With Heart Disease

<table>
<thead>
<tr>
<th>Procedure</th>
<th>noHD</th>
<th>FCHD</th>
<th>LAHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking an extra vial of blood when the doctor is taking blood anyway</td>
<td>24</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Taking an extra vial of blood when the child would otherwise not have a blood draw</td>
<td>7</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Compute tomography scan (no sedation)</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>MRI of the brain, with oral sedation</td>
<td>5</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Spinal tap when the child is already getting anesthesia for another reason</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Skin biopsy with injected numbing medicine</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

* P = .02 LAHD vs noHD.  
* P < .001 for noHD versus LAHD and FCHD versus LAHD.

**DISCUSSION**

We found that parental opinions align well with federal regulations allowing local approval of higher-hazard, no-benefit research only when the research is related to the subjects’ disorder or condition. Parents of children with heart disease were significantly more willing to enroll their children in higher-hazard, no-benefit research when the research was specific to their child’s medical condition. Parents of either healthy children or parents of children with a medical condition could make well-informed decisions to enroll their children in higher-hazard, no-benefit research, but parents of children with medical conditions or disorders are more likely to want to enroll their children in such research.

The significance of these parental opinions is twofold. First, as we discuss further below, we believe that families of children affected by a particular disease form a meaningful community and that their opinions ought to inform regulations affecting that community. Second, we believe that it is more appropriate to offer research participation to a population more likely to be receptive than to a population less likely to be receptive. There are well-documented limitations in parental understanding of the research consent process. Any informed consent process will result in a certain number of “false-negatives” (parents who decline participation, but, on full consideration, would want their child to participate) and “false-positives” (parents who allow participation, but, on full consideration, would not want their child to participate). By offering research participation to families who are more likely to want to participate, we increase the likelihood that those families who choose to participate in research are those who really prefer to do so.

The illegitimacy of “ethics by opinion poll” has been appropriately established, and we do not suggest that parental willingness to enroll their children in higher-hazard, no-benefit research renders such research ethically sound. Nonetheless, the perspectives of parents of chronically ill children ought to be considered. Schincktanz et al argued that the fact of being affected by a medical condition may confer a degree of authority based on deeper knowledge and understanding of the facts and on a unique perspective of the affected population, which

<table>
<thead>
<tr>
<th>Theme: Why not</th>
<th>noHD</th>
<th>FCHD</th>
<th>LAHD</th>
<th>Representative Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not wanting child to have extra tests</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>He is too young to have extra tests done.</td>
</tr>
<tr>
<td>Risks</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>I heard that CXRs are dangerous. CXRs have radiation risks and I do not want her participating. If it was a different test, I would say yes, but extra CXRs are extra radiation.</td>
</tr>
<tr>
<td>&quot;No reason&quot; to do it</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>Doesn’t seem right to do a test for no reason. He is too young to have tests done for no reason.</td>
</tr>
</tbody>
</table>

Numbers indicate the number of parents in each group who volunteered a comment that was categorized according to each theme. CXR, chest radiograph.
results in a qualitatively different (and authentic) type of cognition. They specifically extend this condition of being affected to close family members.

If we accept that parents of sick children are indeed motivated to enroll their children in higher-hazard, no-benefit research, we must still question whether it is acceptable for parents to expose their children to (low-level) risk for the sake of others. Ackerman describes that parents may legitimately intervene in their children's lives (within limits) to inculcate moral character traits or "to enhance the interests of other persons, particularly family members." 28 Digression from the best-interest principle for the sake of others may be somewhat less prone to exploitation. 35 This hypothetical differential in the ability to assess risk, however, is inadequate to support the regulatory distinction between healthy and sick child participation in higher-hazard, no-benefit research.

Parents of sick children have been reported to feel less empowered than parents of healthy children to decline research participation, 35 and some parents have expressed concern about "letting their doctor down" by refusing to enter their child in a study. 34 The potential for coercion has been cited as an argument against the current regulations regarding higher-hazard, no-benefit research, 8,20 but these data stem largely from interventional studies rather than nontherapeutic research. The large majority of participants in our study reported that they would be comfortable refusing study participation, and there was no statistically significant difference among the groups. It is noteworthy, however, that 4 parents of children with LAHD reported that they would be comfortable saying no to a physician they had never met but not to their child's own doctor. One parent of a child with chronic illness stated that being asked by their specialist would be "problematic" because saying no would make her "uncomfortable." We suggest that because of the highly vulnerable state of children affected by significant medical conditions, consent for higher-hazard, no-benefit research ought not to be sought by a child's treating physician.

Our data indicate that parents of children with heart disease feel better able to assess research risk than do parents of children without chronic medical conditions. However, we do not have any data to indicate whether parents of sick children are in fact better able to assess research risk than parents of healthy children. If parents of children with chronic medical conditions are more informed about research risks, they may be somewhat less prone to exploitation. 35 This hypothetical differential in the ability to assess risk, however, is inadequate to support the regulatory distinction between healthy and sick child participation in higher-hazard, no-benefit research.

**CONCLUSIONS**

Parental opinions regarding higher-hazard, no-benefit research align with federal regulations. We believe that the distinction allowing higher-hazard, no-benefit research to be approved by local IRBs only when it involves children with the condition under study helps in the protection of children in the medical research arena without unduly curtailing the conduct of meaningful, low-risk research.
REFERENCES


35. Chantler TE, Lees A, Moxon ER, Mant D, Pollard AJ, Fitzpatrick R. The role familiarity with science and medicine plays in parents’ decision making about enrolling a child in vaccine research. Qual Health Res. 2007;17(3):311–322
Higher-Hazard, No Benefit Research Involving Children: Parental Perspectives
Tanya Sachdeva and Marilyn C. Morris

Pediatrics; originally published online October 14, 2013;
DOI: 10.1542/peds.2013-1700

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/early/2013/10/09/peds.2013-1700