

# Children as Research Subjects: Moral Disputes, Regulatory Guidance, and Recent Court Decisions

LORETTA M. KOPELMAN, PH.D.

## Abstract

The millennium has ushered in a new era of oversight for pediatric research, with renewed moral and legal attention to the upper thresholds of potential harms to which children may be exposed in studies. Watershed events discussed include: First, the deaths of two research subjects, allegedly due to insufficient oversight by the investigators and their institutional review boards. Second, the courts expressed concerns about research policies for incompetent persons or children in two cases, *T.D. v. N.Y.* and *Grimes v. Kennedy Krieger Institute*, and reinforcement of the principle that the best interest standard must be used for incompetent persons even in research. Third, the Best Pharmaceutical for Children Act and the Pediatric Rule created incentives as well as uncertainty among Institutional Review Boards and researchers about conducting pediatric studies. Fourth, the Office of Human Research Protection signaled the start of more rigorous oversight with its public rebuke and suspension of a National Institute of Child Health and Human Development pediatric obesity study. Failure to clarify the meaning of the pediatric regulations has sometimes misled generally risk-averse institutions and dedicated investigators about what is permissible.

**Key Words:** Ethics, legal, research, pediatric, *Grimes v. Kennedy Krieger Institute*, OHRP, Best Interests Standard.

---

IN NOVEMBER 2000, the federal Office of Human Research Protection (OHRP) suspended a National Institute of Child Health and Human Development (NICHD) pediatric study on the causes of obesity, posting its concerns on the World Wide Web for all to see. The OHRP determined that aspects of this research were too risky for healthy children to be enrolled without special federal approval, and this approval had not been obtained. The OHRP required that certain actions be taken by December 8, 2000, including modifying the study and devising a plan about whether or not to contact “the parents or guardians of the subjects who participated in the...research and inform them of their child’s inappropriate enrollment in this research (1).” The OHRP also asked for “a list of active research protocols being conducted by the NIH [National Institutes of Health] of intramural research program that involves normal, healthy children.” The OHRP was particularly concerned about an “in-

sulin tolerance test designed to induce hypoglycemia (a blood sugar less than 50 mg/dL) in normal children.” The dangers of infusion of insulin into healthy children generated the most controversy over the study. The OHRP requested information about the “hundreds” of children that the investigators claimed had been involved in this sort of research.

Investigators in the research community were stunned by the public manner in which these researchers were notified and rebuked. They correctly concluded that a new era in oversight and compliance had begun. Consequently, Institutional Review Boards (IRBs) and pediatric investigators wanted more information and direction about how to determine the upper threshold of research risk that was permissible for children. They wanted to know when local IRBs could make decisions and when they needed special federal approval.

In what follows, I will first state the central moral problem in pediatric research policy, and offer some of the regulatory responses to it. After clarifying the current U.S. regulations governing assessment of these risk thresholds, I will turn to events occurring in the last few years, which have led to a new era of oversight for pediatric research. These include not only OHRP’s suspension of an NICHD pediatric obesity study but also the Best-

---

Professor, Medical Humanities, The Brody School of Medicine at East Carolina University, Greenville, NC. Address all correspondence to Loretta M. Kopelman, Ph.D., Dept. of Med. Humanities, Brody School of Medicine, 2S-17 Brody Med. Sciences Bldg., 600 Moye Boulevard, Greenville, NC 27858.

Presented at the Mount Sinai Medical Conference on Pediatric Ethics, January 30, 2004, and updated as of June 2005.

Pharmaceutical Act, the Pediatric Rule and the deaths of two research subjects. The courts also expressed concerns in *T.D. v. N.Y.* and *Grimes v. Kennedy Krieger Institute* about how well subjects were being protected and it reinforced the fact that the “best interest” standard must be used for incompetent persons, even in research. I will argue that the failure to clarify the meaning of the pediatric regulations has sometimes misled generally risk-adverse institutions and dedicated investigators about what is permissible.

### The Central Moral Problem

The central moral problem in framing pediatric research is how to formulate a policy that promotes the well-being of all children by encouraging research, while at the same time protecting individual research subjects (2). Some policies protect children to such an extent that they do not allow them to be enrolled in any research whatsoever. For example, the Nuremberg Code (3) states that no research may be done without the subjects’ informed, voluntary and competent consent. Such a policy obviously excludes all persons who cannot give informed, voluntary and competent consent, such as most children. The difficulty with this policy is that unless some research is done with pediatric subjects, there can be no genuine improvement in care for children. If clinicians are forced to use untested interventions, they will probably endanger their patients. On the other hand, if they use only tested interventions and research is not permitted, then they are severely limited in their treatment options (2).

The World Health Organization’s Declaration of Helsinki adopted another policy before 2000 (when it radically changed its position) (2, 4). In these pre-2000 policies and revisions, the WHO stated that no research could be done using subjects who could not give informed consent unless the study had direct therapeutic benefits for the individual. This policy was an advance on the Nuremberg Code because it at least allowed testing of different therapies for children, such as different cancer or asthma treatments, if the different arms of the study were genuine therapeutic options that were being compared. Nonetheless, the Helsinki policy seemed unduly restrictive. For example, many important studies on growth and development pose virtually no risks to the subject, yet cannot be regarded as therapeutic studies when the children are not sick. Yet these studies are important in determining whether some children are thriving, since they are needed to compare their growth and development to those of a norm. It

seems unreasonable to claim that one is acting in their best interest by prohibiting these low-risk, but important studies (2).

The U.S. (5), the Council for International Organizations of Medical Sciences (CIOMS) (6), and the U.K., Canada, South Africa and many other countries take a very different approach (2, 7). To determine what studies should be approved, they seek to balance potential harms and benefits. Typically, they set different levels of risk and different sets of requirements at each risk level. I will focus on the U.S. requirements. I will show that these rules are vague and allow such a wide range of interpretation that pediatric investigators dedicated to the well being of children and reasonably risk-averse institutions were caught off guard by a new era of more restrictive standards based upon these rules.

### The U.S. “Balancing Act” Approach: Four Categories of Research

The U.S. regulations established four categories of research (see Table) distinguished primarily by the risk of harm and the potential benefits to the potential subjects (5). The overarching concept is that the greater the risk of harm, the greater the need to justify the benefits and importance of the study, and the greater the need to obtain rigorous consent from guardians and assent from the children, if possible.

#### §46.404

The first research category is for studies with only minimal risk of harm and is often known by its numbering in the U.S. Code as “404” (Table). Because the risks are so low, these studies may be conducted even if there is no direct benefit to the subjects. Such studies require the approval of the local IRB, the assent of the child if possible, and the consent of one parent. Growth and development studies and chart reviews are examples of important low-risk studies that may not directly benefit the subjects. There is considerable advantage to having a study classified under this heading, because it enables investigators to obtain expedited review, modify or waive consent, or allow vulnerable subjects or others who lack decision-making capacity to be enrolled in studies (8).

The U.S. regulations define minimal risk as meaning “that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests.” This definition contains

**TABLE**  
*Research Involving Children, Which DHHS Is Permitted to Fund or Conduct.*

**§46.404 Research not involving greater than minimal risk.**

DHHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

**§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.**

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 holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

- (a) the risk is justified by the anticipated benefit to the subjects;
- (b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- (c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

**§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.**

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 [that] 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.

**§46.407 Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. DHHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:**

- (a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
- (b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
  - (1) the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or
  - (2) the following:
    - (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
    - (ii) the research will be conducted in accordance with sound ethical principles;
    - (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

SOURCE: Quoted from U.S. Code of Federal Regulations (45 CFR § 46.404-407).

DHHS = Department of Health and Human Services, IRB = Institutional Review Board.

two parts, and because there is an "or," only one needs to be satisfied. The first part uses "everyday risks" as a benchmark for minimal research risk, saying that to be minimal, research risk must be like that of everyday risk. However, there needs to be a moral justification for taking "everyday risk" to be a legitimate guide for low-risk studies (7). That is, even if we know the probability and magnitude of the daily risks all of us encounter (which can include drive-by shootings, SARS, and terrorism) well enough to establish the "minimal-risk"

standard for research, it is unclear why everyday risks are morally relevant or justified.

The problem with the "everyday risk" part of the definition is that it allows too high a level of risk. This may be illustrated by the NICHD obesity study. Initially, the IRB decided that this study, with its infusion of insulin into healthy children, had no more than a minimal risk because they judged that these procedures were safer than the everyday risk of playing in traffic. The minutes from this meeting state (1):

Several members of the Committee explored the meaning of minimal risk and what a child might encounter in a visit to the doctor or while playing in traffic. It was felt that spending several hours in the Clinical Center in a clamp experiment would be safer than playing actively on sidewalks and streets.

In halting the study, the OHRP made it clear that "...this research involves greater than a minimal risk. In particular, the hyperglycemic, euglycemic, and hyperinsulinemic clamp procedures involve greater than minimal risk. Other study interventions, such as the two-day, one-night hospitalizations for intensive metabolic evaluation, may also involve greater than minimal risk for some subjects" (1).

The other part of the definition of minimal risk is more promising, since it benchmarks the analysis of "minimal risk" research to the reasonably well-understood notion of routine medical or psychological examinations or tests. I have argued in detail elsewhere that we should drop the "everyday risk" standard and simply understand minimal risk as no more than the sort of risks we all encounter in routine medical or psychological examinations or testing (7). Clearly, risks like the infusion of insulin into the veins of healthy children are unlike the sort of risks encountered by all of us in routine examinations or testing. I discuss this definition and various interpretations more fully elsewhere (7).

#### §46.405

The next category of research is known as "405," again based on its number in the federal regulations. It permits a greater than minimal risk as long as the risks are justified by the anticipated direct benefit to the subject, and if the benefit-to-risk relationship is at least as favorable as that presented by available alternative approaches. In addition, the assent of the subject is needed if possible, as is the approval of parents and an IRB. What constitutes a "direct benefit" is open to interpretation, but is often understood as a direct therapeutic benefit (5). For example, using this category, investigators would be able to compare the efficacy and safety of standard treatments of asthma, cancer, or other diseases. The NICHD obesity study, in contrast, had no likelihood of direct benefit to the subjects; it was done to gain knowledge and so could not be justified under this category.

#### §46.406

The third category of research, known as "406," allows a minor increase over minimal risks

without the prospect of direct benefit to each subject when the subject has a condition (5). "Minor increase over minimal risk" is undefined and, not surprisingly, even wider variation exists about how to understand this definition than exists for "minimal risk." The National Bioethics Advisory Commission (NBAC) (9) and the National Human Research Protections Advisory Committee (NHRPAC) (10) understand a "minor increase over minimal risk" to be just a little more risk beyond what is allowed for healthy children. The NHRPAC includes the following as one-time procedures done with suitable pain relief: a skin punch biopsy, bone marrow aspirate, or lumbar puncture. A central moral and policy question is how can there be a higher risk threshold for some children than for others? I have discussed this in detail elsewhere, but answers require acknowledging two points (2, 7). First, risks of harm and potential benefits for healthy children and children with conditions are often different, and this standard seeks to take this into account, I believe. What is minimal risk for healthy children may be high risk for those with compromised immune systems, and minimal risk for terminally ill children (e.g., discussing loss and death) may be a higher risk for healthy children.

Second, to be consistent with other policies concerning children, I have argued that "minor increase over minimal risk for children with conditions" should be understood as what would be minimal risk for the children with conditions being studied as long as it is understood that the risks for children with medical conditions does not exceed what would be a minor increase over minimal risk for healthy children (2, 7). In addition, to fulfill the 406 category, the research must be likely to yield generalizable knowledge about the child's disorder or condition, which would be knowledge of vital importance for the understanding or amelioration of the disorder or condition that affects the child.

The NICHD investigators and the IRB approving the obesity study apparently believed that having one obese parent constitutes a condition, because it puts these children at some increased risk of becoming obese later in life. OHRP rejected this wide interpretation, as did the Institute of Medicine's Committee on Research Involving Children (1, 11). I have argued elsewhere that "condition" should be understood to be a medical condition and that nowhere is having one obese parent regarded as a medical condition (8). Local IRBs cannot approve studies without direct benefits if they pose more than a minor increase over minimal risks. As noted, the OHRP decided that the obesity study had exceeded this level.

## §46.407

The final regulation, known as “407,” is a mechanism for gaining approval for research that is not otherwise approvable. Research that is not otherwise approvable must still gain parental permission and the child’s assent, if possible, and be approved by the local IRB as presenting a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children. To be approved, the study must also gain the approval of the Secretary of HHS after consultation with a panel of experts in pertinent fields and following an opportunity for public review and comments. The obesity study from NICHD had not gotten the secretary’s approval, as OHRP noted in halting it (1).

Wide discrepancy about how to apply these risk categories has existed ever since the regulations were originally issued. In 1981, Janofsky and Starfield (12) surveyed department chairs and pediatric investigators, and found disagreement about how to classify the risk levels of such common procedures as arterial puncture and gastric and intestinal intubation. According to 14% of respondents, puncturing of the eardrum has no more than a minimal risk, 46% stated it had a minor increment over minimal risk, and 40% thought it involved more than a minor increase. An editorial in the *Journal of Pediatrics* (1981) said that this variation demonstrated the need for more consistent risk assessment (13). However, considerable variation about what is permitted still exists (2, 5, 14). Testimony before the NBAC in 1989 revealed that some respondents viewed a lumbar puncture (spinal tap) as posing no more than a minimal risk of harm if done by experts, despite possible risks of headache, infection, nerve damage, and paralysis (9). In contrast, the NHRPAC listed a single spinal tap as presenting a minor increase over minimal risk (10). As we saw, some investigators and IRB members believed that infusing insulin into the veins of children posed minimal risk, and others believed that it presented a minor increase over minimal risk; OHRP believed the risk was higher than this (1).

### A New Era of Oversight

Failure to clarify the meaning of the regulations allowed wider and narrower interpretations to flourish unchecked until recently. In this section I will discuss some causes of the change. One measure of the uncertainty among investigators and IRB members about how to understand the regulations was a jump in requests for federal approval of

higher-risk studies. After two decades with only two requests for “407” federal approval for studies for which the IRBs believed the risk was too high to approve on the local level, there was a comparative flood (15). Change seems to have been brought on by several factors.

First, there was a shakeup in the Department of Health and Human Services, in which the watchdog committee was taken out of the NIH and set up directly under the Department of Health and Human Services. This new organization, the Office of Human Research Protection, under the leadership of Greg Kosky, began enforcing standards at all research institutions, including the NICHD.

Second, in 1998, the Food and Drug Administration and later the Congress adopted the “pediatric rule,” which offers incentives to do pediatric research (11 16). The rule was designed to address the problem that most drugs and products that are in use for both adults and children lack directions for pediatric use on their labels. In addition, the FDA estimated that about 80% of the pediatric drugs used for children are not FDA approved. Consequently, it began requiring sponsors to include pediatric assessments when applying for new drugs or biological products (2). Applicants had to conduct pediatric studies unless they could make a case that the study should not be done. Valid reasons for not doing a study included that the data already existed, the children didn’t get the disease, or the drug was especially dangerous for children. Given this incentive, many more pediatric studies began to be planned and done and numerous IRBs, often having few to no pediatric experts, were uncertain how to fulfill federal guidelines (11).

Third, the Best Pharmaceutical for Children Act (BPCA) was passed in 2002 (17). It is a law providing an incentive of six months of extended market exclusivity for companies that conduct pediatric studies. BPCA is a voluntary program and “sunsets” in 2007. Unlike the pediatric rule, BPCA is voluntary, but nonetheless provides great incentives to conduct pediatric studies. A \$100,000 investment on a pediatric study, for example, could result in millions of dollars for a drug company gaining exclusivity for six months. The Institute of Medicine has determined that this act should be renewed because it is of great importance (11).

Fourth, two deaths at leading research institutions brought charges that review boards were not protecting subjects properly. Jesse Gelsinger died in September 1999 from a rare liver disease called partial ornithine transcarbamylase (OTC) deficiency (18, 19). This disease causes people to retain toxic levels of ammonia in their blood. Half of all infants with this condition die within the first

month. Jesse Gelsinger was more fortunate, and as soon as he turned 18, he eagerly sought participation in a gene transfer trial at the University of Pennsylvania to help advance knowledge about this disease. He had a mild version of the disease, which was being well managed by diet and drugs. Yet he wanted to be a hero, said his father, and so he volunteered for research. Doctors gave him an injection of a normal OTC gene attached to a therapeutic virus. Shortly after this gene entered his liver, he developed a high fever, his blood began to clot, his immune system malfunctioned, his liver hemorrhaged and he died. There were later questions about the quality of his informed consent. Specifically, Jesse and his family had not been told of the deaths of Rhesus monkeys or of patients who had toxic reactions. The investigators and IRB members were also criticized for failing to use the inclusion criteria properly. Later, there were also questions about conflict of interest. Many of the investigators were heavily invested in the company sponsoring the study; thus they had a strong interest in developing the genetic treatment they were investigating, but had failed to disclose this.

In 2002, there was another tragedy at a prestigious institution, Johns Hopkins Hospital, where 24-year-old Ellen Roche died (20). She was a technician at the Asthma Center there and was paid about \$350 to enroll in the study and inhale Hexamethonium. According to the consent form, the investigators wanted to find out how “tubes carry air into the lungs” despite the presence of irritating substances. Due to adverse reactions recorded in the 1950s, Hexamethonium had been taken off the market in 1970 and was not FDA approved. Subjects were not told of this or about adverse reactions earlier in the study, and risk level was understated on the consent form. Although Jesse Gelsinger and Ellen Roche were young adults, there was a general concern that IRBs were not doing their job to protect the rights and welfare of research subjects.

Finally, for the first time, the courts rendered decisions having implications for pediatric research policy. In *T.D. v. New York* (21), the court ruled that incompetent persons in a state mental hospital could not be enrolled in research studies having more than a minimal risk. Seen more generally, the decision seemed to support the view that incompetent persons, including children, could not be enrolled in non-therapeutic or no-benefit studies having more than a minimal risk (11). This view was reinforced in the first appellate court case to review the U.S. pediatric research policy, *Grimes v. Kennedy Krieger Institute* (22, 23). This ruling alarmed the pediatric research community,

since it seemed to rule out two of the four pediatric categories for research—406 and 407 (Table) (24, 25). It is worth discussing the case in detail, because the investigators and the IRB at Kennedy Krieger Institute (KKI), an affiliate of Johns Hopkins Hospital, were convinced they were acting in the best interests of the children in the study, while the Grimes court compared this research to some of the worst research abuses in recent history, such as the Tuskegee syphilis study. A systematic look at the research and the ruling shows why these perspectives, presumably among reasonable people of good will, were so different.

The KKI study at the center of this dispute was done in the late 1980s and the 1990s; it was called the Lead Abatement and Repair and Maintenance Study (22, 24, 25). Kennedy Krieger investigators had planned the study to find a safe and inexpensive way to remove lead hazards from homes in the Baltimore area. They estimated that 95% of low-income homes in Baltimore had lead hazards. The study focused on five groups of homes, with twenty-five homes in each group. The first three groups were distinguished by the amount to be spent on lead abatement, i.e., repair and maintenance to remove dust, paint or soil containing lead (up to \$1,650, up to \$3,500 or up to \$6,500). Homes in group four had already been extensively abated to make them as safe as possible. Homes in group five were built after 1978, when lead paint was forbidden in homes, although lead hazards might exist in soil or in their neighborhoods.

Parents of two children living in the homes sued Kennedy Krieger. Erica Grimes, in group four, charged that the Institute had found “hot spots” in March and waited until December to tell the family of her elevated blood levels. Her blood levels were 9 on April 9 and 32 on September 15. In addition, the Grimes family charged that they were not told the purpose of the study or the hazards. One of the issues concerns what level of lead poses risks. Lanie Ross, a pediatrician, writes, “The two children whose parents brought suit against the Kennedy Krieger Institute had peak levels of 21  $\mu\text{g}/\text{dL}$  and 32  $\mu\text{g}/\text{dL}$ .... During the last 30 years, the Center for Disease Control and Prevention (CDC) has revised the blood-level at which lead poisoning occurs, from 60  $\mu\text{g}/\text{dL}$  in the early 1960s, to 30  $\mu\text{g}/\text{dL}$  in 1975, to 25  $\mu\text{g}/\text{dL}$  in 1985, and to 10  $\mu\text{g}/\text{dL}$  in 1991. As such, when the research was being done, the researchers should have known that both of these children had blood-levels that posed risks to them” (26, p.55).

The purpose of the study, according to the Maryland Appellate Court, was to compare the efficacy of the abatement with blood levels of lead.

Parents of Myron Higgins, in group two, also sued, claiming that landlords had received a grant for moving a family with young children into a home that had lead hazards. They charged that their child was healthy when they moved in on June 8, 1994. The Higgins family claimed that Kennedy Krieger investigators discovered lead hazards in their home, yet failed to warn them of the danger in a timely way. They also charged that the informed consent was deficient, failing to inform them appropriately of the risks, goals and purposes of the study. Finally, they claimed that the study failed otherwise to prevent the children from being exposed to lead, thus either poisoning the children or putting them at risk of lead poisoning.

KKI was sued for negligence by these parents on behalf of their children. To prove negligence in this case, the parents had to show (a) that the investigators had a duty of care toward the plaintiff, (b) that this duty was breached, and (c) that, as a result, there was an injury or loss. Kennedy Krieger lawyers charged that, as a matter of law, it had no duty of care to the human subjects on the facts alleged by the plaintiffs, and so moved for summary judgment. Even if the children were injured or exposed to risks, KKI lawyers had argued in a lower court, it was not their responsibility to protect the children in the study from unreasonable harm or delays in complete and prompt reporting of potential hazards. The lower trial court agreed with KKI and dismissed the parents' claim, but the decision was appealed on the grounds that there could be a duty of care. The Maryland Court of Appeals reversed the trial court's ruling, stating that the trial court had acted wrongly to grant summary judgment in favor of KKI, because the facts of the case might show that investigators have a duty of care. The court went on to condemn the study, its informed consent document, and the IRB that approved it (22–24).

According to the Grimes court, the informed consent document stated, "We would provide you with specific blood level results. We would contact you to discuss a summary of the house test results and steps that you could take to reduce the risk of exposure" (22, 24). In addition, the consent form failed to state that the study's purpose was to measure the success of the abatement programs by measuring the degree to which the children got lead poisoning, correlating this with the degree of cleanup. Despite the KKI investigators' and lawyers' arguments, the Maryland Court of Appeals found the study to be non-therapeutic. The court was highly critical of the requirement that landlords place children at risk in order to get grants: "The project required that small children be

present in the houses. To facilitate that purpose, the landlords agreeing to permit their properties to be included in the studies were encouraged, if not required, to rent the properties to tenants who had young children." The Grimes court concluded that it cannot be in the best interest of a child to be placed at risk in a non-therapeutic study. Specifically, the court stated that "it is not in the best interest of a specific child, in a non-therapeutic research project, to be placed in a research environment which might possibly [be], or proves to be, hazardous to the health of the child.

Initially, the Grimes decision sent shock waves through the pediatric community, because it seemed as if the Grimes ruling held that a non-therapeutic or no-benefit study that carried any risk could not be done (24). This was widely seen as an untenable position, since many important studies, as we noted, are not directly beneficial and carry low risk. But the court later qualified that they meant non-therapeutic studies having more than a minimal risk could not be done (23). They did not view being in an environment where children might get lead poisoning to be a "condition." So the Grimes decision put parents and investigators on notice that, at least in the Maryland district, they are constrained by the Best Interest Standard (requiring that the best of the available options be selected for legally incompetent persons). Grimes ruled that Kennedy Krieger Institute may have owed a duty to warn participants because a special relationship seemed to exist between the parties, because the consent form seemed to create a contractual duty to give this information, because the danger of lead poisoning was foreseeable and well known to KKI, and because a federal regulation exists creating such a duty.

KKI investigators strongly denied that they had done anything wrong. The suit was eventually settled out of court, so we will never know KKI's side of the story (25). The Grimes decision, however, has raised many questions, including: (a) Do investigators and research entities have duties of care to subjects, and if so, when? (b) Can parents legally consent to placing their child in non-therapeutic studies with greater than a minimal risk of harm? (c) What guidelines should exist for informing and notifying parents of children who are subjects about the risks of harm, when doing so would interfere with collecting good data? (d) What is the acceptable level of risk for non-therapeutic (no benefit) pediatric research studies, especially for young children? (e) Is *Grimes v. KKI* compatible with federal pediatric regulations? and (f) How should other laws and standards, including the Best Interests of the Child Standard, be reconciled

with the federal research rules for children (24)? “We have long stressed [that] the ‘best interest of the child’ is the overriding concern of this court in matters relating to children...” (22, 24). I have argued elsewhere that we should work to find a way to reconcile the pediatric regulations and the “best interest of the child” standard stressed by *T.D. v. N.Y.* and the Grimes court (7, 8, 24).

### Conclusion

The moral question at the heart of all pediatric research is, how can advances be made to benefit children in general while protecting the rights and welfare of particular research subjects? Research regulations are designed to help address this difficult problem. The U.S. federal pediatric guidelines (5) have been in place for almost a generation, yet key concepts are undefined or so poorly defined that relatively wide and narrow interpretations flourished unchecked until a few years ago. With little direction or consequences, investigators and institutions had little reason to question the authority of their interpretations. Investigators at the NICHD, for example, had been confident that they could safely infuse insulin into children having the “condition” of being at risk for obesity because they had one obese parent.

This situation began to change several years ago. The Office of Human Research Protection, in halting the NICHD’s obesity study and stating its reasoning for all to see on the World Wide Web, created a paradigm for others to use in evaluating their own studies. Specifically, they stated that subjects with one obese parent were healthy children and did not have conditions, and that investigators should view hyperglycemic and hyperinsulinemic clamp procedures as posing more than a minor increase over minimal risk of harm (1). Such determinations help clarify what the guidelines mean and limit the plethora of interpretations that have thrived for more than two decades. At the same time, tragic, high-profile events such as the deaths of Jessie Gelsinger and Ellen Roche risked eroding public confidence in the standards used by IRBs to protect subjects’ rights and welfare. Yet even as the IRBs were being criticized, there was more pressure on them to approve pediatric studies. Furthermore, the courts were beginning to consider whether the research regulations were consistent with the well-established best interests standard. Guardians cannot consent for studies that put children at risk without direct and compensating benefit. This standard is so engrained in the law that the Grimes court made it clear that if the “best interest of the child” standard is incompatible with

the federal pediatric regulations and practices, then the pediatric regulations and practices would have to change, and if federal agencies do not clarify the regulations, the courts will.

### References

1. U.S. Department of Health and Human Services. November 3, 2000. Re: Human Research Subject Protection under Multiple Assurance (MPA) M-100 Research Project Population Differences in the Insulin Sensitivity, Resting Energy Expenditure, and Body Composition of Overweight Children and Children of Overweight Parents. Protocol Number 96-CH 0101. P.I. Jack A. Yanovski., 9 pages. Available at: <http://www.nih.gov/sigs/bioethics/internationalresthics.html#guidelines> [Accessed 6/29/05]
2. Kopelman LM. Children as research subjects: a dilemma. *J Med Philos* 2000; 25(6):745–764. (This paper contains a fuller discussion of U.S. Regulations, including studies that are not otherwise approvable by local IRBs.)
3. “Nuremberg Code,” *Trials of War Criminals before the Nuremberg Tribunals under Control Law no. 10*, vol. 2 (Washington D.C.: U.S. Government Printing Office, 1949): 181–183.
4. World Medical Association (WMA), Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, rev. ed. (Edinburgh: 52nd World Medical Association General Assembly, October 2000), available at <http://www.wma.net/e/policy/b3.htm> [accessed 5/27/05]
5. 45 C.F.R. § 46:101-24; 45 CFR § 46:401-409 (“Additional protections for children involved as subjects in research (Subpart D)”; U.S. Department of Health and Human Services (DHHS), “Final Regulations Amending Basic HHS Policy for the Protection of Human Research Subjects,” *Federal Register* 46 (1981): 8366–8391.
6. Council for International Organizations of Medical Science (CIOMS), “International Ethical Guidelines for Biomedical Research Involving Human Subjects” (2002) available at [http://www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm) [accessed 5/27/05]
7. Kopelman LM. Minimal risk as an international ethical standard in research. *J Med Philos* 2004; 29(3):351–378.
8. Kopelman LM. What conditions justify risky nontherapeutic or “no benefit” pediatric studies: a sliding scale analysis. *J Law Med Ethics* 2004; 32(4):749–758.
9. National Bioethics Advisory Commission (NBAC), Ethical and Policy Issues in Research Involving Human Participants. Vol. I: Report and Recommendations. Bethesda, MD, Aug 2001.
10. National Human Research Protections Advisory Committee (NHRPAC), Children’s Workgroup Report (2004), “Clarifying specific portion of 45 CFR 46 Subpart D that governs Children’s Research.” Available at: <http://www.nih.gov/sigs/bioethics/internationalresthics.html#guidelines> [Accessed 6/29/05]
11. Institute of Medicine, *The Ethical Conduct of Clinical Research Involving Children*, National Academy of Sciences, Washington, DC (2004).
12. Janofsky J, Starfield B. Assessment of risk and research on children. *J Pediatr* 1981; 98(5):842–846.
13. Lascari AD. Risks of research on children,” *J Pediatr* 1981; 98(5): 759–760.
14. Shah S, Whittle A, Wilfond B, et al. How do institutional review boards apply the federal risk and benefit standards for pediatric research? *JAMA* 2004; 291(4):476–482.

15. Kopelman LM, Murphy T. Ethical concerns about risky research. *Pediatrics* 2004; 113(6):1783–1789. (This includes a discussion of 407 studies.)
16. P.L. 108-146. Pediatric Research Equity Act of 2003. [This legislation grants authority to the Food and Drug Administration to require pediatric studies of certain drugs to ensure their safety and efficacy for children.], available at <http://www.fda.gov/oc/opt/default.htm> [accessed 6/29/05]
17. P. L. 107-109. Best Pharmaceutical for Children Act of 2002. [The broad purpose of this legislation was to improve the safety and efficacies of drugs for children. One key provision renewed incentives for pharmaceutical manufacturers to test drugs in studies with children, to establish safe doses of medications that had been approved as safe and effective for adults. The legislation also requested a study by the Institute of Medicine, of research involving children.], available at <http://www.fda.gov/oc/opt/default.htm> [accessed 6/29/05]
18. Halim NS. Gene therapy institute faces uphill battle: Investigations may lead to better gene therapy trials. *The Scientist* 2000; 14(3):1.
19. Stoleberg SG. F.D.A. officials fault Penn team in gene therapy death. *The N Y Times*, 1999 Dec 9: Sect. A:22.
20. Altman LK. Volunteer In asthma study dies after inhaling drug. *The N Y Times*. 2001 Jun 15: Sect. A:16.
21. T.D. et al. v New York State Office of Mental Health et al. December 22, 1997. 91 N.Y. 2d 860, 690 N.E. 2d 1259, 668 N.S.Y.S.2d 153 [T.D. v. N.Y. State of Mental Health, 228 A.D.2d 95 (Court 1996).]
22. Grimes v. Kennedy Krieger Institute, Inc., 782 A.2d 807 (Md. 2001).
23. Grimes v. Kennedy Krieger Institute, Inc. (2001). 782 A.2d 807 (Md. 2001) and No. 128. (Md. Oct. 11, 2001) [order denying motion for reconsideration].
24. Kopelman LM. Pediatric research regulations under legal scrutiny: Grimes narrows their interpretation. *J Law Med Ethics* 2002; 30:38–49.
25. Brief of Amici Curiae Association of American Medical Colleges, Association of American Universities, Johns Hopkins University, and University of Maryland Medical System Corporation in Support of Appellee's Motion for Reconsideration of Grimes v. Kennedy Krieger, September 17, 2001.
26. Ross L. In defense of the Hopkins lead abatement studies. *J Law Med Ethics* 2000; 30:50–57.