

Nontherapeutic Research Minimal Risk, and the Kennedy Krieger Lead Abatement Study

From 1993 through 1995, the Kennedy-Krieger Institute (KKI) conducted research that examined the effectiveness of three different methods of reducing environmental lead in older homes—each of which had already been demonstrated to reduce lead dust levels significantly (by 80%) in affected homes. Funded in part by the Environmental Protection Agency (EPA), the “Lead-Based Paint Abatement and Repair and Maintenance Study” was intended to help landlords take advantage of state loan programs to make one of three lead reduction improvements. Environmental lead levels were measured using two different methods, one standard and the other experimental. In addition, blood lead levels of the young children living in the homes were monitored. Elevated blood lead levels in the children were to be reported to the family immediately; environmental lead levels were to be provided as well, but less promptly, allegedly due to delays caused by EPA testing specifications.

According to KKI, approximately 50% of the families involved in the study were already living in older homes before those buildings received the selected lead abatement procedure. The remaining families had previously lived in homes in which no efforts had been made to reduce environmental lead. All three lead reduction strategies seem to have resulted in a significant decrease in dust lead levels. The blood lead levels declined in nearly all the children involved in the study, significantly for some. Based on the demonstrated effectiveness of affordable lead abatement methods, the program has been replicated in 13 other cities.

However, at least two sets of parents have brought suit against KKI, claiming that they were not informed (1) that lead remained a potential hazard in the home and (2) that high dust lead levels were found in the home even as their child’s blood lead levels rose. Apparently one family occupied a home that underwent

one of the three lead abatement procedures, and the other occupied a “control” home that had previously undergone lead abatement. Allegedly, a two-month and a nine-month delay in reporting elevated dust lead levels resulted in continued exposure to environmental lead and an increase in the children’s blood lead level. According to press reports, the blood lead levels of three of the involved children went from 6 to 21, 9 to 32, and 11 to 24 micrograms per deciliter. As a result, it is alleged that at least one child now suffers from learning disabilities and cognitive impairments, both of which are associated with lead poisoning.

Initially, the Baltimore City Circuit Court granted KKI’s motion for summary judgment, dismissing the two lawsuits before lawyers could finish gathering information through discovery. KKI argued that the institute did not have a legal obligation to warn subjects about the risks since the study simply collected data and the signed consent forms are not binding contracts. In addition, they argued that there was no duty to report the elevated dust lead levels to families because they were measured with an experimental device. The Maryland Court of Appeals reversed the lower court. In ordering that the lawsuits proceed to trial, however, the court of appeals also held that a parent or guardian cannot consent to a child’s participation in nontherapeutic research in which there is any risk of injury or damage to the child’s health.

The Appellate Decision

The Maryland Court of Appeals addressed two issues: First, was the Kennedy Krieger Institute (KKI) entitled to summary judgment concerning lawsuits brought on behalf of two children involved in the study? And second, can a parent in Maryland legally consent to placing a child in a non-therapeutic research study that carries with it any risk of harm to the health of the child?¹ The court’s answer to this broader question has generated much attention and fear that most nontherapeutic research involving children would be prohibited in the state of Maryland in

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the absence of prior court approval.

“What right does a parent have to knowingly expose a child not in need of therapy to health risks or otherwise knowingly place a child in danger, even if it can be argued it is for the greater good?”³ This same question concerned the National Commission, whose 1977 report established the special protections for children involved in research now found in Subpart D of 45 CFR 46 (for HHS funded research) and recently adopted by the Food and Drug Administration (21 CFR 50, 56). Essential to these special protections is the category of “minimal risk,” which restricts the risks to which child-participants may be exposed in nontherapeutic research. Emphasizing independent review of “the scientific merits and the acceptability of risks,” the court correctly argued that parental consent is insufficient to justify the risks of research.⁴ The appropriateness of a child’s research participation rests on the “twin protections” of independent IRB review of the risks and benefits and a parent’s voluntary and informed consent.⁵ From the available information, what can be said about the adequacy of these two protections in the KKI lead abatement study?

The KKI Lead Abatement Study Design

The study in question was designed to determine the short-term (6 months) and long-term (up to 24 months) efficacy of three different methods of lead abatement in older homes (groups 1-3) compared to homes that had been abated under a city program (group 4) and homes built after 1978 that contained no lead paint (group 5). Although the different methods of lead abatement may result in different distributions of lead in the home, KKI claims that all three methods reduce lead dust by approximately 80% compared to untreated properties. Outcome measures tested at intervals over the two-year study included environmental lead levels using a standard method of wiping surfaces and an untested method of vacuuming surfaces, and blood lead levels from young children residing in the home. With an increase in blood lead levels of 5 or more micrograms per deciliter or an absolute level of more than 20 micrograms per deciliter, the child’s health care provider, the Health Department, and the landlord would be notified, the home visually inspected, and advice on cleaning and diet provided to the family.⁶

According to KKI, half of the older homes were occupied prior to the study, and the other half were occupied after the study began by “inner city families who likely had no choice but to rent non-abated properties . . .”⁷ In effect, there were two populations of children

involved: those children living in a home selected for abatement (and thus already “at risk” for lead toxicity) and those children moving into a selected home after scheduled abatement (and thus placed “at risk” for lead toxicity). This distinction is crucial to the ethical analysis of the research.

The Prospect of Direct Benefit

For an IRB to approve research involving children, the protocol must either offer the prospect of direct benefit to individual child-participants, or if it does not, it must pose no more than a “minor increase over minimal risk.” Did the interventions or procedures in the research offer the prospect of direct benefit to enrolled children? For a benefit to be “direct,” it should accrue to the particular child involved in the research and not require any additional interventions outside of the research study. A monitoring procedure does not offer the prospect of direct benefit unless it is linked within the research protocol to treatment for the condition detected. Thus, the testing of blood lead levels does not offer a direct benefit in the absence of guaranteed lead abatement or treatment.

Did the lead abatement procedure offer the prospect of direct benefit? Yes, for those children already living in lead-affected homes. For the children who moved into previously lead-abated homes, however, the abatement procedure(s) did *not* offer the prospect of direct benefit. (This is so even if an informed parent voluntarily decided that moving into an abated home was preferable to available alternatives.) To think otherwise would suggest that intentional exposure to environmental lead is a direct benefit—an untenable argument.

The analysis of direct benefit is separate from whether an individual child is better off (or may benefit) from moving into an abated home. A potential benefit from knowledge gained as a result of lead monitoring or of moving into a partially lead-abated home (compared to other less desirable choices) may be included in a consent document without being considered a *direct* benefit. Whether or not the IRB determined that the research offered the prospect of direct benefit is not clearly established from the passage cited by the court.

Greater than Minimal Risk

Did the interventions or procedures involved in the lead abatement study present greater than minimal risk? Minimal risk is defined as “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 or psychological examinations or tests” (45 CFR 46.102(i)). The moral and regulatory function of minimal risk is to restrict the allowable risks to which a child may be exposed to during nontherapeutic research. The National Commission argued that a parent lacks the moral authority to expose a healthy child to research involving more than minimal risk. Accordingly, the proper analysis of research risks must account for statistical (or descriptive) information concerning risks and the normative question of whether a parent should expose a child to those risks. Statistical analysis alone will not address the moral question of whether a parent should expose a child to a given risk, or whether the everyday risks of a particular child’s life justify the risk of nontherapeutic research. Would a “reasonable parent” expose a child to this research risk? Should a “reasonable parent” expose a child to this research risk? The consent of a “reasonable parent” only functions within the moral and legal boundary of appropriate risk exposure. As such, the concepts of minimal risk and parental consent (or permission) both reflect the standard of the “reasonable parent.”

A blood test for lead levels performed at regular intervals is properly considered minimal risk under 46.406. Lead abatement procedures may involve more than minimal risk, since environmental exposure may be increased during the abatement. (This risk can be minimized through removing a child from the home during abatement.) There appears to be uncertainty about the efficacy and safety of the three different methods of lead abatement compared to standard abatement procedures and to one another. Given this uncertainty, the risk of continued lead exposure compared to the standard or full lead abatement procedure is more than minimal. Finally, the intentional exposure to lead (for children moving into the homes) or exposure to potentially ineffective methods of lead abatement (for children already living in them) cannot be considered minimal risk. Simply, a “reasonable parent” would not intentionally expose a child to environmental lead without making every effort to reduce or eliminate that exposure. Participating in a research study involving a comparison of lead abatement procedures may be the best available option for some parents who would otherwise need to live in older homes that had not undergone lead abatement. But this observation does not justify a decision that the study poses minimal risk, or offers the prospect of direct benefit, but it may justify approving such a

study under special protections at 45 CFR 46.407 (discussed below).

Applying the Special Protections of Subpart D

Monitoring children’s blood lead levels is minimal risk, and is an essential safety aspect of the study, with levels pre-established at which (1) a child would be removed from the study and a full lead abatement procedure performed on the home or (2) a child would not be eligible to enter the study given the risks of a partial lead abatement procedure. But as we have seen, monitoring blood lead levels should not be considered a direct benefit of participation in the study.

The study does offer direct benefit to those children already living in a lead-affected home. In addition, there appears to be equipoise among the three different methods of lead abatement, although the information publicly available is insufficient to determine whether “the relation of the anticipated benefit to the risk” of the three different methods is “at least as favorable” as the full lead abatement procedure. If it is, the three lead abatement procedures could be approved under §46.405 (Research involving greater than minimal risk but presenting the prospect of direct benefit) for those children already living in lead-affected homes.

However, the study does *not* offer the prospect of direct benefit for those children who do not already live in a lead-affected home. Moving a child into a home after less than a full abatement procedure is not minimal risk (although moving into such a home may be the “best choice” among alternatives available to a parent). The study qualifies as “minimal risk” only to the extent that children are moved into homes that either have been fully abated or were constructed using nonlead paint. For this aspect of the study to be approved under §46.404, the participation of healthy children should have been restricted to the “control” homes that were lead free.

As the court noted, with respect to children who would be moved into the older homes, an alternative to disapproving the protocol is to seek guidance from the Secretary of HHS under 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). Whether this aspect of the research study would have been approved if the IRB had referred it under 46.407 is uncertain. However, the reasonableness of the hypothesis that the different lead abatement procedures would be equally effective, along with the limited availability of alternative housing, argues in favor of approval under this section. The study

as designed could be approved and conducted according to sound ethical principles. Such approval would not be forthcoming without an appropriate period of public comment, allowing for community discussion of the issues.

Parental Consent (Permission) and the Duty to Warn

In addition to the inadequate risk analysis, the court expressed doubts that parental consent was either voluntary or informed. Given KKI's interest in having young children in the home for the duration of the research study, were the children "enticed" or "encouraged" to "remain" in the lead-affected home?⁹ The court noted that the consent document did not contain information that the "reasonable parent" would want to know: There was no information about the primary aim of the study (i.e., to examine the effectiveness of three different methods of lead abatement), no explanation of the three different methods of lead abatement, no mention of the importance of blood lead levels and the impact on young children of lead exposure, and no discussion of the risks of inadequate lead abatement.¹⁰

One research aim was to compare environmental lead levels obtained using the standard technique of wiping surfaces versus using a vacuum dust collector. Using an ad hoc distinction between risk and hazard,¹¹ KKI argued there was no duty to warn a parent of the results of the vacuum dust analysis, since standards for hazardous environmental exposure are based on the dust wipe technique.¹² This argument ignores that the standard is to inform a subject of any "significant new findings . . . which may relate to the subject's willingness to continue participation" (45 CFR 46.116(b)(5)). Lead is a known environmental toxin with demonstrated harm on a young child's intellectual development. Although interpreting vacuum dust levels may be difficult, parents should be warned of the presence of lead in the home. Similar to existing standards for ionizing radiation, the consent document should include a warning about lead exposure, with acknowledgement that the risks of exposure to levels of lead anticipated in the research are unknown. With a known environmental toxin, a distinction between risk (i.e., an unknown hazard) and hazard does not reflect what a "reasonable parent" would want to know.

Articulating a Legal Standard for Nontherapeutic Research Involving Children

What standard of risk has the court articulated for nontherapeutic research involving healthy children? Although it described unacceptable risk in several ways in its holding, in essence the court affirmed the current federal standard of minimal risk for nontherapeutic research in healthy children. In clarifying its attention to risk, the court noted in a later document that by "any risk" it meant "any articulable risk beyond the minimal kind of risk that is inherent in any endeavor" (emphasis added). The Court nonetheless acknowledged that it had not resolved the questions whether the study offered benefit and could thus be regarded as therapeutic, or whether it involved more than that minimal risk. Those questions were remanded back to the trial court.

In an amicus brief, the Association of American Medical Colleges, among others, argued against a standard of "no risk" in favor of "minimal risk" for nontherapeutic research involving children.¹³ Some of their arguments would do more damage to pediatric research than the most restrictive interpretation of the appellate court's ruling. First, the brief argues that the court's interpretation of risk would preclude a placebo control arm. However, if equipoise exists between a study intervention and a placebo control, clinical trials involving placebos are properly considered under §46.405. To argue that "for the placebo recipients, the research holds no prospect of direct benefit" assumes a priori the truth of the hypothesis that the research is designed to test. Second, "research involving any disease for which there is no known curative treatment or effective prevention" may be reviewed under §46.405 provided that the prospect of direct benefit is justified by preclinical and other studies. To argue that such research is "nontherapeutic" since subjects may "receive an experimental intervention that ultimately proves ineffective" implies that an IRB must know the results of the research before determining the prospect of direct benefit—an illogical position. Finally, the brief suggests that vaccine research would be prohibited since "preliminary trials are conducted with healthy children to demonstrate safety and ability to stimulate an immune response." Although the question is controversial, this argument ignores the legitimate possibility that an IRB may consider vaccine research under §46.405 (based on prior evidence of an immune response) or refer the protocol for review by an expert panel under §46.407.

Minimal Risk, But Not Business as Usual

In overturning the summary judgment and remanding the case back to the lower court, the Maryland Court of Appeals affirmed a minimal risk standard for nontherapeutic research involving healthy children. The court asked the right question about the moral authority of parents, and came to the same conclusion as the National Commission: Parents do not have the moral or legal authority to enroll healthy children in research that does not offer the prospect of direct benefit unless the risks of that research are no greater than the ordinary risks of daily life. However, the affirmation of a “minimal risk” standard should not mean a return to “business as usual.” There exists unacceptable variability in the interpretation and application of Subpart D, indicating a failure to understand the moral underpinnings of the restrictions on risk to which children involved in research may be exposed. Whether more specific guidance on the special protections of Subpart D and improved IRB oversight through accreditation and not-for-cause site visits will reduce this unacceptable variability remains to be seen.

■ **Robert M. Nelson, MD, PhD**, is associate professor of anesthesia and pediatrics at The Children’s Hospital of Philadelphia and a contributing editor to this journal.

References

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3. See ref. 1, p. 79.
4. See ref. 1, p. 7.
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9. See ref. 1, pp. 2, 6,7, 16, 19-20, 23.
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