ARTICLE

Minimal Risk in Pediatric Research as a Function of Age

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The minimal risk standard allows institutional review boards (IRBs) to approve pediatric research when the risks do not exceed the risks children face in daily life or during routine examinations. The fact that the risks children face in daily life vary with age raises the question of whether IRBs should implement this standard by adopting 1, 2, 3, or even more risk standards. The level of research risks to which it is appropriate to expose children depends on their maturity level. While younger children should be exposed to only very low research risks, it can be appropriate to expose older children to somewhat higher risks. This analysis supports 2 thresholds for minimal risk in pediatric research: one for research with younger children and a distinct standard for older children who can understand and who agree to participate.

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Children should be enrolled in clinical research only when it offers a compensating potential for benefit or poses sufficiently low risks.[1-3] To this end, US regulations allow institutional review boards (IRBs) to approve pediatric research interventions that do not offer a prospect of direct benefit only when the risks are minimal or a minor increase over minimal.[4,5] Under the US regulations[4,5] and the regulations of several other countries,[6] research risks qualify as minimal when they do not exceed the level of risks children ordinarily encounter in daily life or during routine examinations.

Recent data[7,8] find that the level of risks children in the US ordinarily encounter in daily life varies significantly with age. It follows that the minimal risk standard for pediatric research can be implemented in several ways. First, IRBs could adopt a single minimal risk threshold that applies to research with children of all ages. Institutional review boards could hold, for example, that the risks of pediatric research interventions qualify as minimal when the risks do not exceed the *average* level of risk children ordinarily encounter in daily life.

Second, IRBs might adopt a different risk threshold for each stage of development. The risks of research with infants would be evaluated by comparing them with the level of risks infants ordinarily face in daily life; the risks of research with toddlers would be compared with the risks toddlers ordinarily face in daily life; and the risks of research with adolescents would be compared with the level of risk in their lives.

Third, IRBs could adopt a minimal risk threshold for children of each age. Research with children 1 year old would qualify as minimal risk when the risks do not exceed the level of risks 1-year-olds ordinarily encounter in daily life, the risks of research with 2-year-olds would be compared with the risks ordinarily encountered by 2-year-olds, and so on.

Given that all 3 approaches are consistent with the federal regulations, individual IRBs can adopt whichever approach they prefer. Nevertheless, some approaches may offer children insufficient protection, and adoption of different approaches across IRBs could inadvertently block multisite pediatric research.

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The present article thus considers whether one of these approaches offers better protection without blocking appropriate pediatric research.

INTERPRETATIONS OF THE MINIMAL RISK STANDARD

The US regulations define minimal risks as risks that do not exceed those "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[5,6] This definition, which is not further clarified, could be interpreted in at least 2 ways. The "relative" interpretation directs IRBs to compare the risks of pediatric research with the risks ordinarily encountered by the specific children to be enrolled.[1] The problem with this interpretation is that it would allow researchers to expose children who live in violent neighborhoods or who face greater than average environmental health hazards to greater risks in research that does not offer a prospect of direct benefit.[1] To avoid taking advantage of some children's unfortunate circumstances in this way, most commentators endorse the "absolute" interpretation.[9] This interpretation directs IRBs to evaluate the risks of pediatric research by comparing them with the risks average, healthy children ordinarily encounter in daily life.[1]

RISKS FOR AVERAGE CHILDREN

Average, healthy children face very low and relatively constant risks from routine examinations.[10] In contrast, although more and better data are needed, existing data find that the risks average, healthy children ordinarily encounter in daily life in the United States vary significantly with age.[7] Average, healthy children younger than 1 year face the greatest risk of mortality in the United States, largely as a result of their almost complete dependence on others.[7] Average infants face approximately a 140 in 1 million risk of suffocation per year, whereas the risk of suffocation for older children is approximately 5 in 1 million per year.[7]

After infancy, the overall risks of mortality diminish substantially before increasing during adolescence. Routine car trips in the United States pose an approximately 0.06 in 1 million risk of death for younger children, but up to an approximately 4.0 in 1 million risk of death for children older than 14 years.[8] Most of this difference can be traced to the fact that adolescents, but not younger children, are allowed to drive and are more likely than younger children to ride in a car driven by a teenager. Although there are fewer data available on morbidity risks, it appears that adolescents face significantly greater risks of morbidity than do younger children. The cumulative daily risk of hospitalization for average children in the United States is approximately 1.5 in 1 million for children up to age 14 years, but approximately 6.0 in 1 million for children older than 14 years.[8]

These age-related differences in morbidity risk likely come from several sources. First, society allows older children, but not younger ones, to participate in riskier activities, such as driving a car. Second, the increased size, weight, and strength of older children increases the risks they pose to their contemporaries in daily life, especially when playing sports. Third, reasonable parents often allow adolescents, but not younger children, to engage in activities such as ice skating and hiking that pose risks without adult supervision. Fourth, adolescents are more likely than younger children to engage in inappropriate activities and behave recklessly.

HOW MANY RISK STANDARDS?

Some of the risks children ordinarily face in daily life are inappropriate and do not provide a standard for determining which risks are appropriate in research.[11] Infants' increased risk of suffocation and the risks teenagers face when driving recklessly are inappropriate; they should be eliminated from daily life and, to the extent possible, not allowed into clinical research.

Other risks in daily life are appropriate for older children but not younger ones. It is acceptable for 17-year-olds, but not 5-year-olds, to face the risks of driving a car. The fact that, in daily life, it is appropriate for older children to face greater risks raises the question of how IRBs should evaluate the risks of pediatric research.

One possibility would be for IRBs to adopt a single threshold for minimal risk based on the average level of risks appropriate for all children. With this approach, IRBs would average the level of risks appropriate for younger children and the level of risks appropriate for older children to develop a single, minimal risk threshold. Although this approach has the virtue of simplicity, it also has the potential to allow younger children to be exposed to risks that are appropriate for adolescents but not for younger children. Institutional review boards could avoid this concern by defining a single, minimal risk threshold based on the level of risks appropriate for younger children. This approach provides appropriate protection for younger children but seems overly restrictive for teenagers. The fact that a given level of risk is inappropriate for younger children does not necessarily imply that it is inappropriate for older children.

To ensure that children are exposed only to research risks that are appropriate for them, IRBs could adopt age-specific thresholds: one threshold for 1-year-olds and separate thresholds for 2-, 3-, and 4-year-olds. This approach, which might offer the most appropriate protection, seems very difficult to implement in practice. It would require IRBs to keep track of at least 17 different minimal risk thresholds. Moreover, because the risks of daily life do not increase substantially at each age, this complexity does not seem justified by increased protection.

A compromise would be to adopt a risk threshold for the different stages of development. This approach should be informed by the fact that several developmental transitions do not justify exposing children to greater research risks. For example, the fact that a child matures from infant to toddler does not provide a justification for exposing the child to greater research risks. In contrast, the fact that children develop the ability to understand and make decisions does provide a reason to allow them to face greater research risks, provided they understand and agree to face the risks.

This analysis points to the possibility of adopting 2 thresholds. The minimal risk threshold for research with

younger children would be based on which research risks are appropriate for them. The second threshold would apply to research with adolescents and would be based on which research risks are appropriate for those who can understand and make their own decisions.

POSSIBLE OBJECTION

Institutional review boards should not allow some children to face greater research risks simply because they happen to face greater risks in daily life. For example, IRBs should not allow some children to face greater research risks simply because they happen to live in unsafe neighborhoods. It is for this reason that most commentators reject the relative interpretation of the minimal risk standard and endorse the absolute interpretation. It might be argued that the current endorsement of 2 thresholds for minimal risk in pediatric research makes the same mistake with respect to older children, allowing them to face greater research risks simply because they happen to face greater risks in daily life.

Allowing children to face greater risks in research on the basis of the fact that they face greater risks in daily life raises the specter of exploitation when the risks the children face in daily life are inappropriate or a matter of injustice. The present proposal to allow adolescents to be exposed to somewhat higher research risks does not seem to involve exploitation, provided the research risks allowed do not exceed those appropriate for adolescents. Rather, this proposal involves recognition of the fact that adolescents can understand and make their own decisions.[12,13] Ackerman[14] endorses this approach, arguing that it can be "appropriate for older children with mature decision-making capacities" to face greater research risks for the benefit of others, provided the children understand the research and agree to participate. Similarly, Nelson[15] would allow the "informed assent of a child to influence the risk restrictions placed on" his or her participation in research.

DATA FOR 2 MINIMAL RISK THRESHOLDS

Empirical studies find that most children younger than 10 years are not able to understand many aspects of clinical research.[16-20] In contrast, children 10 years or older often are able to understand a good deal about clinical research and, by age 12 to 14 years, most children are able to understand clinical research at approximately the same level as the average adult.[21] These data point to age 12 to 14 years as the cutoff between the 2 risk thresholds. Accordingly, IRBs would categorize research with children younger than 12 to 14 years as minimal risk when the risks do not exceed the risks appropriate for younger children who are not able to understand and make their own decisions; research with older children would qualify as minimal risk when the risks do not exceed the risks appropriate for teenagers.

Not all the risks adolescents face in daily life are appropriate in the context of research that does not offer a prospect of direct benefit. Institutional review boards should not approve pediatric research that poses risks similar to the risks adolescents face when engaging in inappropriately risky behavior, such as driving while intoxicated. Again, the standard is whether the risks are appropriate for teenagers.

The existing data provide information needed to apply these 2 risk thresholds. The threshold for what risk of mortality qualifies as minimal for younger children could be based on the risks of mortality from ordinary and acceptable car rides for younger children; the threshold for what risk of mortality qualifies as minimal for adolescents could be based on the risks of mortality for ordinary and acceptable car rides for adolescents. Similarly, what level of morbidity risk qualifies as minimal could be based, in part, on the risk of hospitalization that appropriate activities of daily life pose to children in the 2 age groups. Future research to collect the necessary empirical data would provide more information that IRBs could use to evaluate the risks of pediatric research.

IMPLEMENTING 2 THRESHOLDS

To be cautious, IRBs could adopt age 14 years as the default cutoff for applying the 2 risk thresholds. This default could then be modified in specific cases. Some studies, such as those that do not offer the prospect of direct benefit and pose risks at the top of the range appropriate for adolescents, raise greater ethical concern. The general presumption that adolescents are able to understand and make their own decisions may not provide sufficient protection for these studies. Instead, IRBs might stipulate that eligible children should be formally evaluated and allow enrollment of only those who are found to understand and who agree to participate.

Investigators may have compelling reasons to enroll younger children in some studies that meet the risk threshold appropriate for teenagers but exceed the risk threshold appropriate for typical younger children. For example, studies of normal development may need to enroll some healthy children who have not yet experienced puberty, but pose risks slightly beyond those allowed by the minimal risk standard for younger children. Institutional review boards might consider categorizing such studies as minimal risk for younger children who, on formation evaluation, are found to be mature enough to participate and able to understand and make their own decision to enroll.

Many guidelines and commentators consider the risks posed by lumbar puncture to exceed the risks average, healthy children ordinarily face in daily life.[1] Given this judgment, IRBs that use a single threshold to evaluate the risks of pediatric research would conclude that lumbar puncture qualifies as greater than minimal risk for all children. It follows, under the US regulations, that IRBs would not be able to approve a study designed to perform lumbar puncture in healthy children, even when necessary to gather very important information.

The present proposal directs IRBs to evaluate whether the risks of lumbar puncture exceed the risks younger children face in daily life and then separately evaluate whether these risks exceed the risks appropriate for teenagers. Depending on the actual risks of lumbar puncture, the IRB might find that it poses greater than minimal risk in younger children but only minimal risk in

teenagers. In this way, adoption of 2 risk thresholds would allow IRBs to make a more nuanced evaluation of the risks of pediatric research, limiting research with younger children to very low risks while allowing somewhat greater risks in research with older children who are able to understand and who agree to face the risks in question for the benefit of others.

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"Science is always simple and always profound. It is only the half-truths that are dangerous."
—George Bernard Shaw, *The Doctor's Dilemma*, 1913