A Standard for Assessing the Risks of Pediatric Research: Pro and Con

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To evaluate the safety and efficacy of medical interventions for children, investigators often must conduct research with children, including research that does not offer the children a compensating potential for clinical benefit.[1,2] For example, when evaluating lopinavir/ritonavir therapy in children with human immunodeficiency virus, investigators first gave single doses to a few children to determine what dose levels they could tolerate.[3] These tests, necessary preludes to future efficacy studies, posed some risks to the participating children but did not offer them any potential for clinical benefit.

"Nonbeneficial" pediatric research had been the subject of ethical debate for more than 25 years.[4-6] Most notably, McCormick argued that children, if capable, would consent to nonbeneficial pediatric research when it poses no "discernible risk."[7,8] Ramsey responded that McCormick's argument relies on unwarranted assumptions regarding children's hypothetical choices, ignores the fact that children are neither mature nor autonomous, and disregards adults' obligations to protect children.[9,10]

Although the theoretical debate continues, current guidelines allow enrollment of children in nonbeneficial research when it poses acceptably low risks and is likely to yield information important for improving children's health and well being. Unfortunately, current standards for defining what constitutes an acceptable level of risk have some serious shortcomings. In this article, we evaluate a possible alternative, the "charitable participation" standard, which assesses the risks of pediatric research based on the level of risks to which children may be exposed in appropriate charitable activities.

THE NO SERIOUS HARM THRESHOLD

Guidelines might allow nonbeneficial pediatric research provided that it poses no risk of serious harm. The Council of Europe and the UK Medical Research Council appear to endorse this approach, stipulating that research is acceptable when "it is to be expected that [the research] will result, at the most, in a very slight and temporary negative impact on the health of the person concerned."[11,12] Because this approach blocks research that poses any risk, no matter how low, of serious injury, it has the potential to block a good deal of pediatric research. Even a single blood draw poses some (albeit extremely low) risk of serious harm.

Other guidelines, including those from Kenya and the Indian Council on Medical Research, leave the decision of when pediatric risks are acceptably low to the judgment of reviewing ethics committees.[13,14] However, psychological research has found that individuals often make systematic errors when they rely on their own perceptions to assess risks,[15-17] suggesting the need for more guidance to protect pediatric research participants.

THE ROUTINE EXAMINATIONS STANDARD

The Council for International Organizations of Medical Sciences allows nonbeneficial pediatric research when the risks "do not exceed those associated with routine medical and psychological examination of such persons."[18] As stated, this standard appears to allow those who require risky examinations as part of their routine medical care to be exposed to greater research risks than healthy children. To avoid taking advantage of sick children in this way, several authors define acceptable risks based on the level of risk posed by routine examinations for healthy children.[19,20]

The Bright Futures guidelines, endorsed by the American Academy of Pediatrics, recommend that healthy children be assessed for height, weight, head circumference, vision, and hearing.[21] The only invasive examination recommended for healthy children is a single heel stick at birth to screen for metabolic disorders. In practice, then, the healthy child standard seems to preclude research that poses risks any greater than the level of risk posed by a single heel stick. Moreover, children in some countries do not undergo routine medical examinations, leaving it unclear how this standard applies in those countries.

RISKS OF DAILY LIFE STANDARD

Many guidelines define acceptably low risks based on the level of risk that children face in daily life. Australia's guidelines allow research interventions when "the probability

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and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life."[22] Guidelines from Nepal and the United States combine this definition with the routine examinations standard, defining "minimal" risks as "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."[23-25]

Despite widespread endorsement, the "risks of daily life" standard suffers significant shortcomings.[26] Most importantly, many of the activities of daily life offer children the potential for personal benefit. For example, parents do not allow their children to play basketball because they find the risks inherently acceptable; rather, parents accept these risks because they assume that their children will benefit. It follows that the level of risk considered acceptable in daily life may not be appropriate for evaluating research that does not offer a compensating potential for clinical benefit.

CHARITABLE ACTIVITIES IN DAILY LIFE

Every year, millions of children participate in charitable programs around the world. These programs, designed to benefit others, pose some risks to the participating children. For instance, Youth Service America "partners with thousands of organizations committed to increasing the quality and quantity of volunteer opportunities for young people, ages 5-25."[27] During Global Youth Service Day, millions of children in more than 120 countries carry out local community improvement projects, such as planting crops, visiting sick persons, digging wells, and collecting donations.[28] Many respected international charitable organizations have programs designed for children; for example, UNICEF encourages children to collect money for the poor,[29] and Habitat for Humanity "focuses on engaging youth ages 5 to 25 in [their] mission and work."[30]

When children participate in charitable activities, special safeguards are needed, and some charitable activities are not appropriate for children at all. Habit for Humanity, for example, does not allow children under age 16 to enter construction sites. Nonetheless, it is recognized worldwide that when appropriate safeguards are in place, children's participation in charitable activities to help others can be appropriate, even when doing so poses some risk to them.

PRO: ARGUMENTS FOR THE CHARITABLE PARTICIPATION STANDARD

Charitable activities are similar to nonbeneficial research in a number of ethically salient respects. First, charitable activities and nonbeneficial pediatric research typically are designed to help individuals unrelated to the participants. Second, many charitable activities, like most nonbeneficial research studies, help unidentified individuals. Third, nonbeneficial pediatric research and charitable programs offer only a *chance* that others will be helped; the anticipated benefits of a charitable car wash, like those of a clinical trial, may fail to materialize. The fact that children may participate in charitable activities suggests that their participation in nonbeneficial research may be acceptable, even though such involvement offers only a chance of helping unidentified and unrelated individuals.

One possible difference between research and charitable activities is that children actively participate in charitable activities: they collect donations, wash cars, build homes, and so on. Research participation, in contrast, seems to be inherently passive; children are subjected to research interventions. But in fact, research participation typically requires some active participation; children must come to the clinic, answer questions, remember their schedule, and monitor and report side effects. Even interventions that seem to involve purely passive participation, such as holding still for an magnetic resonance imaging scan, can require more effort than many charitable activities.

A different, and perhaps more relevant, sense of "passive" participation involves the relationship between individuals' participation and their understanding and will. Adults and older children can make their involvement in a given project active by understanding and voluntarily agreeing to it. For example, the collection of blood involves essentially no physical movement on the part of donors, yet as long as the donor understands and agrees, blood donation is described in active terms as the "giving" or "donating" of blood. In contrast, researchers "take" blood from infants who cannot understand and agree.

The claim that such passive exposure to risks for the benefit of others is unethical seems to gain support from the fact that charitable activities typically do not involve infants or toddlers. Alternatively, infants and toddlers may not be involved in charitable activities for the simple reason that they are unable to contribute to most charitable activities. Choosing between these 2 options requires analysis of the moral significance of individuals' understanding and endorsing the charitable activities in which they are involved.

There are at least 2 ways to view the importance of obtaining individuals' informed and voluntary agreement.[31] One view holds that it is ethically unacceptable to expose an individual to risk for the benefit of others without that individual's agreement. This view implies that charitable activities with infants and toddlers are unethical because they cannot understand and agree. A second view holds that it is unacceptable to expose an individual to risks for the benefit of others in a way that is inconsistent with that individual's will. Here informed agreement is not an ethical requirement for those, including infants and toddlers, who lack the capacity to provide it. In these cases, research enrollment cannot be inconsistent with the individual's will and thus may be acceptable provided that alternative safeguards are in place.

Although a complete analysis is beyond the scope of the present article, one way to assess these 2 views is to consider their implications in concrete cases. Imagine that taking a few extra drops of blood from a group of newborns during a clinically indicated heel stick could yield information needed to develop a new treatment for a childhood illness. The view

that individuals should never be exposed to risks for the benefit of others unless they understand and accept them implies that this intervention is necessarily unethical, no matter how low the risks and no matter how important the information to be gained.

The alternative view holds that agreement is not always required for individuals who lack the capacity to provide it. This view implies that obtaining a few extra drops of blood from infants may be acceptable provided that appropriate safeguards are in place, such as the risk is low, the information to be gained is important, there is no other reasonable way to obtain the information, the child's parents give permission, and an independent review committee certifies that these safeguards have been satisfied. This approach raises the question of whether the level of risk acceptable for charitable activities with 5-year-olds provides an appropriate threshold for research risks with infants and toddlers. The fact that infants and toddlers cannot provide even rudimentary informed agreement may imply that the level of risk to which they may be exposed for the benefit of others is lower. If so, then a supplementary standard to the charitable participation standard may be needed to evaluate the risks of nonbeneficial research with infants and toddlers.

CON: ARGUMENTS AGAINST THE CHARITABLE PARTICIPATION STANDARD

Most research guidelines allow children to be exposed to risks for the benefit of others, provided that these risks are not too great and the information to be gained is of sufficient importance to justify the risks. US federal regulations, for example, permit such research if the risk of harm is minimal or a minor increase over minimal and "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" (45 CFR 46.406 c).

Although this approach strikes a utilitarian balance, it does not answer the fundamental ethical question of why this utilitarian approach should override other ethical concerns. The most serious ethical problem that such research represents is that of the obligation of loyalty of powerful persons to less-powerful persons. It is not that all powerful persons must be loyal to all less-powerful persons, but some relationships require such loyalty. In particular, parents are supposed to act in ways that further the interests of their children. Physicians also are supposed to act in ways that further the interests of their patients and do not unnecessarily place the patients at risk.

When a researcher asks a person to be a research subject, the researcher is asking for a gift. A gift is given knowingly and voluntarily by one person to another. If the transaction is not knowing and voluntary, it is not a gift. In general, a gift may not be given by a surrogate. For instance, faced with the possibility of removing a kidney from an incompetent person to "donate" it to a family member, a court ruled that because guardians cannot make gifts of money or property, they certainly cannot make gifts of an organ.[32]

It has been argued that parents should be able to volunteer their children for research that holds out no prospect of clinical benefit for the children and poses some risk of harm. This argument is based largely on the notion that societal values both endorse and recognize parents' authority to expose children to risks for the benefit of unrelated others when the risks are acceptably low. However, the charitable examples cited in the previous section do not support research on very young children. These examples reflect a societal notion that children partaking in activities with their parents is a good thing. Moreover, these examples involve normal childhood activities in which children readily and happily engage. These examples do not seem analogous to a child undergoing a lumbar puncture or insertion of an indwelling catheter in a vein, requiring that he or she lie still for 8 hours.

In my opinion, the major difference is that in medical research, something is being done *to* the child, not with or by the child. When a charitable act is done, it is not done by the child, but rather by the parent who volunteers the child. It is certainly the case that some research requires a child's true participation, as in filling out questionnaires or entering information in a computer. I am not sure anyone would object to this type of research, because the child is active and doing childlike things. Further, the child can always stop doing these activities if he or she becomes bored or tired, unlike a child who is exposed to a drug.

It seems fanciful to argue that children are active participants in biomedical research. They do not come to the clinic; rather, they are brought to the clinic. Indeed, the claim of "passive participation" would seem to be a contradiction in terms. It is difficult to see how the toxicity study of lopinar/ritonavir mentioned earlier required the children's participation. Although the use of children in that study might have been necessary to answer the research question, and the end sought may have been important, the children were a means to that end, not active participants.

It is the class of research that involves children's bodies being invaded with drugs or devices that is the true cause of concern. It is hard to imagine on what ethical basis a parent can permit a researcher to put a needle in a 4-year-old's spine purely for research purposes. This conclusion seems to be supported by the fact that charitable organizations often exclude young children; for instance, the American Red Cross requires that blood donors be at least 16 years old.[33] An individual must be 16 to participate in Habitat for Humanity's building programs; indeed, its programs for 5- to 8-year-olds contain no element of charity, but rather involve activities that may sensitize children to the need for future charity. These differences suggest that the level of risk of charitable activities does not offer an appropriate standard for assessing the risks of nonbeneficial research with children who are unable to give their own informed consent.

CONCLUSION

Many research regulations assess the risks of nonbeneficial pediatric research by comparing them with the level of

risks that children face in daily life. However, some risks of daily life are justified by a potential direct benefit to the child, and others are considered inappropriate. These concerns point to the need to consider other standards for assessing the risks of nonbeneficial pediatric research.

It can be argued that nonbeneficial pediatric research involves a kind of charitable activity. If one accepts this argument, then the level of risk posed by appropriate charitable activities might offer a standard for assessing the risks of nonbeneficial pediatric research. In its favor, this "charitable participation" standard would allow the enrollment of children in nonbeneficial research only when the risks are within societally accepted limits and the children's parents give their permission. The charitable participation standard also may help researchers, review committees, parents, and society come to view nonbeneficial pediatric research in the same favorable light that we now view charitable activities in daily life. Implementation of the charitable participation standard, like other empirical standards, will require research to collect empirical data on the level of risk allowed in charitable activities appropriate for children.

On the other hand, there are arguably important differences between medical research and charitable activities that raise concerns about this approach. In particular, children are active participants in most charitable activities, whereas most medical research is done to the children's bodies. This difference raises a concern that the risks of charitable activities may not offer an appropriate standard for assessing the risks of most clinical research. Similarly, infants and toddlers never engage in charitable activities, so the analogy would appear to not apply to this age group. Furthermore, many children's charitable activities are done alongside or with parents or other adults, whereas research with children is done exclusively to them.

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