Guidelines for the Ethical Study of Drugs in Infants and Children and the FDA Regulations

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There has been increasing acceptance of children as appropriate subjects of research over the past three decades. This arises from recognition that children differ from mature individuals in many critical respects. It is the process of growth and development that distinguishes children from adults. In addition to size, children differ from adults in many respects, including body proportions, susceptibility (or lack of it) to certain diseases, responses to treatments, vulnerability to certain drug toxicities, nutritional requirements, and their dependent status in society. It is precisely because children differ from adults in many important characteristics that they must share in the research process in order to benefit from advances in diagnosis and treatment unique to their needs. In other words, research in adults cannot necessarily be applied directly to children.

Because of the uniquely dependent status of children in society, special protections must be provided when they participate in research. It is the nature of and basis for these special protections that are discussed in this chapter. In addition, the current status of the Food and Drug Administration (FDA) regulations pertaining to labeling of drugs for children is presented.

HISTORICAL CONTEXT

The evolution of codified guidelines and regulations for the ethical conduct of research in humans, including children, is a relatively recent phenomenon. Before World War II, research in humans of all ages, including children, was conducted with little or no public scrutiny. During the 18th, 19th, and early 20th centuries, much of the research involving child subjects was directed toward preventing or treating infectious diseases, which represented the primary causes of childhood mortality. Nutritional experiments to elucidate the causes of rickets and scurvy also were conducted.

In 1914, Hess and Fish described experiments at the Hebrew Orphan Asylum in which orange juice was withheld from institutionalized infants until they developed
the characteristic signs of scurvy (1). Hess and Unger also conducted studies of rickets using similar methods to induce vitamin D deprivation (2). Some of the children apparently did not fully recover from the effects of these experiments. Children were selected as research subjects in most studies primarily on the basis of their availability and convenience, with little or no thought of their personal rights or exposure to undue risk. As a result, child research subjects typically were from impoverished backgrounds or were institutionalized in hospitals or orphanages (3). Although sporadic criticism of such human research practices appeared, and several attempts were made to legislate against use of children in research during the early 1900s (3), formal regulation of human research did not occur until after World War II.

Abuse, exploitation, and murder of prisoners in the name of human experimentation carried out by the Nazis during World War II was revealed during the Nuremberg trials from 1946 to 1949. Revulsion at the atrocities perpetrated on prisoners and residents of concentration camps led to the Nuremberg Code (4), a code of ethics for human experimentation intended to prevent the repetition of such atrocities. However, the Nuremberg Code did not specifically address research in children and received little general attention before the late 1960s.

In 1964, the World Medical Association published the Declaration of Helsinki, in which the need for special protections for individuals with limited capacity to consent to participate as research subjects was recognized (5).

A 1966 paper published in the New England Journal of Medicine by Dr. Henry Beecher, entitled "Ethics and clinical research" (6), proved to be a major catalyst for development of guidelines for ethical conduct of human research. Dr. Beecher criticized 22 clinical studies published in prestigious American medical journals for violating basic ethical principles. Two of the 22 studies involved institutionalized children. One of the targets of Beecher's criticism was a study performed at Willowbrook State School, in which 51 mentally retarded children were fed infectious fecal extracts to study the natural course of viral hepatitis. The other involved performing vesicourethrogramy requiring extensive x-ray exposure in 26 healthy infants to study ureteral reflux in infants with normal urinary bladders. The outcry and debate precipitated by Beecher's article culminated in establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974. In 1977, the National Commission released a report on research involving children (7) and, in 1978, published the Belmont Report, which outlined ethical principles for protection of human subjects of research (8). United States federal regulations reflecting the content of the Belmont Report and addressing protection of human subjects, including children, followed shortly thereafter (9). Additional regulations providing further protection for children were published in 1983 (10). In 1991, a common rule consolidating all federal regulations on human research—including those pertaining specifically to children—was issued (11). These regulations provide current guidance for conduct of federally sponsored human research in the United States.

Between 1974 and 1977, the American Academy of Pediatrics (AAP) Committee on Drugs, under contract with the FDA, also developed guidelines for the ethical
study of drugs in infants and children. These guidelines were initially published in 1977 (12) and were recently revised and republished in 1995 (13). The AAP guidelines are consistent with the federal regulations and, together, the two documents provide the current guidelines for ethical conduct of research involving pediatric subjects. The following discussion is based primarily on the current AAP guidelines and summarizes the ethical considerations of conducting clinical research in infants and children.

ETHICAL CONSIDERATIONS

Ethical guidelines for the protection of all human subjects are based on three fundamental premises articulated in the Belmont Report:

- Respect for the rights of the individual;
- The obligation to protect the individual from undue risk;
- Fairness in distribution of the burdens and benefits of research.

The basic rights of children as research subjects are no different from those of adults. However, because of their cognitive immaturity and dependent status in society, children are more vulnerable to violation of their rights than adults. Special measures must be taken to protect their personal rights and ensure that they are not exploited or placed at undue risk when they participate as research subjects. Several specific areas of particular importance to children deserve further discussion.

INFORMED CONSENT

The principle of respect for the individual’s rights requires that a person should not participate as a research subject without freely consenting to do so with an informed understanding of the nature of the study and the possible benefits and risks of such participation. However, children have limited ability—which varies with level of maturity—to understand the implications and relative risks of participating in research or to make independent decisions regarding their participation. Because of their limited capacity to make independent decisions, children also are not recognized under federal or state laws as autonomous individuals. Therefore, consent or permission for their participation in research must be given by a surrogate consentor—usually a parent—who presumably is competent to understand the implications of the child’s participation. It is assumed when surrogate permission is accepted that the surrogate consentor is acting only in the best interests of the child and is not influenced by factors that may not be in the child’s best interest. Unfortunately, this assumption is not always true.

As children mature and develop greater ability for abstract thinking, their capacity to participate in the consent process increases. To the extent of their ability, children should be allowed to give their “assent” or consent in addition to the adult surrogate. The U.S. federal regulations and AAP guidelines generally agree that consent of
children more than 13 years old and assent of children of more than 7 and less than 13 years should be obtained unless there is an overriding reason why this should not be done. The AAP guidelines state that “Assent may be waived in therapeutic research studies in which, in the opinions of the parents, investigators, and the IRB [investigational review board], the child’s participation in an investigational treatment may be of such benefit that the child’s welfare would be significantly jeopardized by failing to provide assent” (13).

RISK/BENEFIT

The obligation to protect the individual from undue risk requires that risk of participation in research be carefully evaluated and minimized. Any decision to participate as a research subject must weigh the known or potential risks against the benefits. Benefits should be construed broadly to include benefits to the population at large as well as benefit to the individual participant. Likewise, risks should be evaluated in the broadest sense and may include inconvenience, pain, fear, discomfort, and separation anxiety for the child as well as physical or psychological risks arising directly from the experimental procedure. Because of their particular vulnerability and inability to give consent independently, extra precautions must be taken to ensure that children are not subjected to undue or unfair risk. In marginal situations, investigators and investigational review boards should err on the side of avoiding risk to the subject.

The federal regulations and AAP guidelines divide risk/benefit into four categories:

1. *Research not involving greater than minimal risk*. Minimal risk is defined as the degree of risk a child would encounter during usual life activities and routine medical care. In general, children may participate in studies involving minimal risk if the study promises benefit to the larger society of children, to a specific group of children, and/or to the individual child. Under certain circumstances, participants in such studies could include normal children.

2. *Research involving more than minimal risk but offering the prospect of direct benefit to the individual subject*. Children may participate in studies entailing more than minimal risk with the prospect of direct benefit to the child if: (a) the risk is justified by the anticipated benefit; (b) the risk/benefit ratio is at least as favorable as that from available alternative nonexperimental approaches; and (c) the child’s assent/consent is solicited as well as that of the surrogate consentor.

3. *Research involving more than minimal risk and no prospect of direct benefit to the individual but likely to yield important generalizable knowledge about the subject’s disorder or condition*. Children may be considered for this category study if: (a) the risk represents a minor increase over minimal risk; (b) the intervention presents the subject with experiences commensurate with those encountered in their actual or expected medical, dental, psychological, social, or educational life experiences; (c) the study is likely to yield important generalizable
information; and (d) the child is provided the opportunity to give assent/consent to participate.

4. Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. This category is difficult to define and would rarely be invoked. It requires that the investigational review board determines that the research presents an opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children and that the Secretary of Health and Human Services (HHS), after consultation with a panel of experts in pertinent disciplines, concurs and finds that the research will be conducted in accordance with sound ethical and scientific principles.

SELECTION OF SUBJECTS

Fairness in distribution of the burdens and benefits of research requires that no individual be excluded from participation or preferentially included primarily because he or she belongs to a particular socioeconomic, gender, or ethnic group within the larger society unless the selection is a necessary part of the study (for example, study of cystic fibrosis in whites or sickle cell anemia in African Americans). Subjects enrolled in a study should represent, so far as possible, a cross-section of the population from which they are recruited. There should be an equitable distribution of risks, inconveniences, and benefits throughout societal groups.

COMPENSATION AND REWARD FOR PARTICIPATION

Assent and consent to be a research subject is to be given freely and without coercion. Therefore, it is imperative that rewards or compensation for participation be commensurate with the subject’s contribution and not of such an extent or nature as to be unduly coercive. At the same time, reimbursement for direct expenses, time, and inconvenience associated with participation may be appropriate. Compensation for contributing to a research endeavor also may be appropriate, although it is important to avoid incentives that are sufficient in themselves to induce parents or guardians to give permission for a dependent child to participate in a study or be subject to painful or invasive procedures. If the child is to receive something of value for participating, it is best to not discuss the reward before the decision to participate, so it is not a consideration in the decision. In general, compensation should not go beyond a token gesture of appreciation for participation and should not remove the element of free choice from the decision on whether or not to participate.

USE OF PLACEBO CONTROLS

Experimental designs that employ placebo controls are frequently desirable to demonstrate efficacy of a new treatment or to identify adverse effects specifically
caused by an experimental treatment. However, use of placebo controls in studies involving children must be carefully examined to ensure that doing so will not expose children to undue risk, pain, or discomfort. This is essential because children are typically incapable of fully understanding the implications of participation in such a study and cannot provide independent, competent consent to participate. The American Academy of Pediatrics has recognized five conditions under which placebos may be ethically used in pediatric studies (13):

1. There is no generally accepted therapy of the condition, and the agent under study is the first one that may modify the course of the disease process;
2. The commonly used treatment for the condition is of questionable efficacy;
3. The commonly used treatment carries with it a high frequency of undesirable side effects, and the risks may be significantly greater than the benefits;
4. The placebo is used to identify the incidence and severity of undesirable side effects produced by adding a new treatment to an established regimen;
5. The disease process is characterized by frequent, spontaneous exacerbations and remissions, and the efficacy of the accepted treatment has not been demonstrated.

ESPECIALLY VULNERABLE POPULATIONS

Certain pediatric subpopulations are potentially more vulnerable to coercion or exploitation and require particular attention to protection of their individual rights. These special groups of children must be protected from disproportionate participation in research while at the same time their access is ensured to research studies from which they may receive direct benefit.

Institutionalized and Handicapped Children

Children may be institutionalized for various reasons including severe physical or mental handicap, orphaning, or incarceration for criminal offense. Such children are particularly vulnerable to exploitation because they typically have less freedom of choice in all aspects of their daily life. In addition, surrogate consent presents a special problem in these populations because a parent is often not available, and the legal guardian may not always be acting exclusively in the child’s interest. In general, institutionalized children should not be included in studies unless they benefit directly from participation or unless the subject of the research pertains to their special circumstance of being institutionalized. Likewise, such children should not be excluded from research that may provide an important direct benefit not otherwise available to them.

Children with Permanently Debilitating or Lethal Diseases

Children with life-threatening or progressive chronic illness are particularly dependent and vulnerable. Their condition in and of itself may instill a degree of anxiety
and desperation in the parents to induce agreement for the child to participate in investigations that entail considerable risk, morbidity, and suffering. This sense of desperation also may be shared by the responsible physicians and investigators. In some instances, potentially effective drugs can only be studied in these populations. Furthermore, investigational treatments may represent the standard of care or the only available treatment for some chronically progressive or potentially fatal diseases. This imposes a heavy responsibility on the investigator and the investigational review board to assure that benefit and risk are thoroughly evaluated and that the parent(s) and child, when appropriate, fully understand the implications and are emotionally capable of making a reasoned decision before agreeing to the child’s participation in a research protocol.

Other Especially Vulnerable Populations

The AAP guidelines (13) address ethical issues when dealing with several other vulnerable populations. These include patients requiring emergency care, the dying patient, and the newly dead patient. The reader is referred to the Academy publication for a full discussion.

FDA REGULATION OF DRUG LABELING FOR CHILDREN

Although guidelines for the ethical inclusion of children in research have been available for the past 20 years, there is still a reluctance to include children in clinical trials. Ethical constraints are a frequently cited reason for not studying new medicines in children. There is a sense that children “should not be experimented on.” However, not including children in research that potentially benefits not only the individual but the larger peer group deprives children of the benefits and protections of research enjoyed by the adult population. For example, 70% to 80% of prescription medications currently available in the United States have not been studied in children sufficiently to meet FDA requirements for including pediatric indications in the official labeling. Because of this, children often receive drugs that have not been adequately studied to establish appropriate doses or toxicities that may be unique to children. This common practice may expose individual children to greater risk than would be entailed if they were receiving the medication as part of a rigorously controlled clinical trial. Such practice is difficult to defend ethically.

The 1962 Kefauver–Harris amendments to the U.S. Food, Drug, and Cosmetic Act (14) provide that, in addition to being safe, a new drug must be shown by substantial evidence to have the effect it is purported to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling before it may be legally introduced into interstate commerce. Substantial evidence is defined as evidence consisting of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved,
on the basis of which it could fairly and responsibly be concluded by such experts that
the drug will have the effect it purports or is represented to have. . . .

Regulatory interpretation of the statutory efficacy requirements by the FDA typically
has required at least two prospective, blinded, placebo-controlled clinical trials that
include sufficient numbers of patients to establish efficacy with acceptable statistical
probability. Data generated by such trials are submitted in the New Drug Application
(NDA) and become the basis for approval and labeling of the drug for general use.
The approved labeling for a drug may contain only those indications and dosage
recommendations supported by data submitted in the NDA and approved by the
FDA. If the patient population included in the submitted studies excludes certain
patient subpopulations (for example, infants and children), the labeling cannot con-
tain indications for use or dosage recommendations for those excluded subpopu-
lations.

During the past 30 years, the majority of drugs have been approved in the United
States on the sole basis of studies in adult subjects. At the same time, there has been
acknowledgment that data derived from adult studies cannot always be extrapolated
to infants and children. Unfortunately, this recognition has resulted in exclusionary
language pertaining to children in the labeling of most drugs rather than the conduct
of studies in children to support child-appropriate information in the labeling. This
has created the current situation in which physicians must choose between prescrib-
ing a great many drugs for children off label or deny the child access to those
medications. It clearly is in the best interests of children to have drugs studied in
and labeled for children, so they enjoy the same protections under the Food and
Drug Laws as adults.

During the past 4 years, the FDA has taken several important steps to address
the gap in drug labeling for children. In 1991, a pediatric studies page was introduced
into the NDA review process for new drugs and for drugs that already have approved
indications if they are being evaluated for new indications or dose formulations.
The pediatric studies page requires the FDA and sponsoring company at the time
of NDA submission to identify whether pediatric studies are being conducted or
planned and, if not, to explain why. Almost 3 years ago, new regulations were
promulgated to facilitate labeling of drugs for children (15). Under the new rule,
manufacturers must reexamine existing information to determine whether the pediat-
ric labeling of their marketed products can be modified on the basis of existing data,
and, if so, they have 2 years to submit an application for supplemental labeling. In
addition, the FDA has the authority to request specific pediatric use information if
it deems it necessary. Pediatric labeling may be approved, in part, on the basis of
adult efficacy studies for some new drugs for which the pediatric diseases and
indications are substantially the same as for adults. In such cases, pediatric studies
may be limited to safety, metabolic, pharmacokinetic, and dosing studies. A special
pediatric subcommittee of the Medical Policy Coordinating Committee of the
Center for Drug Evaluation and Research has been formed within the FDA, with
representatives from each division. This group is to track the implementation of
the new regulations and to facilitate the inclusion of pediatric testing in the drug development process.

It is too early to determine the impact of these initiatives by the FDA, but they are intended to increase the number of new drugs approved for use in children. Clinical trials in children are feasible and essential for safe and effective use of medications in children. The time is long past when drugs with therapeutic potential in children should be marketed with labeling restricted to adults.

SUMMARY

Because of the uniquely dependent status of children, special protections must be provided when they participate in research. The evolution of codified guidelines and regulations for the ethical conduct of research in humans, including children, is a relatively recent phenomenon. The Nuremberg code of ethics for human research was published following World War II in the aftermath of the Nuremberg war crimes trials. In 1964, the Declaration of Helsinki addressed the need for special protection for individuals with limited capacity to consent. Between 1977 and 1983, the report of the National Commission for the Protection of Human Subjects of Biomedical Research, U.S. federal regulations governing human research, and the AAP guidelines for the ethical study of drugs in children were published. Revised AAP guidelines were republished in 1995. Ethical guidelines for the protection of human subjects are based on three fundamental premises: (a) respect for the rights of the individual; (b) the obligation to protect the individual from undue risk; and (c) fairness in distribution of the burdens and benefits of research. The application of these principles to special ethical considerations for children is discussed. Recent regulatory changes by the U.S. FDA to facilitate more studies of drugs in children are presented.

REFERENCES

DISCUSSION

Dr. Perman: You touched on the issue of compensation. How does one affix compensation? When is it compensation, and when is it bribery?

Dr. Kauffman: I think it varies with the situation and with the particular subject. This is why it is so important to be aware of the issue and to consider it, knowing that in a particular situation, there is more than one answer. For me, the bottom line is that any compensation should be noncoercive. What is coercive? There might be coercion where a fee is offered in the case of a child who comes from a very impoverished background, though the same fee might not be coercive for a middle-class family. So, there is more than one answer to this. I also think that a reward potentially becomes coercive when the possibility of the reward is discussed before the consent decision, and when the reward is of a nature or quantity to clearly be coercive to most children who might participate in a given study.

Dr. Perman: In a type of study that all of us have been involved in—that is, studies of infant formulas—formula is generally provided as part of the study. For impoverished families, that may make a big difference. Is that appropriate, or is that coercive?

Dr. Kauffman: Again, I don’t think there is a single answer to that. If you have an impoverished parent with a new infant who has an available source of food or formula, from a WIC (Women, Infants, Children) program, for example, they will have formula either way, so getting a specific formula through a study doesn’t change that. It may be coercive, however, if that parent has no other source of formula available, and this is the only way they can feed their baby.

Dr. Iber: You mentioned that the reward system should be discussed only after the acceptance of the study, but all of the IRBs I have dealt with require a highly legistically written document that is offered to the parents to go over and that always includes details of the compensation. How can you achieve this particular aim within the guidelines of a written informal consent that does at least require that compensation be specifically outlined.

Dr. Kauffman: We have differentiated fair compensation from reward. I think you can argue that it is ethical to compensate a family and/or a child for the out-of-pocket cost, inconvenience, and time that they contribute to participation in the study that they would not otherwise do—in other words, transportation cost, food away from home, a minimal compensation for the time they put into the experimental interventions, and so forth. I think that can be ethically defended because that is compensation to individuals for a contribution that they are making not only to their own welfare but also for the benefit of others. A reward can be considered as being over and above that type of compensation. The compensation...
clearly has to be detailed in a consent form because the parent and/or the child needs to understand what is available to them if they participate in the study. I think most consent forms would include that type of compensation. The reward could vary from, for example, certificates to children after participation in the study commending them for their contribution to a reward of several hundred dollars when they complete all aspects of the study. I think rewards that have tangible value in excess of compensation should be presented as a possibility after the formal consent decision is made.

**Dr. Klish:** You hit upon two issues that I think deserve a bit more discussion. One is the concept of minimal risk; because if you subject control populations to any kind of change to their normal routine, you are perhaps introducing some risk. So, this is something we have discussed a lot in many different protocols that contained control populations. The other has to do with the age of consent and assent, because there are regional differences in those ages. What are your thoughts on those two issues?

**Dr. Kauffman:** First of all, the minimal risk issue. Again, one has to use judgment in each case. The risk depends on the environment in which the children live. For some children, life is full of horrible risks every day, including tremendous violence. I don’t think we considered that as an acceptable normal everyday risk, but we talked about such things as 4-year-olds falling off a piece of playground equipment and skinning their knees—that is a part of their daily risk environment; and school-age children crossing the street or riding their bicycle down the street. Is that an acceptable daily risk? And how does that compare to a venipuncture for drawing blood for sampling during a study? So, one has to look at the environment in which a particular child lives and then decide if this is a reasonable acceptable risk. We have used this guide in considering the ethics of doing vaccine studies in normal children. An acceptable risk, in the United States at least, and in most other developed countries, is that children will have the risk of being vaccinated against certain infectious diseases during their childhood. How do you alter that risk if you expose them to an experimental vaccine? We have accepted that there is either a minimal or a slightly greater than minimal risk in doing such vaccine studies in normal children.

As to the age of consent, in using the term consent in the guidelines, we distinguished between independent consent or permission, which in most places would be the age of majority, and nonindependent consent of the older child. For example, the recommendation is that for the 14-year-old who is not emancipated from parental care, you would be required not only to get informed permission from the parent but also to ask the child to give consent as well; both are necessary to enroll that child in the study. The age is very arbitrary. We know that some children at the age of 10 are much more mature than others at the age of 14 or 15, but you have to have some guidelines, and we assume that the majority of children have the ability to make these kinds of abstract decisions at these approximate ages.

**Dr. Guesry:** I would like to start with a suggestion. Your first example of an unethical study was done with food, not with a drug, and all your guidelines could equally well be applied to special foods such as infant formulas or to drugs. So, I would suggest that you remove the word drugs from your title. Also, you put all of the burden of decision making on the ethics committees, but my feeling is that not all ethics committees are born equal, and more guidelines would be useful. It might help to have a more detailed breakdown of the four categories of clinical trial.

**Dr. Kauffman:** A more detailed breakdown would probably be desirable for an individual IRB or an individual organization. However, we were reluctant to write more detailed guidelines, and I suspect that the individuals who wrote the federal regulations were reluctant also, because they did not want to write guidelines that were so restrictive that they would become
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obsolete or not be applicable to certain situations now or in the future. So, these are an attempt to categorize risk and benefit in very broad categories within which you can develop more specific rules within your own organization or for your specific study.

Dr. Perman: Dr. Guesry, what have you observed that makes you think there ought to be more detail with regard to categorization?

Dr. Guesry: One of the arguments that the medical community in general uses is to stress the benefit that other children or other people would get from a given study, while in fact, the children or perhaps the premature babies who are the object of the study often barely benefit from it. To me, this is the real issue; I think the decision may vary from one ethics committee to another, and it is not always completely impartial. I am sure that one study would be passed in one university and not in another.

Dr. Kauffman: You are right. That was shown a number of years ago in a survey in which representative protocols were distributed to some 20 IRBs around the United States, and there were approximately 20 different decisions on them! But I would argue that ethical considerations should not be on the basis of hard and fast rules. I think the purpose is to raise the issues and to point out the principles that need to be followed. With respect to your example of the premature infant as a subject in a study that could benefit other infants in the future, but not necessarily that infant at that moment, I think that falls into the category of minimal risk. In addition, it may be considered ethical because it would benefit either that child in the future or other children in the future. The test is, is this either minimal or only slightly greater than minimal risk? If there is a possibility that you might produce a nutritional problem that could result in irreversible damage to a premature infant, that constitutes greater than minimal risk, and it would be difficult to defend it ethically. If you can argue legitimately and credibly that your protocol would produce only slightly greater than minimal risk, then I think that under these guidelines, you could justify including a premature infant who may not benefit directly from being in the protocol.

Dr. Hamburger: I want to take the opposite side to Dr. Guesry. Dr. Haschke mentioned in his opening statement that the United States is a leader in defining ethical research, but I wonder whether in that leadership role, we haven't made so many rules and regulations, and made it so complex, that this is one of the reasons we see 20 different responses to the same protocol; in fact, we may have begun to handicap really innovative clinical research.

Dr. Kauffman: I am not sure I would agree with that totally, though it is an excellent debate point. I agree that there was a backlash in the 1960s to what occurred during the previous 30 to 40 years to the extent that people may have overreacted a little bit. My experience in interacting with IRBs over the years has been that implementation of the guidelines is frequently the problem rather than the guidelines themselves. There is a lack of information and understanding about the ethical principles that are being applied and about the guidelines themselves. I see our IRB every month getting bogged down in trivia that it shouldn't be arguing about, and I think that is a bigger problem than the guidelines themselves. The HHS has tried to address this over the years by holding workshops around the country to help IRBs become more informed and do their job better, but it is a constant struggle.

Dr. Haschke: The rules we have discussed should also be followed by infant-food-producing companies. For example, specialty formulas for premature infants or formulas for very sick babies should be subject to the same rules as drugs. We should also follow strict rules for infant formulas. But how about cereals? If an infant food company produces an infant cereal that does not fall within the guidelines, say one with a low protein content, should there be different rules?

Dr. Kauffman: From an ethical point of view, I think, in general, it would be wise to follow these guidelines. For example, if you are developing a food product to give to a small
subpopulation of children with, say, an inherited metabolic disorder, you will probably study it in that population rather than in the normal child population. In that situation, introducing a formula that has a putative beneficial effect for that inherited metabolic disorder would be ethically justifiable because the child or the population of children may benefit from that formula. On the other hand, if you are testing a cereal product that may cause a major alteration in vitamin content, or salt content, or some other content in the general population of children, then I think there needs to be an assessment of how much this intervention may alter the daily risk for that child that is incurred just from living in his or her usual environment. This is a difficult issue when one is altering the content of major nutrients. It has to be approached very carefully. One way is to have the protocol and the risks assessed by a totally independent body that has no interest in the product and looks at it purely from the child’s advocacy point of view.

*Dr. Uary:* In assessing the risk/benefit analysis, of course benefit becomes as crucial as risk, because if benefit is small, then the ratio is infinite. Experimental design then becomes crucial to assess potential benefit. Is the IRB the place to examine benefit and experimental design, or should that precede the ethical review? Many studies that have questionable ethics are also inadequately designed to answer the question. So, shouldn’t an independent assessment of benefit precede any IRB consideration? At the present time, this is often left to the speculation of the investigator. Which is the best body to examine benefit?

*Dr. Kauffman:* This is a very important issue, and I see the IRB becoming embroiled in debate with investigators. Investigators will say that it is not the role of the IRB to judge the scientific value of the study. It should simply look at the risk/benefit equation and protect the rights of the patient without worrying about whether the study is scientifically valid or whether the design is good or not. The IRB will say that a poorly designed study that is not going to yield interpretable results can never be ethical because you should never subject a child to participation in a study, even with minimal risk, if the study has no scientific value. I believe the IRB must consider scientific validity and experimental design in assessing the risk/benefit issue because, as stated in the AAP guidelines, poor science is never ethical. I think the two issues go hand in hand. You can’t make one judgment without the other.

*Dr. Glasnman:* My point was exactly the same. You cannot consider the IRB’s function without taking into account the study design. Normally in these cases, I believe that what you are doing is testing some gold standard against a new intervention. You can make an IRB much more comfortable if you set very clear criteria for termination of the study and for looking at the potential adverse events as they occur during the course of the study. So, there is a safety factor, and there are clear rules for termination.

*Dr. Saovedra:* When we look at the benefits of a study, the risk for a patient, or the relative value of a compensation, what we are really looking at is the relative value of each one of those items within the environment of the patient. From that point of view, it would make relatively little sense to be very specific about guidelines. In other words, if a particular IRB is made responsible for examining the relative value of compensation or the relative risk within a particular population, taking into account the geography, socioeconomic status, and the ethical standards of that population, it makes for a much better informed decision. In that sense, it may not be bad that for the same study, 20 IRBs came up with 20 different decisions, if they truly took into consideration the immediate environment of the population in which that study was to be made. So, I don’t think different decisions necessarily make for a bad judgment, and I think that defining the balance between what is a generalizable guideline and what is the specific benefit and relative value of the risks that need to be taken is particularly important.
Dr. Kauffman: I want to add that in United States, we have an ethnically and culturally diverse population, particularly in the major metropolitan areas, and these decisions also have to be very culturally sensitive, because what is important or coercive or negative for one culture may not be so for another, or what might be quite positive for one cultural group may not be for another cultural group.

Dr. Lucas: We have been making some very important general comments, but there is one rather specific one that I want to clarify, and this is the question of where it is reasonable for assent to be waived in a child. Are you saying that a 6-year-old child, for instance, who refuses to be part of a research project, could have that decision overridden by the parents, the IRB, and the investigators if they felt that the study could be of benefit to the child in a way that the child could not perceive? If that is the case, could you give some examples of why that might be legitimate?

Dr. Kauffman: This is a difficult question. The intent of this waiver is to address a situation such as the following: a 6-year-old child has a life-threatening malignancy, say acute lymphocytic leukemia in the third relapse, when the usual chemotherapy protocols are no longer effective. The only hope is some investigational protocol. The child says "I don't want to participate in this, I don't want the blood tests, I don't want the bone marrow done, I don't want the central catheter, I don't want these drugs because they make me sick." The parents, the physician, the investigator, and the IRB concur that this investigational protocol offers a reasonable hope, that the risk/benefit ratio is reasonable, and that it is in the child's best interests to proceed, although the child is too immature to understand that at this point. The other situation is the 10-year-old who, for whatever reason, is mentally incapacitated and cannot comprehend anything even to the level of concurs or not concurs with participation. In that situation, it is appropriate to waive the requirement for assent. So, those are two examples of specific situations that represent what was intended by this waiver.

Dr. Rey: First, I will give an example of differences between states in the United States in the appreciation of the risk of a study. It is a classical one—a study by Selma E. Snyderman and Emmet Holt at the beginning of the 1950s on amino acid requirements. You remember that they deprived young infants of one essential amino acid for a few days, and, in a review paper of their work (1), they said that they were obliged to move from New York to Texas to continue their research. I think this is a good example of the differences.

I would like to comment on Dr. Haschke's question about cereals. We have mainly discussed ethical rules for research, and research tries to increase knowledge. If we don't try to increase our knowledge, we should be more careful with the children or the infants than if we expect a direct or indirect benefit for the child or for science. So, I believe that the same rules apply more strictly if you intend to compare two different types of cereal in normal children than if you wish to study a disease treatment. You should be more careful with cereals than with the treatment of malignant diseases.

I agree with Dr. Guesry that, perhaps, you should delete drugs from the title of your paper. But I am interested in drugs because they represent a particular trial model. If we don't try new drugs in normal children, we will never obtain a license to use them in sick children, and the peculiarity of drugs is that they are sometimes toxic. In infant nutrition, we also have problems with toxicity. A good example is the maximum level of pesticides in infant formulas, about which there is debate in Europe. The Germans are for no more than 10 ppm, but other countries in the European Union have a different opinion. We also have a debate in Brussels about the level of lecithins that we can add to infant formula, and you know that, in rats, high levels of soybean lecithin have produced some behavior disturbances. I am not at all convinced of the reality of this, but I would be happy if you could explain to us, with your
expertise in pharmacology, what is the main target that we should be aware of when we are studying drugs in infants: is it the central nervous system, the hormone receptors, the reproductive capacity?

Dr. Kauffman: In the infant particularly, the central nervous system is very important because it is rapidly developing at that age. From the eliminatory organ point of view, obviously the liver and the kidney are very important. But we know from past tragic experience that there can be surprises, and any assumption we make about a particular target organ may not be correct. How could people know in the 1950s that giving tetracycline to young children would cause permanent dental dysplasia, for example? Who would have thought of looking at the teeth and the bones and the thyroid when you give tetracycline? So, we always have to be on the alert that there may be nasty surprises. The bottom line is to look at the places where, at that particular stage of development, the most rapid and dramatic changes are known to be taking place.

REFERENCE