2009

Making All the Children Above Average: Ethical and Regulatory Concerns for Pediatricians in Pediatric Enhancement Research

Jessica W. Berg
Case Western University School of Law, jessica.berg@case.edu

Maxwell J. Mehlman
Case Western University School of Law, maxwell.mehlman@case.edu

Daniel B. Rubin

Eric Kodish

Making All the Children Above Average: Ethical and Regulatory Concerns for Pediatricians in Pediatric Enhancement Research

Jessica W. Berg, Maxwell J. Mehlman, Daniel B. Rubin and Eric Kodish

CLIN PEDIATR 2009 48: 472 originally published online 21 January 2009
DOI: 10.1177/0009922808330457

Clinical Pediatrics
Volume 48 Number 5
June 2009 472-480

10.1177/0009922808330457
http://clp.sagepub.com
hosted at
http://online.sagepub.com

Making All the Children Above Average: Ethical and Regulatory Concerns for Pediatricians in Pediatric Enhancement Research

Jessica W. Berg, JD, Maxwell J. Mehlman, JD, Daniel B. Rubin, MA, and Eric Kodish, MD

Building on the knowledge generated by the long history of disease-oriented research, the next few decades will witness an explosion of biomedical enhancements to make people faster, stronger, smarter, less forgetful, happier, prettier, and live longer. Growing interest in pediatric enhancements is likely to stimulate the conduct of enhancement research involving children. However, guidelines for the protection of human subjects were developed for investigations of therapeutic modalities. To date, virtually no attention has been paid to whether these rules would be appropriate for investigations to establish the safety and efficacy of technologies intended for enhancement rather than therapeutic uses and, if not, whether ethically acceptable rules could be designed. This article discusses whether the current guidelines for pediatric research provide appropriate protections for pediatric subjects in enhancement research and considers what additional protections might be necessary.

Keywords: enhancement; research; genetics; ethics

In spite of ethical objections, biomedical enhancements for pediatric populations are substantially available and in serious demand. Parents have reportedly sought human growth hormone injections for children of normal height to make them better basketball players.[1] In 2006, 1.4% of cosmetic procedures were performed in persons below 18 years of age, including more than 16 000 rhinoplasties, almost 8000 Botox injections, and more than 3000 breast augmentations.[2] Prescribing patterns for Ritalin (methylphenidate) suggest that the drug is being used in an effort to improve focus and cognitive skills in normal as well as in attention-deficit children.[3-5] Given the fierce competition for scarce societal resources, such as access to elite educational institutions, pediatric demand for safe and effective biomedical enhancements is likely to grow. Moreover, because enhancements are not covered by health insurance, they can be provided free of price and utilization controls, making them a potentially financially attractive addition to a medical practice.

To date, no intervention has been approved by the Food and Drug Administration (FDA) specifically for enhancement use in the pediatric population, and there have been few reported clinical trials of enhancement interventions in this population. By and large, pediatricians who wish to prescribe drugs for enhancement purposes, therefore, must do so on an off-label basis, and surgeons who perform pediatric cosmetic surgery must rely on anecdotal evidence of safety and effectiveness. Growing interest in pediatric enhancements, however, is likely to stimulate the conduct of enhancement investigations in children. Formal trials may be needed to assess the safety of off-label enhancement use of approved products. In addition, manufacturers may sponsor studies to obtain FDA approval for enhancement indications to avoid FDA restrictions on marketing products for off-label uses

From the School of Law and Department of Bioethics, Case Western Reserve University, Cleveland, Ohio (JWB, MJM); University of Michigan Law School, Ann Arbor (DBR); and the Department of Bioethics, The Cleveland Clinic Foundation, Cleveland, Ohio (EK).

Research for this article was funded by a grant from the National Human Genome Research Institute (NIH 1 R01 HG003879-01).

Address correspondence to: Jessica Berg, Case Western Reserve University School of Law, 11075 East Blvd., Cleveland, OH 44106; e-mail: jessica.berg@case.edu.

and to meet agency requirements that product approvals be based on clinical investigations in pediatric as well as in adult populations. Pediatricians may, therefore, find themselves being asked to serve as investigators and as members of institutional review boards (IRBs) evaluating proposed pediatric enhancement studies, they may be consulted by families about enrolling their children as subjects, and they may participate in professional and public debate about the wisdom of conducting this type of research. It is therefore important to consider whether this type of research would ever be ethical and, if so, under what conditions.

Distinguishing Between Enhancement and Treatment

Before considering how enhancement technologies should be tested in children and whether the current guidelines for pediatric research provide an appropriate framework, some definitional issues must be addressed. We focus on biomedical interventions both because those are likely to involve a greater degree of risk (and thus be of more concern from a pediatric research standpoint) and because we wanted to be able to distinguish these issues from the multitude of common parental choices regarding their children's activities, such as tutoring, music lessons, and the like, designed to create smarter and more talented youth. We adopt the following working definition of a biomedical enhancement: It is an intervention that uses medical and biological technology to improve performance, appearance, or capability and does not aim to prevent, treat, or mitigate the effects of a disease or disorder. Thus, according to Julian Savulescu, it increases the chances of leading a good life.[6]

The distinction between enhancement and health-oriented research, however, is not a bright line. Immunization, which makes children's immune systems better than normal, would not qualify as an enhancement because its aim is to prevent disease. Similarly, a drug to improve cognitive function in children with below-normal cognitive ability ordinarily would not be considered an enhancement. But consider a proposed trial of a hypothetical pharmacological agent intended to improve pediatric cognitive functioning, which acts by increasing short-term memory, consolidating long-term memory, increasing the speed and accuracy of mental calculation, increasing attention span, facilitating abstract integrative thinking, and/or improving inventiveness and creativity. If the drug were found to be so effective that some subjects exceeded population norms for cognitive functioning, the drug clearly would qualify as an enhancement. But many also would regard the experimental intervention as an enhancement if it improved cognition in normal children, even if their performance remained within population norms. Similar concerns have been raised by the use of growth hormone for children who are within the normal height range for the population.[7]

The concept of normality, of course, is itself elusive. In some cases, it refers to the frequency with which a trait or capability occurs within a population. In other circumstances, it may have no relationship to the distribution of a trait. Normal eyesight is deemed to be 20/20, for example, but only about 35% of adults have 20/20 vision without some form of correction.[8] Standards of normality may also vary from place to place and time to time, and can be expected to change as the use of enhancements increases. For example, body shapes that were associated with health a hundred years ago are now considered obese. Furthermore, the concepts of disease and disorder themselves may be hard to pin down. Homosexuality is regarded by some as a disorder rather than a lifestyle. Moreover, there is a tendency to regard more and more health states as diseases and more and more interventions as treatments.

In short, the distinction between health-oriented and enhancement research will not always be clear, and invariably, there will be borderline cases. Moreover, studies designed initially as health-oriented clinical studies but that use normal subjects as controls might detect enhancement as well as health-oriented benefits. For example, in the process of studying the drug Tolcapone, an inhibitor of catecholamine-*O*-methyltransferase, to ascertain if it improved cognitive function in schizophrenics, Apud et al[9] detected a cognition-enhancing effect in their normal controls. This raises the possibility that investigators who are concerned that they might not be allowed to conduct enhancement studies in children might seek to hide enhancement research within health-oriented investigations. Insofar as enhancement research raises special ethical concerns, pediatricians who serve on IRBs must be aware of the possible admixture of medical research and enhancement objectives.

The difficulty of clearly identifying enhancement research complicates the task of determining the conditions, if any, under which it would be ethical to perform such research with children as subjects. Nonetheless, we believe that our working definition will be sufficient to allow us to draw some initial conclusions about the ethical propriety of conducting pediatric enhancement trials under the current regulatory framework and the sufficiency of the protections afforded under that framework. The extent to which one remains troubled by the borderline cases may depend on how well the existing safeguards for pediatric research are viewed as sufficient.

The Current Regulatory Framework

Although research ethics is not limited to the federal regulations governing human subjects, the regulations provide a useful starting point for analysis. For example, how should a pediatrician serving on an IRB evaluate the hypothetical study of the cognitive enhancement described previously under the federal regulations governing research with human subjects? Research with children is subject to the standard requirements in the regulations of the Department of Health and Human Services (HHS) and the FDA governing research with competent adults,[10-12] which mandate that properly constituted IRBs assure themselves that the investigators have maximized the benefits and minimized the risks; that the risks are reasonable in relation to the anticipated benefits, including benefits to subjects and the importance of the knowledge to be gained; that subject selection is equitable; and that appropriate informed consent will be obtained from the subjects. Mehlman and Berg[13] discuss the ethical issues raised by enhancement research under the general research requirements elsewhere, and we address these only to the extent that there are specific issues raised by the inclusion of children. This article focuses primarily on the additional protections that apply to research involving children, under Subpart D of the HHS regulations (corresponding in most details to Subpart D of the FDA regulations).

General Protections: Risk–Benefit and Equitable Subject Selection

For pediatricians serving as IRB members or clinical investigators, it is important to consider whether the potential benefits outweigh the risks. Many bioethicists and health care professionals object to giving biomedical enhancements to children on a wide variety of grounds, including that it would deprive them of an "open future"[14,15] and that by turning childhood into a proving ground for traits that serve parental or socially reinforced ambitions, enhancements may eclipse the intrinsic value of childhood as a time for exploration and self-cultivation. The American Society of Plastic Surgeons disapproves of breast augmentation in teenagers below 18 because they may not have reached full physical development and because they may lack the maturity to make informed decisions.[16] In connection with sports, the American Academy of Pediatrics has declared that "the intentional use of performance enhancement is unfair, and therefore morally and ethically indefensible."[17] Moreover, enhancements may produce particularly serious side effects in children, as is the case with anabolic steroids and other ergogenic drugs.[18,19] According to these views, there would never be any net benefit to society in giving enhancements to children, and therefore, it would never be ethical to enroll children in clinical trials of biomedical enhancements.

On the other hand, the potential benefits of an experimental enhancement intervention could outweigh the risks, such that it might be ethical to conduct a study in an appropriate pediatric population under certain carefully controlled conditions. The experimental cognition-enhancing drug described in the previous section might be one such candidate, especially if it had been studied extensively in adults and found to be extremely effective while producing at most only minor side effects in a very small number of subjects and if there were no physiological or pharmacological reasons to suspect that the drug would perform significantly less effectively or be substantially less safe in pediatric subjects. In fact, there have been at least 7 studies on the effects of caffeine in normal children.[20] The potential benefits of an experimental drug that produced cognition-enhancing effects in adults superior to caffeine, especially by enhancing higher order types of cognitive ability and with fewer side effects, might be considered to outweigh the risks sufficiently to permit at least limited study in certain pediatric subjects. Pediatricians who believe that the goals of enhancement are inconsistent with the best interests of children and the ethical dimensions of medicine have the right to desist from engaging in

enhancement research and to discuss their ethical reservations with patients and their families. At the same time, however, they have a responsibility to provide information about the risks and potential benefits of participating in enhancement research in an accurate and unbiased manner.

Even if risks and benefits balance out in the context of the specific trial, there are broader issues. It is unclear to what extent IRBs are authorized to consider the ethical and social implications of this type of research. On one hand, IRBs may approve a proposed study only if they conclude that the risks are reasonable in relation to the anticipated benefits, including benefits to subjects and the importance of the knowledge to be gained. On the other hand, the regulations specifically prohibit IRBs from considering "possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy)."[21(§46.111(a)(2))] Thus it appears that IRBs are allowed to consider long-term benefits to society as a whole but not potential long-term societal risks. This might be interpreted as preventing IRBs from rejecting a protocol for a biomedical enhancement study in children on the basis that providing enhancements to children would be bad public policy, for example, because it might limit future children's right to an open future. This limitation is not unique to research involving children nor to enhancement research, and thus we simply note it here and consider it in greater detail elsewhere (Juengst & Rubin, "Long-Term Benefits," unpublished draft manuscript).

Another general regulatory requirement is that subject selection be equitable and that the burdens and benefit of research be fairly distributed. There is some concern that enhancement benefits in research would be especially attractive to less affluent families but that because enhancements would not be covered by third-party health insurance, they would be available outside of the experiment only to families with sufficient resources to pay for them out-of-pocket. For example, the use of prescription psychostimulants, including presumably their use to enhance cognition, is positively correlated with higher economic status and greater access to health care resources.[22] Consequently, risks inherent in the experimentation might be borne by persons least likely to obtain the benefits from the experimental intervention outside of the experiment. This potential inequity will exist for both pediatric and adult subject populations but may be exacerbated in pediatric populations. There is some evidence that poor and minority children are more likely to be enrolled in health-oriented pediatric trials requiring healthy subjects.[11(p44)] This same problem may occur for trials of enhancement interventions, which also require healthy volunteers. Justice concerns may dissuade pediatricians from pursuing enhancement research.

Specific Protections: Assent and Parental Permission

Risk–benefit evaluation and subject selection analysis are only part of the regulatory protections. In addition, subjects must give their informed consent to be enrolled in a clinical trial. In the case of children, their parents or legal guardian must give permission, and the children themselves must give their "assent." Enhancement research raises concerns regarding both the role of the parents and the role of the children.

Some ethicists believe that parents who enhanced their children would be jeopardizing their children's health to further their own ambitions or social status, or that they would be valuing the children too much in terms of their capabilities, that is, "commodifying" them.[23] On the other hand, parents clearly have broad latitude in determining how to bring up their children, including what risks to expose them to and how to shape and maximize their talents. It is unclear why parents who can enroll their children in experimental educational settings, for example, should be discouraged from enrolling their children in a study simply because it involves a biomedical enhancement, assuming risks were acceptable. Moreover, the concerns raised by the involvement of children in enhancement research wane as the age of the subjects increases, and they near the decisional capacity of adults. The question ought to be whether reasonable parents, being adequately informed about the risks and potential benefits, and having paramount regard for their children's welfare could give permission for their children to participate in a particular experiment. The debate about parental permission for enhancement research is at base a debate about whether parents have the ability to assent to their children's participation in *any* research not designed to provide a direct, health-oriented benefit.

Assuming, without argument, that parents do retain this authority,[24] enhancement research raises

some novel concerns. First, as with any clinical trial, it is important that parents avoid a type of "therapeutic misconception" that subjects invariably will receive whatever enhancement benefit the experimental intervention is assessing.[25] This may be made more complicated by the fact that although the benefit is not directed at health-oriented therapeutic ends, the subjects, along with their parents, may be expecting a direct "therapeutic" benefit. There is little research on the implications of the therapeutic misconception for children's assent and for parental permission[26(pp302-303)] and no research addressing its role in an enhancement context.[13] Second, and perhaps more significantly, it is not clear how to categorize the benefits of enhancement research under a regulatory structure that assumes that research studies can be divided clearly into either health-oriented or non-health-oriented studies. Subpart D, described in more detail below, depends on determinations of benefit (and risk), and thus, the acceptability of an enhancement study will depend on how enhancement benefits are classified. There are 4 categories of research allowed with children, corresponding to regulatory sections 404 through 407, and each is discussed in detail below.

Subpart D specific protections. Section 404 allows IRBs to approve research with children that entails no greater than "minimal risk." According to the regulations, minimal risk means that "the probability and magnitude of harm or discomfort anticipated in the research are no greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[21(§46.102(i))] A 1977 report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research on research involving children recommended that the ages of potential subjects should be taken into account in considering what risks are ordinarily encountered in daily life. It also provided a nonexclusive list of minimal-risk procedures: "routine immunization, modest changes in diet or schedule, physical examination, obtaining blood or urine specimens, developmental assessments, . . . questionnaires, observational techniques, noninvasive physiological monitoring, [and] psychological tests and puzzles."[27(ppxx-xxi,23,25)] The Institute of Medicine's Committee on Ethical Conduct of Clinical Research Involving Children focuses on well-child visits as the standard against which to judge minimal risk.[28,29(pp597-599)] Others have argued that the minimal-risks standard is incoherent, and the survey by Shah et al[30] of IRB chairs reveals both wide variation in and illogical views about what constitutes "minimal risk." Although we agree that more work must be done to clarify the concept of minimal risk, it is very likely that experiments in which child subjects were given biomedical enhancements would be deemed to present greater than minimal risk by most IRBs, so section 404 would not apply.

Section 405 allows an IRB to approve research with children that entails greater than minimal risk as long as there is a prospect of direct benefit to the individual subjects from the intervention in question or the protocol entails "a monitoring procedure that is likely to contribute to the subject's well-being."[21(§46.405)] The IRB must determine that the risks are justified by the anticipated benefits to the subjects and that the benefit is at least as favorable as that presented by available alternative interventions. The regulations fail to define "direct benefit" and thus provide no guidance on whether a direct enhancement benefit would qualify as a benefit under section 405. The survey by Shah et al[30] demonstrated that IRB chairs were unclear about what constituted a direct benefit. The National Commission's report explaining the importance of research involving children emphasized, on one hand, the need to gain knowledge about innovative "treatments," but the Commission also acknowledged that research will be important to evaluate nonmedical practices.[27(ppxx-xxi,23,25)] Moreover, the regulation speaks in terms of "direct benefit" rather than direct *medical* benefit. Therefore, it might be possible to conduct enhancement research presenting more than minimal risk on children under section 405, so long as the IRB determined that the more-than-minimal risks were balanced by the potential benefits to the subjects.

Section 406 deals with research that presents a "minor increase over minimal risk." Like the concept of "minimal risk" itself, this standard is not well defined, and Shah's survey showed that IRB chairs were uncertain about how to apply it. In determining whether a proposed study would represent a minor increase over minimal risk, IRBs are told that the interventions must be reasonably commensurate with "actual or expected medical, dental, psychological,

social or educational situations."[21(§46.406(b))] As the National Commission explained, "the requirement of commensurability of experience should assist children who can assent to make a knowledgeable decision about their participation in research, based on some familiarity with the intervention or procedure and its effects."[27(ppxx-xxi,23,25)] Under section 406, the experimental intervention must be "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."[21(§46.406(c))] On its face, this requirement seems to indicate that research under section 406 is appropriate only in subjects who have a "disorder or condition." But the regulations do not define "disorder or condition." Therefore, it is conceivable that section 406 might permit enhancement studies to be conducted on subjects who fall within the lower end of the normal range for the target trait, such as height or cognitive ability. In other words, "falling below the normal range" may be considered a disorder or condition under the regulations. The interpretation of "disorder or condition" is also important because of the tendency to "medicalize" what were regarded previously as behavioral problems in children.[31]

The final section of the regulations pertaining to research in pediatric subjects, section 407, allows research "not otherwise approvable" if both the IRB and the Secretary of HHS find that "the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children."[21(§46.407)] This might enable risky pediatric enhancement research to proceed on the basis that the risks to the subjects are outweighed by the broader benefits that safe and effective enhancements might offer children as a group.

IRBs make the initial determination as to whether a protocol should go through the 407 review process. After referral by an IRB, the NIH Office for Human Research Protections (OHRP), the oversight body for the federal research regulations, convenes a panel of experts in pertinent disciplines, referred to as a 407 Panel, to review the protocol and make recommendations to the secretary of HHS.[32] The 407 process has been criticized on a number of grounds, including that panels may lack both appropriately broad expertise and public transparency.[33]

Some sense of how the 407 process might function in the case of an enhancement study can be gleaned from a proposed experiment titled "Effects of a Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder: A Functional Magnetic Resonance Study."[34] The authors of this proposal sought permission to conduct a double-blind placebo-controlled study of the effects of dextroamphetamine on children with attention-deficit hyperactivity disorder (ADHD) as well on their non-ADHD peers. Under this research plan, these non-ADHD children, who exhibited no symptoms of this condition, would receive dextroamphetamine, a potent psychostimulant, which along with methylphenidate is reported to be the cognition-enhancing drug of choice among students in higher education.[35] The goal of the study was to determine whether stimulant medication caused different patterns of neural activation, as measured by MRI, in children with ADHD as compared with children who did not have this condition. If so, then an MRI might be a useful diagnostic tool for ADHD. The protocol was submitted to the IRB at the National Institutes of Mental Health on October 28, 2003. The IRB could not agree on whether the study represented greater than minimal risk, even though it would expose healthy children to a controlled substance that has potential for abuse/addiction.[36] Therefore, the IRB voted to refer the protocol to a 407 panel for further review. The panel was charged with determining whether

> risks to the subjects [are] reasonable in relation to the anticipated benefits, and is the research likely to result in generalizable knowledge about the subjects disorder or condition; and . . . [d]oes the research present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children?[36]

The panel agreed that the study should be performed and recommended that it be approved by the secretary of HHS. However, on March 7, 2005, the investigators withdrew the protocol following a black box warning regarding the risk of stroke for children, which was issued for dextroamphetamine in the Canadian market.[36] This experience suggests that there might be circumstances in which a 407 panel would allow studies of biomedical enhancements in pediatric subjects.

Recommendations

From this effort to apply the current federal regulations to pediatric research specifically involving biomedical enhancements, it becomes clear that the regulations do not clearly prohibit the conduct of enhancement experiments on children, and they also do not provide clear guidance on the circumstances, if any, under which this research should proceed. One way to address this problem is for HHS and/or FDA to issue additional guidance for IRBs regarding the way in which enhancement research should be evaluated under existing guidelines and the role of the 407 process in this context. Perhaps HHS and FDA should consider establishing specific regulations to govern the conduct of research on biomedical enhancements, especially research involving children.

Given the wide variation in IRB review and concerns about the 407 process, it may be advisable to establish a special federal body to review proposals for pediatric enhancement research, similar to the Recombinant DNA Advisory Committee, which was established to address concerns about the risks posed by recombinant DNA technology.[37] IRBs confronted with protocols for pediatric enhancement research would refer them to this body, which would include ethicists and members of the public as well as pediatricians, researchers, and experts in child psychology and development, and which would be charged with striking a proper balance between the potential benefits of the research and the paramount need to protect the welfare of children as subjects. A new process, however, may be extremely expensive to implement. Moreover, because there is clear overlap between health-oriented research and enhancement research, it may be difficult for IRBs to identify which protocols should go to the special review body.

Even if specific guidelines, review processes, or regulatory oversight for enhancement research are not warranted, the application of the regulatory framework to pediatric enhancement research highlights a number of problems in the existing regulations, which should be addressed. Others have pointed out the difficulty of interpreting the phrases "minimal risk" and "minor increase over minimal risk," but enhancement research also raises questions about how to evaluate direct but non-health-oriented benefits. There have already been discussions in the literature about how to assess a range of nonhealth benefits such as money and altruistic feelings, but enhancement benefits stretch the concept of direct benefit in different ways. The pediatric regulations rely heavily on the definitions of risk and benefit for determining what categories of research are allowable. Likewise, the scope of parental authority to grant permission for children to participate rests on an understanding of whether enhancement research involves acceptable benefits. Additionally, as pointed out above, we must consider whether to remove the regulatory limitation on IRBs' consideration of long-range effects of applying knowledge. This issue will have broad implications for many types of research.

Besides concerns about the regulatory protections, there are other ethical questions that should be addressed. Specifically, should we, as a society, be funding either this type of research or these types of interventions? From a policy standpoint, some pediatricians might object to publicly funded pediatric enhancement research on the ground that research funds should be allocated instead to health-oriented investigations. Even privately funded research might be objectionable if it improperly diverted scarce resources, such as the limited number of pediatric subjects and research institutions, from more socially compelling projects. Although funding sources, therefore, must consider carefully the value of the research they support, it is not clear that enhancement research should always be considered less socially valuable than health-oriented research. A study of the hypothetical cognitive enhancement drug described earlier, for example, may well deserve priority over an experiment concerning a minor disease or condition.

Another concern is that enhancement research could direct public resources toward providing access to enhancements rather than toward more promising options. A cognition-enhancing drug, for instance, even one that was inexpensive and widely available, might produce less total improvement in cognitive ability than early education, lead abatement, or better prenatal and early-childhood nutrition. This requires careful evaluation of the cost-effectiveness of competing alternatives for public investment.

Finally, if the burdens of enhancement research fall unfairly on low-income populations, perhaps we have a societal responsibility to ensure access to safe and highly effective enhancements for low-income families. In terms of enhancement trials themselves,

one solution would be to offer subjects free or affordable access in the future to any interventions that emerged from the experiment.

Conclusion

Biomedical enhancement research raises complex ethical issues. Some of the issues raised have broader implications for a variety of pediatric research. Given the growing demand for pediatric enhancements, we must consider now the appropriate safeguards for trials of new interventions. Better guidance is needed from HHS and FDA regarding some aspects of the current regulations. Pediatricians must consider whether or not this research should be conducted, what information should be given to patients and families interested in this research, and how public policy should be shaped so that children who are potential research subjects are adequately protected.

References

1. Rubin R. Giving growth a synthetic hand: use of hormone sparks debate. *Dallas Morning News*. July 7, 1987:A1.
2. American Academy of Aesthetic Plastic Surgeons, Cosmetic Surgery National Data Bank: Statistics. http://www.surgery.org/download/2006stats.pdf. Published 2006. Accessed November 25, 2007.
3. Weber RL. A drug kids take in search of better grades. *Christian Science Monitor*. November 30, 2004:Sect. 11.
4. Teter CJ, McCabe SE, Boyd CJ, Guthrie SK. Illicit methylphenidate use in an undergraduate student sample: prevalence and risk factors. *Pharmacotherapy*. 2003;23:609-617.
5. McCabe SE, Teter CJ, Boyd CJ, Guthrie SK. Prevalence and correlates of illicit methylphenidate use among 8th, 10th, and 12th grade students in the United States, 2001. *J Adolesc Health*. 2004;35:501-504.
6. Savulescu J. Justice, fairness, and enhancement. *Ann N Y Acad Sci*. 2006;1093:321-338.
7. Allen DB, Fost N. hGH For short stature: Ethical issues raised by expanded access. *J Pediatr*. 2004;144:648-652.
8. Johnson, T. What is 20/20 vision? http://www.uihealthcare.com/topics/medicaldepartments/ophthalmology/2020vision/index.html. Revised October 2004. Accessed June 7, 2007.
9. Apud JA, Mattay V, Chen J, et al. Tolcapone improves cognition and cortical information processing in normal human subjects. *Neuropsychopharmacology*. 2007;32:1011-1020.
10. Kodish E. *Ethics and Research With Children: A Case-Based Approach*. Oxford, UK: Oxford University Press; 2005.
11. Ross LF. *Children in Medical Research: Access Versus Protection*. Oxford, UK: Clarendon Press; 2006.
12. Field MJ, Behrman RE, eds. *Ethical Conduct of Clinical Research Involving Children*. Washington, DC: National Academies Press; 2004.
13. Mehlman MJ, Berg JW. Evaluating biomedical enhancement research: assessing risk and benefit and obtaining informed consent. *Am J Law Med Ethics*. In press.
14. Feinberg J. The child's right to an open future. In: Aiken W, LaFollette H, eds. *Whose Child?: Children's Rights, Parental Authority, and State Power*. Totowa, NJ: Rowman & Littlefield; 1980:125-127.
15. Davis DS. Genetic dilemmas and the child's right to an open future. *Hastings Cent Rep*. 1997;27(2):7-15.
16. American Society of Plastic Surgeons. Policy statement on breast augmentation in teenagers. http://www.plasticsurgery.org/d.xml?comp=x983. Published 2004. Accessed December 30, 2008.
17. Gomez J. Use of performance-enhancing substances. *Pediatrics*. 2005;115:1103-1106.
18. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med*. 2004;34:513-554.
19. National Institute on Drug Abuse (NIDA). NIDA InfoFacts: Steroids (Anabolic-Androgenic). http://www.drugabuse.gov/Infofacts/Steroids.html. Updated June 26, 2008. Accessed December 18, 2008.
20. Castellanos FX, Rapoport JL. Effects of caffeine on development and behavior in infancy and childhood: a review of the published literature. *Food Chem Toxicol*. 2002;40:1235-1242.
21. Protection of Human Subjects: Code of Federal Regulations, 45 CFR §46.102(i)-46.407 (1983) (Rev. as of March 8, 1983).
22. Bokhari F, Mayes R, Scheffler RM. An analysis of the significant variation in psychostimulant use across the U.S. *Pharmacoepidemiol Drug Saf*. 2005;14:267-275.
23. Robertson JA. Genetic selection of offspring characteristics. *Boston Univ Law Rev*. 1996;76:421-482.
24. Coleman DL. The legal ethics and pediatric research. *Duke Law J*. 2007;57:517-624.
25. Lidz CW, Appelbaum PS. The therapeutic misconception: problems and solutions. *Med Care*. 2002;40(9 suppl):V55-V63.
26. Berg JW. Children and placebos. In: Kodish E, ed. *Ethics and Research With Children: A Case-Based Approach*. Oxford, UK: Oxford University Press. 2005: 294-309.
27. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (NCPHS). *Research Involving Children: Report and Recommendations*. Bethesda, MD: The Commission; 1977.

28. Field MJ, Behrman RE. *Institute of Medicine (U.S.). Committee on Clinical Research Involving Children. Ethical Conduct of Clinical Research Involving Children*. Washington, DC: National Academies Press; 2004.
29. Kopelman LM. Children as research subjects: moral disputes, regulatory guidance, and recent court decisions. *Mt Sinai J Med.* 2006;73:596-604.
30. Shah S, Whittle A, Wilfond B, Gensler G, Wendler D. How do institutional review boards apply the federal risk and benefit standards for pediatric research? *JAMA*. 2004;291:476-482.
31. Conrad P. Prescribing more psychotropic medications for children: what does the increase mean? *Arch Pediatr Adolesc Med.* 2004;158:829-830.
32. Office for Human Research Protections. Children involved as subjects in research: guidance on the HHS 45 CFR 46.407 ("407") review process. http://www.hhs.gov/ohrp/children/guidance_407process.html. Published May 26, 2005. Accessed August 8, 2007.
33. Kopelman LM, Murphy TF. Ethical concerns about federal approval of risky pediatric studies. *Pediatrics*. 2004;113: 1783-1789.
34. Office for Human Research Protections. Effects of a single dose of dextroamphetamine in attention deficit hyperactivity disorder: a functional magnetic resonance study. http://www.hhs.gov/ohrp/children/adhd.html. Published October 19, 2005. Accessed August 8, 2007.
35. Vedantam S. Millions have misused ADHD stimulant drugs, study says. *The Washington Post*. February 25, 2006:A09.
36. Office for Human Research Protections. 46.407 Review of protocol entitled "Effects of a single dose of dextroamphetamine in attention deficit hyperactivity disorder." http://www.hhs.gov/ohrp/panels/jreview01/withmemo.rtf. Published October 19, 2005. Accessed August 8, 2007.
37. Berg P. Potential biohazards of recombinant DNA molecules. In: Andrews LB, Mehlman MJ, Rothstein MA, eds. *Genetics: Ethics Policy and Law*. St. Paul, MN: West; 2002.