

Guidelines for Adolescent Health Research

A Position Paper of the Society for Adolescent Medicine

Research is essential to advance health. Participation by specific populations in health research is critical in order for those populations to receive the full benefits of research. Owing to uncertainty about the legal and ethical status of adolescent involvement in research, adolescents are frequently excluded from research that is needed to improve adolescent health care and to inform health policy. Individual adolescents and adolescents as a class of persons may benefit from research; as such, their inclusion in research is essential if adolescents are to fully benefit from research.

Protection of adolescents in research should be based on a scientific and empathetic understanding of their developing capabilities and a careful assessment of the risks and benefits of including them. The important roles of parents and communities as protectors of adolescents should be respected and enhanced at the same time as we acknowledge and respect developing adolescent autonomy. The *Guidelines for Adolescent Health Research*, a consensus product of numerous professional experts and groups that was written in the early 1990s, [1] provides a framework to interpret the federal regulations for protection of human subjects in light of the unique legal, ethical, developmental, contextual, and cultural issues that affect adolescents. The *Guidelines* are designed to protect individual adolescent research subjects and to promote the inclusion of youth in research that may benefit all adolescents. In revising this Position Paper, we have not revised the 1995 *Guidelines for Adolescent Health Research*, believing they remain a clear statement regarding the appropriate inclusion of adolescents in health research.

Since the *Guidelines* were published in 1995, the field of research ethics has seen several important developments, many of them directly affecting adolescents. Requirements for broader inclusion in research have emerged at the same time as demands have been made for more rigorous protection of research subjects. Specific developments affecting adolescents include the issuance in 1998 by the National Institutes of Health (NIH) of a policy requiring appropriate inclusion of children in research, the adoption of similarly motivated policies at the Food and Drug Administration (FDA), the promulgation of new regulations concerning the privacy of personal health information (known as the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule), and the FDA's adoption of revised regulations concerning children and adolescents (who may be considered children). These changes affect the appropriate involvement of adolescents in research and thus bear on the potential to improve adolescent health.

Adolescent Health and Adolescent Health Research

Numerous national commissions, panels, and reports have articulated their great concern about adolescent health and the urgent need for research that can guide interventions and inform public policy in this area [2–7]. Violence, human immunodeficiency virus (HIV) infection and other sexually transmitted diseases (STDs), alcohol and other drug use, and unintended pregnancy pose continuing and serious challenges to the health and well-being of youth in communities across the country. Many potentially deleterious health behaviors begin in adolescence, including sexual activity, smoking and alcohol consumption, illicit drug use, interpersonal

Address reprint requests to: Society for Adolescent Medicine, 1916 Copper Oaks Circle, Blue Springs, MO 64015.

This position paper represents views of the Society for Adolescent Medicine and should not imply endorsement by any other organization.

violence, and behaviors that cause unintentional injuries. The timing of pubertal development also affects adolescent health behaviors and health status; an historic decline in the age of puberty has been accompanied by social pressures for extended schooling and delayed marriage.

Research with adolescents has produced important benefits for this population in recent years, with significant insights emerging about the ways in which adolescents differ from both children and adults. For example, differences between pediatric and adult patient populations are substantial in drug elimination and therapeutic response [8]. In addition, studies of the Human Papillomavirus have demonstrated an unexpectedly high prevalence in sexually experienced adolescents and have informed clinical practice in screening for cervical cancer [9–11]. Research into adverse pregnancy outcomes (e.g., low birth weight, infant mortality) of young adolescents has demonstrated that these outcomes are related to social deficits and *not* age or physical maturity and that comprehensive prenatal care can address these deficits and improve outcomes [12,13]. Finally, research on school and community health education has documented an evolution in program efficacy over the past 25 years; from this research have emerged principles for effective prevention that can be incorporated into programs to prevent HIV infection, other STDs, and unintended pregnancy among teens [14,15].

Unfortunately, the successes of research involving adolescents are often overshadowed by persisting gaps in knowledge. For example, significant deficits remain in our knowledge of the effects of puberty on a drug's action or elimination [16]. In addition, the optimal design of clinical preventive services for adolescents is limited by a lack of health service research data [17]. Furthermore, significant gaps remain in the knowledge needed to create effective HIV prevention for gay and bisexual youth, who are often at exceptionally high risk [18]. Prevention of delinquency and violence [19] and treatment for mental health problems have also been hindered by a dearth of research to guide interventions that will help young people successfully navigate the difficult and sometimes deadly challenges to their future health and productivity [20]. Equally disconcerting is the paucity of information about the factors that support the resiliency of adolescents against psychosocial risks or about how to disseminate successful model programs in prevention to other communities [21–23].

Although numerous threats to adolescent health continue to be evident, the ability to conduct research with adolescents remains difficult. A critical problem is the difficulty that researchers and Institutional Review Boards (IRBs) have with interpreting the federal regulations as they apply to research involving adolescents. Not surprisingly, adolescents as a class have often been excluded from participation in clinical trials, studies in public health prevention, and other critical research efforts from which this age group would benefit [24–26]. The result is that treatment options and the design of interventions for adolescents must often be extrapolated from studies involving either children or adults [26,27]. The wisdom of this approach is suspect, because the period of adolescence is marked by significant changes in physical and psychosocial development that set adolescents apart from their younger and older counterparts. Adults are often uncomfortable dealing with adolescents and their health issues. As such, research agendas are often vulnerable to the influence of political currents. [25,28].

Researchers and IRBs have reported a wide variation in the interpretation of the federal regulations as they apply to research involving adolescents [29–32]. Interpretations have been particularly disparate with respect to issues related to an adolescent's capacity to consent to research participation without parental permission, the protection of confidentiality for adolescent research participants, and the conduct of research that addresses "socially sensitive" subjects, such as illicit drug use, violence, and sexuality. These differences are not surprising, because the current federal regulations [33] do not specifically address the inherent differences between adolescents and children.

Ethical Principles

The Belmont Report, published in 1978, provides the moral foundation for the ethical conduct of research in the United States, including current federal regulations and discussions about ethics conducted at IRB meetings [34]. The 1999 Code of Research Ethics of the Society for Adolescent Medicine builds upon the ethical principles in the Belmont Report, recommending standards for the conduct of adolescent health researchers [35]. The Belmont Report emphasizes three basic ethical principles: respect for persons, beneficence, and justice. Respect for persons means treating a person as an autonomous being and not as a means to an end. Special protections are

needed for groups with diminished autonomy. Beneficence is the ethical obligation to do good and to avoid harm; for research it means maximizing benefits and minimizing harm. Justice entails a fair distribution of the benefits and burdens of research; it also contains the notion that vulnerable persons should be protected from the burdens of research.

With adolescents, respect for persons means balancing respect for the emerging capacity of an adolescent for independent decision-making with the need for continued special protections, where necessary. The notion of diminished autonomy of children and adolescents is based on limitations in cognition and judgment. During early and middle adolescence, most teens attain adult cognitive capacity, albeit at varying rates and ages (see "Adolescent development and capacity to consent to research participation" below.) This limited but emerging capacity is recognized both in state laws that allow adolescents who are still legally minors to give their own consent for medical care and in the federal regulations governing research.

Beneficence provides an ethical basis for conducting research that may improve health and a basis for maximizing the benefit of research and minimizing its risk. Research with adolescents may have important benefits to individual adolescents, and it may benefit adolescents as a group as well. For example, research on school-based and clinical intervention programs to reduce HIV risk behaviors may benefit individual teens while also helping future generations of teenagers. On the other hand, survey research to understand adolescent HIV risk behaviors may have no immediate individual benefit but may benefit adolescents generally if the research is used to design more targeted or more effective intervention programs. Federal policies to extend the benefits of research to women, minorities, children, and adolescents by including them in studies are motivated by the principle of beneficence.

The principle of justice demands a fair sharing of both risks and benefits. If certain groups of persons are systematically excluded from participation in research, these groups may not share in the beneficial results of that research. Promoting full participation by groups that historically have been excluded from research and its benefits is founded on the principle of justice. The interests of justice demand that adolescents not be exploited for the benefits of others, but also that adolescents not be excluded from participation in research that may have direct or indirect benefit. Recent research suggests that adolescents have often been excluded from participation in re-

search, to the detriment of adolescents as a group [7,24–26,36]. Recent federal policies regarding inclusion of women, minorities, and children, including adolescents, in NIH-supported research are also motivated by the ethical principle of justice [37].

Legal Context

An important context for these *Guidelines* is the legal status of children and adolescents [38]. The legal status of children has evolved from that of property (chattel) under traditional English common law to persons with limited autonomy [27]. The "personhood" of children was recognized implicitly by states as they enacted child abuse reporting laws and medical consent laws during the 1960s and explicitly by the United States Supreme Court in the 1967 decision *In re Gault*, which extended the due process protection of the Fourteenth Amendment to children as well as adults. These legal changes acknowledge that there is not always a congruence of interests among children, their parents, and the state. These legal changes seek to protect the welfare of children and adolescents [39].

Limited autonomy for adolescents who are minors includes both the right to consent to disease-specific medical care and to privacy during the course of that treatment. Beginning in the 1960s, laws in many states began to accord minors the right to consent to emergency care and to medical treatment of conditions such as pregnancy, STDs, and drug, alcohol, and mental health problems [40–43]. Similarly, state laws have recognized the right of minors with a certain status, such as "mature" or emancipated minors (including those who are married or in military service) to consent to their own care [40–43]. Other minors authorized to consent may include those who are parents, are living independently of their own parents, have graduated from high school, or have reached a specific age [42].

In addition to the explicit state statutes, minors' autonomy in health care decision-making and privacy has been protected in federal law. In *Planned Parenthood of Missouri v. Danforth*, 1976, *Carey v. Population Services International*, 1977, and *Bellotti v. Baird*, 1979, and a long line of other cases, the United States Supreme Court recognized that the constitutional right of privacy protects minors as well as adults, particularly for reproductive health care, including contraceptives and abortion, albeit with some limitations related to abortion that do not apply in the case of adults [44,45]. Federal law has

also provided confidentiality protection for family planning and drug and alcohol treatment services to minors [45,46].

Most recently, the federal government has promulgated broad medical privacy regulations, the HIPAA Privacy Rule, which provides confidentiality protection for the health care information of adolescents as well as adults and younger children [47]. The HIPAA rules contain important provisions that affect the conduct of research and adolescent health researchers must understand and comply with these [48]. The HIPAA Privacy Rule treats adolescents who are minors as individuals who can exercise rights under the rules if they are allowed, by state or other law, to consent for their own care. With respect to the specific issue of disclosure of information to parents and parents' access to protected records, the HIPAA Privacy Rule defers to the provisions of state and other law. If state or other law is silent, the Rule defers to the discretion of health care professionals to determine whether information should be accessible to parents [49].

Importantly, only a few states have laws that directly address the involvement of adolescents in research. A review by CDC (Marjorie Speers, personal communication from , formerly Associate Director for Science, Office of the Director, Centers for Disease Control and Prevention, September 5, 2002.) found just four states with statutes that address the participation of minors who are adolescents in research, and these statutes generally deal with some limited aspect of research. The definition of "children" in the federal regulations (which includes adolescents who are minors) specifically references state laws (i.e., "the law of the jurisdiction" in which the research is conducted) on treatment for health care and the age at which an individual can independently consent under these laws to specific treatment or care. Relevant state laws include those addressing age of majority, emancipation status, age to consent for general medical care, and care of minors for specific conditions based on their own consent, discussed above. Researchers in adolescent health need to be cognizant of their own state's law regarding age of majority and emancipation, as well as with minor consent statutes.

An ethical basis for these developments in the legal status of children and adolescents can be found in the principle of beneficence. These changes primarily reflect a concern for the health and well-being of children and adolescents, recognizing that it is preferable to provide necessary treatment to an adolescent minor on a confidential basis, independent

of involving a parent, than to insist on parental involvement and risk the adolescent's refusal to seek care. Moreover, these legal developments implicitly recognize that under certain circumstances minors are capable of making independent judgments and that this emerging capacity should be respected.

Adolescent Development and Capacity to Consent for Research Participation

Understanding the emerging capacity of adolescents to provide informed consent is essential to considering their participation in research. The ethical principle of respect for persons demands attention to this emerging capacity. Growth into adolescence is marked by an increasing capacity to make independent and intelligent decisions, and developmental psychologists recognize emerging cognitive abilities (i.e., changes in the ability of the human organism to understand increasingly complex and abstract concepts) [50,51]. Research ethicists have recognized a related concept, capacity, the ability to provide informed consent (i.e., to appreciate the risks and benefits of participation in research activities and to make reasoned choices) [50,51]. Capacity is linked to both developing cognition [50] and previous life experiences. Lack of experience with decision-making in real-world situations may reduce adolescent capacity. Conversely, adolescents who have experienced chronic illness, with all its experiences and choices, may have been challenged to develop increased capacity. A possible beneficial effect of involvement in the carefully controlled research environment is an increase in capacity that comes from expanding the adolescent's experience base [52,53].

Research on cognition and capacity suggests that both adolescents and younger children show significant ability to provide informed consent [51,54]. For mid- and late adolescents (aged 14 years old or older), understanding of research and the cognitive ability to make decisions about research participation are similar to these abilities in adults. Weithorn [51] found that 14-year-olds were as skilled as adults in understanding multiple viewpoints and in considering conflicting information. Children at age 9 years could understand risk and benefits but were less able to consider multiple conflicting points. Both younger and older adolescents, however, reach decisions regarding research participation that are similar to those made by adults. Even children aged 6 to 9 years are capable of a basic understanding of research considerations, supporting current federal

regulation that requires the assent of minors to research participation [51]. Formal operational thinking, the ability to understand and use abstract concepts, begins to appear in adolescents from age 11 years [55], although many adults never attain the ability to engage in this kind of formal operational thinking. Susman [54] found that among both children and adults, concrete information was better understood than abstract information. She found that chronologic age (7–20 years) was not related to an understanding of the elements of informed consent.

The capacity of an individual adolescent (or adult) to provide informed consent is an empirical question. For adults we assume capacity unless we have evidence to the contrary; for children we assume the opposite. The *Guidelines* suggest that for research of low risk (e.g., confidential or anonymous survey research), capacity can be assumed based on the reasonable expectation of capacity for the group of adolescents to be studied. For research involving greater risk, the *Guidelines* propose an individual assessment of capacity.

Adolescents display an emerging desire for autonomy and privacy and may be threatened by disclosure to parents of health information, including research data [55]. In addition, adolescents may display a differential and even enhanced “vulnerability” to research in comparison with younger children [56]. For example, adolescents may have a heightened developmental sensitivity to particular issues (e.g., self-concept or body image). Their increasing cognitive abilities may lead to greater vulnerability when deception is used in research studies or when comparisons are made between their personal performance and the performance of others [56].

The National Bioethics Advisory Commission noted that group-based regulations classify certain persons as vulnerable rather than classifying situations in which individual people might be considered vulnerable [57]. Circumstances that may reduce adolescent (and adult) capacity to provide informed consent include stress, bias in framing questions, and monetary compensation [55]. The Commission also noted that current regulations neither offer a definition of vulnerability nor suggest the circumstances that might render individual people vulnerable. The current list of vulnerable groups, including children, is both overly broad and incomplete. Further, vulnerability is sensitive to context, and individual people may be vulnerable in one situation but not in another. The Commission concluded that an analytic

approach that evaluates types of vulnerability would better serve to protect research volunteers. The Society for Adolescent Medicine would urge that when assessing the nature and level of protection needed for youth enrolling in research studies, IRBs focus on the specific circumstances that might contribute to vulnerability rather than the definition or identity of the group who will participate.

Access to Research and its Anticipated Benefits

Participation in research is essential if individuals or groups are to receive the full benefits of research. Over the past decade, children and adolescents, women, and minority groups have won rights to increased access to participation in research. During the latter part of the 1980s, AIDS activists, women, and minority health advocates led highly successful campaigns demanding access to research, which led to significant changes in the priorities and protocols of federal clinical trials, including the enactment of the NIH Revitalization Act of 1993 [58,59]. Similarly, in 1998 the NIH, at the urging of the Academy of Pediatrics (AAP), issued *NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects* [37]. The policy states that:

“children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all NIH conducted or supported research involving human subjects, including research that is otherwise “exempt” in accord with Sections 101(b) and 401(b) of 45 CFR 46 - Federal Policy for the Protection of Human Subjects. The inclusion of children as subjects in research must be in compliance with all applicable subparts of 45 CFR 46 as well as with other pertinent federal laws and regulations. Therefore, proposals for research involving human subjects must include a description of plans for including children. If children will be excluded from the research, the application or proposal must present an acceptable justification for the exclusion.”

The policy defines seven ethical and scientific exclusionary circumstances, for example, if the disease does not affect children or if law or regulation bars the participation of children. The NIH policy is based upon scientific information, demonstrated human need, and considerations of justice for children in receiving adequately evaluated treatments. The policy states that the need reaches across a broad

spectrum of clinical research, including studies on pharmaceutical and other therapeutic agents; behavioral, developmental, and life cycle issues, including childhood antecedents of adult disease; and prevention and health services research [37].

The FDA, as well, has promulgated policies to promote inclusion of children in research. The 1997 FDA Modernization Act created the *Pediatric Exclusionary Provision*, which grants a 6-month patent extension in return for testing of safety and efficacy in children [60]. In 1998, the agency issued the *Pediatric Rule* which requires that manufacturers of certain new and marketed drugs and biologics conduct studies to provide adequate labeling for the use of these products in children [61]. (Legal action regarding the validity of the Pediatric Rule as issued by the FDA is pending in the courts. While that litigation is proceeding, legislation to codify the rule has been introduced in Congress.) A primary concern of the NIH, AAP, and FDA has been the issue of children as "therapeutic orphans" [62], and these policies are an important ethical endorsement for the appropriate inclusion of children and adolescents in research. The *Guidelines on Adolescent Research* [1] and the Society for Adolescent Medicine's other efforts to increase participation of adolescents in research are consistent with these new policies.

Policies promoting inclusion in research draw their roots from the principle of justice and the concept of nondiscrimination; these regulatory changes represent a fundamental "sea change" in federal approaches to the regulation of research [58]. Research has been "transformed" from a perception as a fundamentally dangerous activity from which persons must be protected to a more balanced view of risk and benefit. While research may entail risk, it also may bring much benefit. Demands for increased participation of adolescents in research have occurred coincident with a changing societal understanding about the risks and benefits of participation in research for other groups [58].

Given continued concerns about the risk of research, a variety of efforts have been made recently to reinvigorate the system of research protections, including the creation of a National Bioethics Advisory Commission [57]. After several high-profile cases of research misconduct or potential misconduct, the federal regulators at the Office for Human Research Protections (OHRP) halted research at a number of leading health institutions [63]. Such suspensions of an institution's ability to conduct federally funded research have engendered painful

soul-searching in academic circles and have focused debate in the research ethics community. In such a climate, researchers need to become more knowledgeable about research ethics and sensitive to the potential risks and benefits of their activities. Researchers in adolescent health are challenged to provide the very best protections to their study participants and to conduct research in a scrupulously ethical way [35].

Behavioral Research and Parents

Reflecting the Belmont principle of beneficence, behavioral research, like other research with youth, has provided great benefit to adolescents as a group. The principal threats to adolescent health and well-being are social and behavioral: personal behavior and the behavior of peers. Behavioral research includes intervention programs to reduce harmful behaviors and increase protective behaviors as well as projects designed to improve understanding of the factors influencing adolescent behavior. Behavioral research commonly collects questionnaire data on personal behaviors and behavioral determinants, including sexual practices, alcohol and other drug use, delinquency, mental health concerns, peer pressure, self-efficacy, and perceived support for prevention practices. In contrast to biomedical research, behavioral research generally presents little risk to the individual adolescent. Behavioral interventions based on research may benefit the individual adolescent or adolescents as a group by reducing involvement in health risk behaviors and preventing adverse health outcomes. For example, research on the prevention of HIV and teen pregnancy has resulted in more effective prevention programs to reduce sexual risk behavior [14].

The primary risks to the adolescent participant from behavioral research, particularly survey research, are potential embarrassment and disclosure of sensitive information to others [24]. This is true for survey research involving adults as well. However, disclosure resulting from survey research is a rare phenomenon. An underlying fear for parents is that surveys may harm their adolescents by promoting or inducing unhealthy behavior or causing other harm. Our review of the research literature provides little evidence that communicating with adolescents about health behaviors, either in traditional health educational settings or in behavioral surveys, increases harmful behaviors. Given the contrary, the relevant research has documented great difficulties in chang-

ing behaviors: for example, cognitively focused or knowledge-based school sex education has had little impact, positive or negative, on adolescent sexual behavior [14].

While adolescents as a group receive the primary benefits of survey research on adolescent behavior, individual teens may also reap benefits. Completion of surveys may increase self-understanding of the risk from one's own behavior, and by raising such understanding, survey research may facilitate the process of seeking care. Benefits of involvement in the informed consent process for research include an increased sense of self-control and increased decision-making capacity [52].

Even though behavioral research may pose little actual risk to an adolescent, it is important to acknowledge parents' anxiety. Parenting an adolescent is often a challenge, as parents must deal with their adolescent's increasingly autonomous behavior. Involving parents and other adults from the community in the research process may help allay their concerns and also improve the quality of the research. The practice of involving parents and other community representatives on advisory boards can bring added benefit, as these boards can communicate parental concerns to research staff and advise on the most appropriate and effective response.

Community

Research with children, adolescents, and adults has also been hindered by the perceived inability of researchers to adequately address the concerns and needs of certain communities, particularly communities of color and sexual minorities. Communities may view the intentions of researchers with skepticism, and these perceptions are not without justification. The legacies of Nazi atrocities, the Tuskegee Syphilis Study, and hepatitis studies with retarded children at Willowbrook State Hospital in Staten Island, New York, gave rise to a deep mistrust of research [64–67]. In addition, communities may fear that unflattering research results will stigmatize their members, and they may have little faith that the findings will be used to improve their lives [26,64–66]. Many communities have demanded they be consulted in decisions about the kind of research that will be conducted, the methods that will be employed, and how the results will be used [26,58,64,66]. The *Guidelines for Adolescent Health Research* also reflect the perspectives and recommendations of researchers, ethicists, community-based or-

ganizations, and education associations that have responded to the legitimate concerns of the communities where research is conducted.

The involvement of community and community institutions may enhance the quality of research and may be an important protection for adolescent participants in research. This may be particularly helpful when parental permission is waived. Community involvement engenders a communitarian response to the project that serves to enhance the safety of the youth who will be involved. Speaking with the community may allay parents' fears and enhance parents' understanding of potential risks and benefits.

Community consultation gives breadth and context to the research question and helps the researcher understand the meaning of behavior. In addition, community involvement may provide important insights into the underlying forces influencing health and may strengthen efforts to create programs to improve health. Early and timely advice on the feasibility and acceptability of study approaches can save resources or even salvage studies. Furthermore, community involvement may provide critical support for dissemination of health practices and programs shown to be effective. Early dissemination of research findings to the community may increase parents' confidence in the research process and help them understand the potential benefits from research. When communities partner with researchers, they are left with important data and expertise that can position them to be better advocates for programs and services. The Society for Adolescent Medicine urges its members undertaking community-based research to view community advisory boards as integral partners in the research effort.

Research Context

The research setting or context may influence considerations of confidentiality, consent, community consultation, and justice in research participation [68]. Practical considerations in maintaining confidentiality vary, for example, between health care settings, school classrooms, parents' homes, and shelters for runaways. Nevertheless, the ethical standard for research participation should not vary among these sites; one should not, for example, accept a lower ethical standard for research conducted in one type of setting than in another.

Research in Schools

Federal educational law governs certain research conducted in schools, and health researchers working in schools are advised to become knowledgeable about these laws. The Family Educational Rights and Privacy Act (FERPA) [69] addresses the privacy of student educational records and the circumstances under which educational records may be accessed, amended, or disclosed. FERPA applies to all educational agencies and institutions that receive funds from the U.S. Department of Education. The Protection of Pupil Rights Amendment (PPRA) [70] specifically addresses surveys administered in schools. It requires written parental permission before students who are unemancipated minors may be required to participate in surveys, analyses, or evaluations funded partially or fully by the U.S. Department of Education (DOE) that collect information about eight specific topics, including: mental health, and psychological problems; sexual behaviors or attitudes; illegal, antisocial, self-incriminating, or demeaning behaviors; critical appraisals of individuals with whom respondents have close family relationships; religious practices, affiliations, or beliefs; political affiliations or beliefs; income; and legally recognized privileged relationships such as those with physicians, lawyers, or ministers [71]. Surveys addressing any of these eight topics that are not funded by DOE in whole or in part may be conducted after parental notification and after allowing the parent an opportunity to opt their child out of participation. Parents have a right to inspect questionnaires and instructional material used in conjunction with surveys, analyses, or evaluations. Local education agencies must notify parents at least annually about school policies regarding these rights and any upcoming surveys. These rights transfer to student when a student becomes an adult or is emancipated.

Federal Regulations Concerning Participation of Adolescents in Research

a. Regulatory Framework for Research

The current federal regulations on research provide for a nationwide system of local IRBs, regulated by the Office for Human Research Protections in the Department of Health and Human Services, which must review and approve all federally funded research involving human subjects [33]. For each study, the appropriate IRB must assess the risk and benefits to human subjects, ensure informed consent procedures, and provide special protections for vul-

nerable populations. Special safeguards cover "children," defined in the regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."

The basic ethical framework for evaluating research studies was proposed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (AKA the National Commission) in 1978 in its seminal *Belmont Report* [34]. The National Commission had issued a separate report a year earlier, *Research Involving Children* [72], which presented a compelling case for conducting research with children and delineated important procedures for children as research subjects. Given the history of horrible abuses in research, the emphasis of these reports was on protection of human subjects from research abuse [58,67].

b. Regulatory Framework for Research Involving Children and Adolescents

Under the federal regulations, children are considered to be a vulnerable population for which special protections must be provided. A hierarchy of risk and benefit is used in defining the specific protections required. The four categories of research recognized by this hierarchy are as follows:

- (1) involves no more than minimal risk;
- (2) involves more than minimal risk, but there is a potential for direct benefit to individual research subjects;
- (3) involves a minor increase over minimal risk without direct benefit, but research is likely to yield generalizable knowledge about the subject's disorder or condition; and
- (4) not otherwise approvable but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Minimal risk is defined as follows: "The probability and magnitude of harm or discomfort anticipated . . . are not greater . . . than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." Specific requirements exist for each category of risk and benefit (Table 1). The structure of the *Guidelines* [1] is based on this categorization of risks and benefits.

All four categories require the assent of the child or adolescent and the permission of one or both

Table 1. Categories of Research Involving Children, Including Minor Adolescents

Category of Research	Regulatory Requirements	Examples of Research/ Research Procedures
1. Research not involving greater than minimal risk	<ol style="list-style-type: none"> 1. Assent of children/adolescents. 2. Permission of one parent/guardian. 	Surveys Blood drawing X-rays Educational interventions
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.	<ol style="list-style-type: none"> 1. Assent of children/adolescents. 2. Permission of one parent/guardian. 3. The risk is justified by the anticipated benefit to the subjects. 4. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches. 	Randomized clinical trials
3. Involves greater than minimal risk and no prospect of direct benefit to individual subjects but is likely to yield generalizable knowledge about the subject's disorder or condition.	<ol style="list-style-type: none"> 1. Assent of children/adolescents. 2. Permission of both parents/guardians. 3. The risk represents a minor increase over minimal risk. 4. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations. 5. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition. 	Bone marrow aspiration Lumbar puncture
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.	<ol style="list-style-type: none"> 1. Assent of children/adolescents. 2. Permission of both parents/guardians. 3. The IRB finds 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. 4. The Secretary, after consultation with a panel of experts in pertinent disciplines (For example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined the research will be conducted in accordance with sound ethical principles. 	

parents. The federal regulations deliberately use the terms "permission" and "assent" to distinguish these processes from the usual informed consent process. Parents are not providing "informed consent" because they are not the research subjects and do not experience risks or benefits from the research. Children often lack the intellectual capacity or judgment to make decisions about research, although the concept of assent recognized the importance of emerging capacity for informed consent. Based on the recommendations of the National Commission in 1977 [72], assent is commonly obtained from children who are aged 7 years and older. As noted above, adolescents may

be fully capable of making sound decisions about research involvement.

c. Waiver of Parental Permission

The primary ethical purpose of obtaining parental permission is to ensure that vulnerable children are protected from research risk. The National Commission recognized, however, that parental permission is not always a good way to protect children who are research subjects:

"The Commission recommends that whenever parental permission is not a reasonable requirement to protect the well-being of the child, alternatives should be required by

the IRB. Here (the Commission) operates under the general moral principle to avoid harm as well as to respect the autonomy of older children.” [72]

Under the federal regulations governing research [33], the IRB may waive parental permission for research involving children (including minor adolescents) where parental permission is problematic. Parental permission may be waived under two sections of the regulations: 45 CFR 46.408(c) or 45 CFR 46.116 (d). A waiver needs to be justified under the criteria found in one section or the other, not both.

Institutional Review Boards use section 46.116(d) to waive informed consent for research with children and adults where it would be impracticable to obtain informed consent from each subject, the waiver would not adversely affect the rights and welfare of the subjects, and the research involves no more than minimal risk. For example, section 46.116(d) is often used to waive informed consent when conducting research that involves review of existing medical records. Section 46.116(d) can be used to waive the parental permission requirement where such a waiver would not adversely affect the rights and welfare of the child or adolescent, the risk is minimal, and the research could not be practicably carried out without the waiver. The impracticability standard may be difficult to define, but low response rates and sampling bias may be considered evidence of impracticability.

Section 46.408(c) states:

“In addition to the provisions for waiver contained in 39 46.116 of Subpart A, if an IRB determines that a research protocol is designed for conditions or a subject population for which parental permission is not a reasonable requirement to protect subjects (e.g., neglected or abused children), it may waive consent requirements provided an appropriate mechanism for protecting the children who will participate as research subjects is substituted and provided the waiver is not inconsistent with federal, state, or local law.”

Under section 45 CFR 46.408(c), the regulations specifically allow for a waiver of parental permission where such permission is not a reasonable requirement for the protection of research subjects and the waiver would not be inconsistent with federal, state, or local law. If parental permission is waived an alternative mechanism is required to protect human subjects. The federal regulations offer a single example of a situation where parental permission is not a reasonable requirement: child abuse.

The report of the National Commission [72] noted that IRBs may determine that parental permission would not be appropriate because of the nature of the subject under investigation; health care for contraception and drug abuse are given as examples. They suggested additional circumstances in which parental permission was not a reasonable requirement [24,58,73]:

“ . . . research designed to identify factors related to the incidence or treatment of certain conditions in adolescents for which they may legally receive treatment without parental consent; research in which the subjects are “mature minors” and the procedures involved entail essentially no more than minimal risk that such individuals might reasonably assume on their own; research designed to meet the needs of children designated by their parents as “in need of supervision,” and research involving children whose parents are legally or functionally incompetent . . .”

The commission thus recognized the reality of adolescents’ independent access to care [24] and acknowledged the developing capacity of adolescents and the concept of the mature minor. Examples of alternative mechanisms include consent of a mature minor, court approval, appointment of a child advocate who is unconnected with the research project, and permission from a surrogate parent [58,73]. Community consultation also has recently been suggested as a means to protect adolescent research subjects [24].

The Children’s Health Act of 2000 mandated that all federally regulated research comply with Subpart D and in consequence the FDA adopted Subpart D of the federal regulation dealing with children [74]. In so doing, the agency specifically removed section 45 CFR 46.408(c), which allows for a waiver of parental permission. This decision would seemingly prevent the waiving of parental permission in FDA-regulated research such as randomized trials of new drugs and the testing of new diagnostic devices, such as unlicensed STD tests. This change in Subpart D was pointedly challenged by the National Human Subjects Protections Advisory Committee (NHRPAC, the federal advisory committee to OHRP) which cited the SAM-sponsored *Guidelines* in recommending the adoption of 408(c) [75]. Where a researcher believes that inclusion of minor adolescents in an FDA-regulated study is important and that parental permission is ethically problematic, researchers and IRBs should consider whether a minor adolescent is a “child” under the definition of children in the federal regulations (see below).

d. Are Adolescents Considered Children under the Federal Regulations for Research?: Definition of Children

The *Guidelines* address the definition of children as found in the federal regulations, which read, "children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." Under this definition, not all adolescents who are under the legal age of majority are defined as children. This definition references state laws, including laws addressing age of majority, age to consent for general medical care, emancipation, and treatment for specific conditions such as STDs and substance use; few states have laws addressing participation of adolescents in research. All states recognize the concept of emancipated minors. In almost every state the age of majority is 18 years. [76] In addition, several states establish an age that is lower than the general age of majority at which any minor may give consent for general health care. [76]. Moreover, all states authorize certain groups of minors to give their own consent for specific types of health care. [76]. These state minor consent laws vary widely but allow adolescents to consent independently to a number of treatments and procedures such as, in every state, diagnosis and treatment of sexually transmitted infections and, in almost every state, counseling for substance use. Under this definition, adolescents who have reached the age of majority or the age to consent for general health care or are emancipated are not children. Likewise, adolescent minors, who are allowed to consent to treatments or procedures involved in the research, should not be considered children.

Investigators and IRBs should assess all these legal complexities in considering research with adolescents. Specifically, they should assess their own state law in determining whether adolescents who are proposed research subjects should or should not be considered children under the federal regulations. If they are not considered children, parental permission is not required. Even if adolescent subjects are considered children, the investigators and IRB may still decide that parental permission should be waived.

Guidelines for Adolescent Health Research, A Summary

The Society for Adolescent Medicine continues to believe that the *Guidelines for Adolescent Health Re-*

search [1] offer a reasonable and ethically nuanced interpretation of the federal regulations based on the principles from the Belmont Report, a scientific understanding of adolescent decision-making capacity, and a balanced understanding of research risk and benefit. These *Guidelines* respect both the important role of parents as protectors of their children and the emerging capacity of the adolescent for independent decision-making. These *Guidelines* promote a consistent interpretation of the federal research regulations that have been variably interpreted in the past. In revising this Position Paper, we have not amended the *Guidelines* themselves, because we believe they remain a clear statement regarding the appropriate inclusion of adolescents in health research.

Current federal regulations (45 CFR Part 46) and the underlying principles of respect for persons, beneficence, and justice provide an essential framework for evaluating the circumstances under which adolescent minors can and should be involved as subjects in research. Respect for persons demands a balancing of respect for the adolescent's emerging capacity for independent decision-making and the need for continued special protections for potentially vulnerable individuals. Beneficence provides the ethical basis for conducting health-enhancing research and for maximizing benefit and minimizing risk. Justice demands that adolescents not be exploited for the benefits of others but also that adolescents not be excluded from participation in research that may have direct or indirect benefit.

The *Guidelines on Adolescent Research* and the Society for Adolescent Medicine's other efforts to increase participation of adolescents in research are consistent with federal policies to increase their involvement in research. The 1998 NIH *Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects* demands that children and adolescent must be included in all human subjects research supported by the NIH, "unless there are scientific and ethical reasons not to include them." [37] The FDA has recently promulgated similar policies to promote inclusion of children in research.

The protection of adolescents in the research process should be informed by a scientific understanding of adolescent cognitive, psychological, and social development. Research on cognition and capacity suggests that adolescents show significant ability to provide informed consent. By mid- to late adolescence, the ability to understand research and to make decisions about research participation are similar to these abilities in adults. The *Guidelines* suggest that for research of low risk (e.g., confidential or

anonymous survey research) capacity can be assumed based on the reasonable expectation of capacity for the group of adolescents to be studied, and that the informed consent of the adolescent can be substituted for parental permission. For research involving greater risk, and where circumstances merit waiving parental permission, the *Guidelines* propose an individual assessment of capacity.

Under the federal regulations governing research, the IRB may waive the requirement for parental permission for research involving children (including minor adolescents) if parental permission is deemed not reasonable or ethically problematic. The National Commission noted that IRBs may determine that parental permission may not be appropriate, in certain studies, for example, health care for contraception and drug abuse. Adolescents' rights to both clinical care and research may be compromised if parental permission is required for research participation, under circumstances where parental permission is not required for health care.

The definition of children in the federal regulations recognizes the legal status of mature and emancipated minors under state law and the ability of adolescents to consent for specific health services. These state minor consent laws implicitly recognize that under certain circumstances minors are capable of making independent judgments and that this emerging decision-making capacity should be respected. Parental permission is not required under the federal regulations, where adolescents do not fit the regulatory definition of children.

Our review of the research literature provides little evidence that communicating with adolescents about negative health behaviors, either in traditional health educational settings or in behavioral surveys, increases those behaviors. To the contrary, completion of surveys may increase self-understanding of the risk from one's own behavior, and by raising such understanding, survey research may facilitate the process of seeking care. Benefits of involvement in the informed consent process for research include an increased sense of self-control and increased decision-making capacity.

Community involvement can be an important protection for adolescent participants in research. The involvement of community and community institutions may enhance the quality of research and the quality of research protections. Community involvement may provide important insights into the underlying forces influencing health and strengthen efforts to create programs to improve health.

Adolescent health researchers need to be knowledgeable about research ethics and sensitive to the potential risks and benefits of their activities. Researchers in adolescent health are challenged to provide the very best protections to their study participants and to conduct research in a scrupulously ethical way. Research with adolescents may benefit individual adolescents or adolescents as a group. Ethical research with adolescents should focus on the twin goals of protection from research risk and appropriate inclusion in research.

Prepared by:

John S. Santelli, M.D., M.P.H.
 Audrey Smith Rogers, Ph.D., M.P.H.
 Walter D. Rosenfeld, M.D.
 Robert H. DuRant, Ph.D.
 Nancy Dubler, L.L.B.
 Madlyn Morreale, M.P.H.
 Abigail English, J.D.
 Sheryl Lyss, M.D.
 Yolanda Wimberly, M.D.
 Anna Schissel, J.D., M.B.E.

References

1. Anonymous. Guidelines for Adolescent Health Research. *J Adolesc Health* 1995;17:264-9.
2. U.S. Congress, Office of Technology Assessment. Adolescent Health-Volume I: Summary and Policy Options. Washington, DC: U.S. Government Printing Office, 1991; OTA-H-468.
3. National Commission on the Role of the School and the Community in Improving Adolescent Health. Code Blue: Uniting for Healthier Youth. City, state: National Association of State Boards of Education and American Medical Association, 1991.
4. Task Force on Education of Young Adolescents. Turning Points: Preparing American Youth for the 21st Century. Washington, DC: Carnegie Council on Adolescent Development, Carnegie Corporation of New York, 1989.
5. National Commission on AIDS. Preventing HIV/AIDS in Adolescents. Washington, DC, National Commission on AIDS, 1993.
6. National Research Council (Miller HG, Turner CF, Moses LE, editors). AIDS: The Second Decade. Washington, DC: National Academy Press, 1990.
7. Moolchan ET, Mermelstein R. Research on tobacco use among teenagers: Ethical challenges. *J Adolesc Health* 2002;30:409-17.
8. Milsap RL, Hill MR, Szefer SJ. Special pharmacokinetic considerations in children. In: Evans WE, Schentag JJ, Jusko WJ (eds). *Applied Pharmacokinetics*. 3rd edition. Vancouver, WA: Applied Therapeutics, 1992.***-***.
9. Rosenfeld WD, Vermund SH, Wentz SJ, Burk RD. High prevalence rate of human papillomavirus infection and association with abnormal smears in sexually active adolescents. *Am J Dis Child* 1989;143:1443-7.

10. Moscicki AB, Ellenberg JH, Vermund SH, et al. Prevalence of and risks for cervical human papillomavirus infection and squamous intra-epithelial lesions in adolescent women: Impact of infection with human immunodeficiency virus. *Arch Pediatr Adolesc Med* 2000;154:127-34.
11. Crowley-Nowick PA, Ellenberg JH, Vermund SH, et al. Cytokine profile in genital tract secretions from female adolescents: Impact of human immunodeficiency virus, human papillomavirus, and other sexually transmitted pathogens. *J Infect Dis* 2000;181:939-45.
12. Strobino DM. The health and medical consequences of adolescent sexuality and pregnancy: A review of the literature. In: Hayes CD, Hofferth SL (eds). *Risking the Future: Adolescent Sexuality, Pregnancy and Childbearing: Working Papers and Statistical Appendices*. Vol. II. Washington, DC: National Academy Press, 1987:888-***.
13. Korenbrot CC, Showstack J, Loomis A, Brindis C. Birth weight outcomes with case management in a teenage pregnancy program. *J Adolesc Health Care* 1989;10:97-104.
14. Kirby D. *Emerging Answers: Research Findings on Programs to Reduce Teen Pregnancy*. Washington, DC: The National Campaign to Prevent Teen Pregnancy, 2001.
15. DiClemente RJ. Preventing HIV/AIDS among adolescents. Schools as agents of behavior change. *JAMA* 1993;270:760-2.
16. Rogers AS. A research agenda for the study of therapeutic agents in adolescents. *J Adolesc Health* 1994;15:672-8.
17. Elster AB, Kuznets NJ. *AMA Guidelines for Adolescent Preventive Services (GAPS): Recommendations and Rationale*. Baltimore, MD: Williams and Wilkins, 1993.
18. Wilson CM, Houser J, Partlow C, et al. Adolescent Medicine HIV/AIDS Research Network, The REACH Project (Reaching for Excellence in Adolescent Care and Health): Study design, methods, and population profile. *J Adolesc Health* 2001;29(Suppl):8-18.
19. DuRant RH, Pendergrast RA, Cadenhead C. Exposure to violence and victimization and fighting behavior by urban black adolescents. *J Adolesc Health* 1994;15:311-8.
20. Levine C. Children in HIV/AIDS clinical trials: Still vulnerable after all these years. *Law Med Health Care* 1991;19:231-7.
21. DuRant RH, Cadenhead C, Pendergrast RA, et al. Factors associated with the use of violence among urban black adolescents. *Am J Public Health* 1994;84:612-7.
22. Rutter M. Psychosocial resilience and protective mechanisms. *Am J Orthopsychiatry* 1987;57:316-31.
23. Resnick MD, Bearman PS, Blum RW, et al. Protecting adolescents from harm: Findings from the National Longitudinal Study of Adolescent Health. *JAMA* 1997;278:823-32.
24. Rogers AS, D'Angelo L, Futterman D. Guidelines for adolescent participation in research: Current realities and possible resolutions. *IRB* 1994;16:1-6.
25. Select Committee on Children, Youth, and Families, US House of Representatives. *A Decade of Denial: Teens and AIDS in America*. Washington, DC: U.S. Government Printing Office, 1992.
26. Levine C, Dubler NN, Levine RJ. Building a new consensus: Ethical principles and policies for clinical research on HIV/AIDS. *IRB* 1991;13:1-17.
27. Grodin MA, Alpert JJ. Children as participants in medical research. *Pediatr Clin North Am* 1988;35:1389-401.
28. Gardner W, Wilcox BL. Political intervention in scientific peer review: Research on adolescent sexual behavior. *Am Psychol* 1993;48:972-83.
29. Mammel KA, Kaplan DW. Research consent by adolescent minors and institutional review boards. *J Adolesc Health* 1995;17:322-9.
30. Sieber JE, Stanley B. Ethical and professional dimensions of socially sensitive research. *Am Psychol* 1988;43:49-55.
31. Janofsky J, Starfield B. Assessment of risk in research on children. *J Pediatr* 1981;89:842-6.
32. Rogers AS, Schwarz DF, Weissman G, English A. Adolescent participation in clinical research: Eleven sites, one common protocol, and Eleven IRBs. *IRB* 1999;21:6-10.
33. Department of Health and Human Services, National Institutes of Health, Office for Protection from Research Risks. *Code of Federal Regulations: Title 45-Public Welfare; Part 46: Protection of Human Subjects*. November 13, 2001.
34. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, DC: US Government Printing Office, DHEW Pub. No. (OS) 78-0012, 1978.
35. Society for Adolescent Medicine. *Code of Research Ethics: A Position Paper of the Society for Adolescent Medicine*. *J Adolesc Health* 1999;24:277-82.
36. Bleyer WA, Tejada H, Murphy SB, et al. National cancer clinical trials: Children have equal access; adolescents do not. *J Adolesc Health* 1997;366-73.
37. National Institutes of Health. *NIH Policy and Guidelines On The Inclusion Of Children As Participants In Research Involving Human Subjects*. March 6, 1998. Available at: <http://grants1.nih.gov/grants/guide/notice-files/not98-024.html>. Accessed April 10, 2003.
38. Glantz LH. The law of human experimentation with children. In: Grodin MA, Glantz LH (eds). *Children as Research Subjects: Science, Ethics, and Law*. New York: Oxford University Press, 1994:103-30.
39. Melton GB. Children's rights: Where are the children? *Am J Orthopsychiatry* 1982;52:530-8.
40. Holder AR. Legal issues in adolescent sexual health. *Adolesc Med: STAR* 1992;3:257-68.
41. English A. Treating adolescents: Legal and ethical considerations. *Med Clin North Am* 1990;74:1097-112.
42. English A, Matthews M, Palamountain C, et al. *State Minor Consent Statutes: A summary*. San Francisco: National Center for Youth Law, 1995.
43. English A, Morreale M. A legal and policy framework for adolescent health care: Past, present, and future. *Houston J Health Law Policy* 2001;1:63-108.
44. Melton GB. Ethical and legal issues in research and intervention. *J Adolesc Health Care* 1989;10(3 Suppl):365-44S.
45. English A. Adolescent reproductive health services for adolescents: Critical legal issues. *Obstet Gynecol Clin North Am* 2000;27:195-211.
46. Gans J (ed). *Policy Compendium on Confidential Health Services for Adolescents*. Chicago: American Medical Association National Coalition on Adolescent Health, 1993.
47. Department of Health and Human Services. *Standards for Privacy of Individually Identifiable Health Information; Final Rule*. 65 Fed. Reg. 82462 (2000); 67 Fed. Reg. 53182 (2002) (to be codified at 45 CFR Parts 160 and 164).
48. Department of Health and Human Services. *Protecting personal health information in research — Understanding the HIPAA Privacy Rule*. Department of Health and Human Services. Washington, DC: Department of Health and Human Services, 2003.
49. Department of Health and Human Services. *Standards for Privacy of Individually Identifiable Information; Final Rule*, 67 Fed. Reg. 53267 (2002) (to be codified at 45 CFR 164.502(g)(3)).

50. Leikin SL. An ethical issue in biomedical research: The involvement of minors in informed and third party consent. *Clin Res* 1983;31:34–40.
51. Weithorn LA. Children's capacities to decide about participation in research. *IRB* 1983;5:1–5.
52. Weithorn LA, Scherer DG. Children's involvement in research participation decisions: Psychological considerations. In: Grodin MA, Glanz LH (eds). *Children as Research Subjects: Science, Ethics, and Law*. New York: Oxford University Press, 1994:133–79.
53. Melton GB. Toward "personhood" for adolescents. *Autonomy and privacy as values in public policy*. *Am Psychol* 1983;38:99–103.
54. Susman EJ, Dorn LD, Fletcher JC. Participation in biomedical research: The consent process as viewed by children, adolescents, young adults, and physicians. *J Pediatr* 1992;547–52.
55. Peterson AC, Leffert N. Developmental issues influencing guidelines for adolescent health research. *J Adolesc Health* 1995;17:298–305.
56. Thompson RA. Vulnerability in research: A developmental perspective on research risk. *Child Dev* 1980;61:1–16.
57. National Bioethics Advisory Commission. *Ethical and Policy Issues in Research Involving Human Participants, Volume I. Report and Recommendations of the National Bioethics Advisory Commission*. Bethesda, MD: Office of the President, 2001.
58. Levine RJ. Adolescents as research subjects without permission of their parents or guardians: Ethical considerations. *J Adolesc Health* 1995;17:286–96.
59. Mastroianni AC, Faden R, Federman D (eds). *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies, Volume I*. Washington: Institute of Medicine, National Academy Press, 1994.
60. Food and Drug Administration. *The Pediatric Exclusionary Provision, January 2001 Status Report to the Congress* (January 9, 2001). Website: <http://www.fda.gov/cder/pediatric/reportcong01.pdf>. Accessed April 10, 2003.
61. Food and Drug Administration. *Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule*. 21 CFR Parts 201, 312, 314, and 601. Website: <http://www.fda.gov/ohrms/dockets/98fr/120298c.txt>. Accessed April 10, 2003.
62. Shirkey HC. Therapeutic orphans. *J Pediatr* 1968;72:119–20.
63. Levine RJ. Institutional review boards: A crisis in confidence. *Ann Intern Med* 2001;134:161–3.
64. Melton GB, Levine RJ, Koocher GP, et al. Community consultation in socially sensitive research. Lessons from clinical trials of treatments for AIDS. *Am Psychol* 1988;43:573–81.
65. Jenkins R, Parron D. Guidelines for adolescent health research: Issues of race and class. *J Adolesc Health* 1995;17:313–21.
66. Thomas SB, Quinn SC. The Tuskegee Syphilis study, 1932 to 1972: Implications HIV education and AIDS risk education programs in the black community. *Am J Public Health* 1991;81:1498–1504.
67. Lederer SE, Grodin MA. Historical overview: Pediatric experimentation. In: Grodin MA, Glanz LH (eds). *Children as Research Subjects: Science, Ethics, and Law*. New York: Oxford University Press, 1994:3–25.
68. Gans JE, Brindis CD. Choice of research setting in understanding adolescent health problems. *J Adolesc Health* 1995;17:305–12.
69. 20 U.S.C. § 1232g; 34 C.F.R. Part 99.
70. 20 U.S.C. § 1232h; 34 C.F.R. Part 98.
71. U.S. Department of Education. *Recent Changes Affecting FERPA & PPRRA*. October 28, 2002. Available at: http://www.ed.gov/offices/OII/fpca/pdf/ht_102802.pdf. Accessed May 6, 2003.
72. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Report and Recommendations: Research Involving Children*. Washington, DC: US Government Printing Office, DHEW Pub. No. (OS) 77-0004, 1977.
73. English A. Guidelines for adolescent health research: Legal perspectives. *J Adolesc Health* 1995;17:276–85.
74. Food and Drug Administration. *Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products*. 21 CFR Parts 50 and 56. *Federal Register*: April 24, 2001 (Volume 66, Number 79), Rules and Regulations, Pages 20589–600. Available at: <http://www.fda.gov/OHRMS/DOCKETS/98fr/042401a.pdf>. Accessed April 10, 2003.
75. National Human Research Protections Advisory Committee. *Comment letter to the FDA on 45 CFR 46 408(c)*. August 13, 2001. Available at: <http://ohrp.osophs.dhhs.gov/nhrpac/documents/fda.pdf>. Accessed September 1, 2002.
76. English A, Morreale MC, Stinnett A, et al. *State minor consent laws: A summary*. Chapel Hill, NC: Center for Adolescent Health & the Law. (In press.).