The American College of
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WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

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Committee on Adolescent Health Care

The North American Society for Pediatric and Adolescent Gynecology endorses this document. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care in collaboration with committee member Veronica Gomez-Lobo, MD.

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Guidelines for Adolescent Health Research

ABSTRACT: Considerable uncertainty exists about what constitutes appropriate levels of protection for adolescents as research participants and about the need for parental permission. The ethical principles that govern research include respect for individuals, beneficence, and justice, as articulated in the *Belmont Report*. Researchers should be familiar with and adhere to current federal regulations 45 C.F.R. § 46, and federal and state laws that affect research with minors. Investigators should understand the importance of caregiver permission—and ethically appropriate situations in which to waive caregiver permission—for the protection of adolescent research participants.

Recommendations

The American College of Obstetricians and Gynecologists supports the following ethical guidelines for adolescent health research:

- Researchers should be familiar with and adhere to current federal regulations 45 C.F.R. § 46, and federal and state laws that affect research with minors.
- Investigators should understand the importance of caregiver permission—and ethically appropriate situations in which to waive caregiver permission—for the protection of adolescent research participants.
- Caregiver permission when adolescents are involved in a study may be waived by an Institutional Review Board under two circumstances: 1) when requiring parental permission is not a reasonable requirement to protect adolescents; or 2) when the waiver would not adversely affect the rights and welfare of the adolescent, the study poses no more than a minimal risk to the adolescent, and the study could not be practically carried out without a waiver.
- In certain studies involving pregnancy, treatment of sexually transmitted infections, and contraceptive and abortion services, an adolescent can provide informed consent and parental permission is not required.

Background

Considerable uncertainty exists about what constitutes appropriate levels of protection for adolescents as research participants and about the need for parental permission. This document is designed to clarify protection afforded minor adolescents and issues related to informed consent and parental permission, in order to promote the appropriate inclusion of minor adolescents in health research. The U.S. federal government has promulgated regulations that govern research involving human participants (also referred to as human subject research) when the research is supported, conducted, or otherwise subject to regulation by the federal government. Many universities and research institutions apply these regulations to privately funded research as well. This document provides citations to 45 C.F.R. § 46, which are the regulations that apply to the U.S. Department of Health and Human Services. Several non-Health and Human Services departments and agencies have additional regulations for research involving human participants.

Research Principles

The ethical principles that govern research include respect for individuals, beneficence, and justice, as articulated in the *Belmont Report* (1). These U.S. federal government regulations, known as the Code of Federal Regulations: Title 45-Public Welfare; Part 46: Protection of Human

Subjects (2), dictate the requirement for ethical review of specific proposals through a nationwide system of local Institutional Review Boards (IRBs).

These regulations require that risks to research participants be minimized and that they be reasonable relative to the anticipated benefits and the importance of the knowledge that may be expected to result from the research. The regulations also require that the selection of research participants be equitable and that informed consent be obtained from each prospective research participant or the participant's legally authorized representative. General requirements for informed consent are described in 45 C.F.R. § 46.116 (2). Subpart D of 45 C.F.R. § 46 contains special protection for children, including minor adolescents, who participate in research.

Consent and Confidentiality

Research that involves adolescents often raises questions about how to obtain adequate informed consent and protect research participants' confidentiality. The Society for Adolescent Health and Medicine led the development of consensus guidelines to promote the ethical conduct of health research involving adolescents as research participants that stress the appropriate inclusion of adolescents in research (3).

Adolescents generally exhibit cognitive capacity to provide informed consent similar to young adults, but judgment is often not fully developed (3). The content and wording of informed consent forms for adolescents should resemble those used with adults. Assent should be sought from adolescents even when parental permission is obtained. Researchers should be aware of the unique vulnerabilities of young people, the rapid developmental changes of adolescence, and specific health risks at this age. They also should be prepared to offer assistance to adolescents when health needs are identified in the course of research, such as rapid referral for adolescents who exhibit imminent risk of harm to themselves or others.

When considering the legal complexities of adolescent health research, it is important to recognize that laws regarding emancipation and minor consent for specific health services vary considerably among states; thus researchers in adolescent health should be familiar with current state statutes regarding age of majority and emancipation, as well as with minor consent statutes. An up-to-date listing of these statutes can be found at www.guttmacher.org/statecenter/spibs/spib_OMCL.pdf (4).

Parental Permission and Waivers

Investigators should understand the importance of caregiver permission—and ethically appropriate situations in which to waive caregiver permission—in the protection of adolescent research participants. Caregiver permission when adolescents are involved in a study may be waived by an IRB under two circumstances: 1) when requiring parental permission is not a reasonable requirement to protect adolescents; or 2) when the waiver would not adversely affect the rights and welfare of the adolescent, the study poses no more than a minimal risk to the adolescent, and the study could not be practically carried out without a waiver. In the federal regulations governing research, *children* are defined in 45 C.F.R. § 46.102(a) 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 (2).*

This federal definition refers to laws, primarily state laws, related to minor consent for treatment of specific health conditions such as pregnancy and contraception, age of majority, and emancipation status. Thus, in certain studies involving pregnancy, treatment of sexually transmitted infections, and contraceptive and abortion services, an adolescent can provide informed consent and parental permission is not required.

Federal regulations that govern human participant research require parental permission and child assent for participants who meet the regulatory definition of children. Assent means a child has given affirmative agreement to participate; mere failure to object should not be construed as assent. Assent is required when, in the judgment of the IRB, the children are capable of providing it (2). Federal regulations deliberately use the terms "permission" and "assent" to differentiate this process from the usual informed consent process; therefore, parents give only permission for their child to be involved in research, not consent.

In 1977, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research recommended that individual IRBs be allowed to determine that parental permission is not required in certain research studies, including research involving assessment for or care related to contraception and drug abuse (5). According to the federal regulations, informed consent and parental consent may be waived under 45 C.F.R. § 46.116(d) and parental permission may be waived under 45 C.F.R. § 46.408(c) (2).

Four criteria set forth by 45 C.F.R. § 46.116(d) allow an IRB to waive the requirement to obtain the informed consent for adult research participants or permission of a parent or guardian for research participants who are children: 1) the research involves no more than "minimal risk" (which means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychologic examinations or tests; 2) the waiver will not adversely affect the rights and welfare of the participants; 3) the research could not practically be carried out without a waiver; and 4) whenever appropriate, the participant will be provided with additional pertinent information after participation. This

section is commonly used when waiving informed consent for research that involves existing data such as medical records (2).

In addition, 45 C.F.R. § 46.408(c) specifically allows for a waiver of parental permission under Subpart D (addressing research with children). Section 408(c) of 45 C.F.R. § 46 states

> *. . . 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 (eg, 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 . . .* (2)

In discussing the waiver of parental permission, the National Commission cited examples of when the requirement for parental permission might not be a reasonable one (5),

> *. . . [r]esearch designed to identify factors related to the incidence or treatment of certain conditions in adolescents for which, in certain jurisdictions, they legally may receive treatment without parental consent; [and] 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 . . .*

Based on these criteria, either 45 C.F.R. § 46.408(c) or 45 C.F.R. § 46.116(d) may be used to waive parental permission in a variety of studies, including for example, surveys of adolescents. It is important to note that if these surveys are conducted in a school setting, federal educational law governing certain research conducted in schools applies. Health researchers working in schools, therefore, are advised to become knowledgeable about these laws (Family educational rights and privacy 34 C.F.R. § 99 [2008]; Family educational and privacy rights 20 U.S.C. § 1232(g) [2008]; Student rights in research, experimental programs, and testing 34 C.F.R. § 98 [2008]; and Protection of pupil rights 20 U.S.C. § 1232(h) [2008]) (6–9).

In 2001, the U.S. Food and Drug Administration adopted Subpart D of the federal regulations related to children (which indicates that the IRB may approve clinical investigations that involve greater than minimal risk and no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the participant's disorder or condition) (10). In so doing, the agency specifically removed section 45 C.F.R. § 46.408(c), which allows for a waiver of parental permission. When a researcher believes that inclusion of minor adolescents in a U.S. Food and Drug Administration-regulated study is important and that parental permission is ethically problematic, researchers and IRBs should consider whether an adolescent is a child under the definition of children in the federal regulations.

Research that involves adolescents is essential to improve adolescent health care, yet adolescents often are underrepresented in research and trials. In recognition of this disparity, the Best Pharmaceutical for Children Act was signed into law in 2002 to promote pharmaceutical research in children and adolescents. In 2007 the Best Pharmaceutical for Children Act was reauthorized and gave the FDA the ability to issue requests to manufacturers for pediatric testing. Furthermore, the Pediatric Research Equity Act mandates pediatric testing of drugs that are likely to be used in this population. Although this legislation encourages pharmaceutical research in children, it remains difficult to involve adolescents in research. Researchers should be familiar with and adhere to current federal regulations, 45 C.F.R. 46 (2), and federal and state laws that affect research with minors.

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