On the following pages you will find 8 cases for an IRB to review. The IRB must decide if these studies are in fact ethical to be done in children and adolescents. Please read these cases, identify the salient points of concern, and propose a recommendation to approve or defer. Consider if you propose to defer what you might ask the applicants to address. Included for your review and to help with your determination of the ethical issues of these cases is the text of 45 CFR 46 Section D. To put Section D in context, we have included the prefatory material to 45 CFR 46 including its table of contents.

CASE STUDIES IN PEDIATRIC RESEARCH
Example 1: Researchers propose a study in which healthy 2-month-old children will be recruited from the community and receive as part of a double-blind, randomized controlled trial either a novel pneumococcal conjugate vaccine that contains 25 serotypes or the standard vaccine currently licensed and recommended that contain only 13 serotypes. All 25 cause significant rates of disease ranging from mild to severe in children. The researchers will get parental permission. The study involves randomization and allocation concealment as well as blinding. No one will receive a placebo. Patients will get vaccines at 2, 4, 6, and 15 months-- the age when the 13-valent vaccine is recommended to be given and is routinely received. All will undergo blood draws at one month and six months and one year. All will be followed closely for safety data.

Example 2: Researchers propose a study of healthy 2-month-old children who will be recruited from the community and receive as part of a double-blind, randomized controlled trial either a novel pneumococcal conjugate vaccine that contains 25 serotypes or the standard vaccine currently licensed and recommended that contain only 13 serotypes. All 25 cause significant rates of disease ranging from mild to severe in children. The researchers will get parental permission. The study involves randomization and allocation concealment as well as blinding. No one will receive a placebo. Patients will get vaccines at 2, 4, 6, and 15 months-- the age when the 13-valent vaccine is recommended to be given and is routinely received. All will undergo blood draws at one month and six months and one year. All will be followed closely for safety data. In addition, children will undergo swabs of their nares weekly for carriage rates of pneumococcal strain specific organisms. The study will continue for each patient one year and all will be enrolled during a single calendar month to avoid variation from seasonality.

Example 3: Researchers propose a study of healthy, 2-year-old children to be recruited from the community and receive as part of a double-blind, randomized controlled trial either a novel pneumococcal conjugate vaccine that contains 25 serotypes or a placebo. All 25 serotypes cause significant rates of disease ranging from mild to severe in children. The researchers will get parental permission. The study involves randomization and allocation concealment as well as blinding. Patients will get 1 dose of the vaccine or placebo at 2 years of age. All must have
previously received the routinely 13-valent vaccine. All will undergo blood draws at one month and six months and one year. All will be followed closely for safety data. In addition, children will undergo swabs of their nares weekly for carriage rates of pneumococcal strain specific organisms as well as blood cultures. The latter requires 2 mL weekly and over 8 weeks requires 16 mL. The study will continue for each patient one year and all will be enrolled during a single calendar month to avoid variation from seasonality.

Example 4: Researchers propose a study of healthy 2-4 year old children enrolled in the community’s Head Start program. The children will all receive a single dose of a novel pneumococcal conjugate vaccine that contains 25 serotypes. Studies in older children show that the vaccine is safe. All the children recruited must have previously received the routinely 13-valent pneumococcal vaccine. The researchers will get parental permission. The additional 12 serotypes in the experimental vaccine rarely, if ever, cause significant rates of disease in children. Still there is a fear that the 12 serotypes may one day cause disease in humans. All will undergo blood draws at one month and six months and one year after vaccination. All will be followed closely for safety data. All will be enrolled during a single calendar month to avoid variation from seasonality.

Example 5: Researchers propose a study of healthy children who will undergo routine blood sampling for antibodies to serotypes of pneumococcus. These 25 serotypes all cause significant rates of disease ranging from mild to severe in children. The researchers will get parental permission and for children 7 and older, their assent. All children will undergo blood draws upon enrollment and once a year for five years. At the time of their yearly blood draw, their parents will be interviewed about the child’s past year in terms of medical illnesses, medical encounters, laboratory testing, and prescription medications to ascertain if the child developed during the interim disease consistent with pneumococcal infection.

Example 6: Researchers propose a study of children hospitalized with pneumococcal infections. Recruited patients will begin the study only upon successful completion of their antibiotic treatment. The researchers will get parental permission and for children 7 and older, their assent. They will begin a prophylactic course of antibacterial nasal washes and mouth rinses hypothesized to clear occult carriage of the organisms. The antibacterials proposed have proven safe in mice and primates but have not undergone FDA licensure.

Example 7: Researchers propose a study of children admitted for accidental injuries. The researchers will get parental permission and for children 7 and older, their assent. Despite the wide variety of admitting diagnoses, all would be considered at equal risk for pneumococcal infection since none of the admitting conditions would be risk factors for infection. Those recruited will undergo routine blood sampling for antibodies to serotypes of pneumococcus and for blood cultures as well as diagnostic imaging for occult pneumonia. The serotypes all cause significant rates of disease ranging from mild to severe in children. All will undergo a single additional blood draw and a chest x-ray. Parents would be especially interviewed about the child’s health in terms of symptoms and signs to ascertain if the child had a clinical condition consistent with a positive blood culture or x-ray.
Example 8: Researchers propose to recruit children newly diagnosed with asthma. They will get parental permission and for children 7 and older, their assent. They intend to randomize half of the children to have an electronic asthma action plan available on the web for the parents, providers, and school staff to access. The other half will receive usual care, which includes having a paper-based asthma action plan to be stored in the child’s medical record. A paper copy will be provided to the parent. All children enrolled will be monitored for one year with monthly assessments by asthma care managers who will assess the patient’s previous month in terms asthma symptom control. Asthma action plans will be modified as necessary by the asthma care managers by protocol based on the monthly assessments.

Example 9: Researchers propose to recruit fifty pediatric and fifty family medicine practices in the state. They intend to randomize half of the practices to use in their asthmatic children an electronic asthma action plan available on the web for the parents, providers, and school staff to access. The other half will continue with its usual care of asthmatics, which includes, at best, a paper-based asthma action plan to be stored in the child’s medical record, usually allowing a paper copy to be provided to the parent. Enrolled practices will monitor their asthmatic children for the sake of the study for one year with monthly assessments by asthma care managers who will assess the patient’s previous month in terms asthma symptom control. Asthma action plans will be modified as necessary by the asthma care managers by protocol based on the monthly assessments. Because the practices are being enrolled rather than individual patients, the researchers are not proposing individual informed consent procedures for the parents or children.

Example 10: Researchers are proposing a survey of parents of adolescents. The survey concerns a review of the parent’s knowledge, attitudes, skills, and practices regarding discipline of adolescent children under their care as parents in their home. Parents will be identified through their adolescents via school registration in the local school district. The investigators propose that they do not need adolescent assent.

Example 11: Researchers are proposing a survey of adolescents concerning birth control practices. The survey concerns a review of the adolescent’s knowledge, attitudes, skills, and practices. Potential recruits will be identified as through school registration in the local school district. The investigators request that the IRB waive parental permission given that it would make the study unworkable.
Title 45 CFR Part

Code of Federal Regulations

TITLE 45 PUBLIC WELFARE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 46
PROTECTION OF HUMAN SUBJECTS

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Revised June 23, 2005
Effective June 23, 2005

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Editorial Note: The Department of Health and Human Services issued a notice of waiver regarding the requirements set forth in part 46, relating to protection of human subjects, as they pertain to demonstration projects, approved under section 1115 of the Social Security Act, which test the use of cost-sharing, such as deductibles, copayment and coinsurance, in the Medicaid program. For further information see 47 FR 9208, Mar. 4, 1982.

Note: As revised, Subpart A of the HHS regulations incorporates the Federal Policy for the Protection of Human Subjects (56 FR 28003). Subpart D of the HHS regulations has been amended at Section 46.401(b) to reference the revised Subpart A.

The Federal Policy for the Protection of Human Subjects is also codified at

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Subpart D Additional Protections for Children Involved as Subjects in Research

Source: 48 FR 9818, March 8, 1983, unless otherwise noted.

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.
(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (i) of §46.101 of subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of subpart A are applicable to this subpart.


§46.402 Definitions.

The definitions in §46.102 of subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) 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.

(b) Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) Parent means a child's biological or adoptive parent.

(e) Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§46.404 Research not involving greater than minimal risk.
HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) 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;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

(a) 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; and

(b) 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 either:

(1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or
(2) the following:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) the research will be conducted in accordance with sound ethical principles;

(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

§46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §46.406 and §46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
(c) In addition to the provisions for waiver contained in §46.116 of subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117 of subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.