American Academy of Pediatrics
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Guidance for the Clinician in Rendering Pediatric Care

Clinical Report—Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations

abstract

The proper ethical conduct of studies to evaluate drugs in children is of paramount importance to all those involved in these types of studies. This report is an updated revision to the previously published guidelines from the American Academy of Pediatrics in 1995. Since the previous publication, there have been great strides made in the science and ethics of studying drugs in children. There have also been numerous legislative and regulatory advancements that have promoted the study of drugs in children while simultaneously allowing for the protection of this particularly vulnerable group. This report summarizes these changes and advances and provides a framework from which to guide and monitor the ethical conduct of studies to evaluate drugs in children. *Pediatrics* 2010;125:850–860

THE NEED TO STUDY DRUGS IN CHILDREN

The performance of research studies to evaluate drugs in children is critical for determining the safety and efficacy of medications in children. Without this type of research, medication use in children will be limited to extrapolation from adult studies or off-label use for indications that have not been studied in children, thereby putting children at increased risk of adverse effects. Growth and maturation can alter the kinetics, end-organ responses, and toxicities of drugs used in infants, children, and adolescents compared with adults. Without proper drug studies in children, children may not benefit from and may even be harmed by drugs that are available to adults. Also, certain disorders affect children primarily, necessitating drug testing on appropriately aged subjects. It is morally imperative, therefore, to formally study drugs in children so that they can enjoy appropriate access to existing and new therapeutic agents.

Since enactment of the exclusivity program in the US Food and Drug Administration (FDA) Modernization Act in 1997 (Pub L No. 105–115), drug studies in children have greatly increased in number. The reauthorization of this exclusivity program as the Best Pharmaceuticals for Children Act in 2002 (Pub L No. 107–109) and again in 2007 (Pub L No 10–85) and the enactment of the Pediatric Research Equity Act (Pub L No. 108–155) have allowed for increased motivation for pharmaceutical companies and other sponsors to partner with investigators to carry out drug trials in children.[1] Increased interest in pediatric drug research has been accompanied by increased numbers of pediatric drug-research studies and increased variability of the studies. Achieving proper balance between the overall good that comes from perform-

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KEY WORDS
ethics, drugs, children

ABBREVIATIONS
FDA—Food and Drug Administration
AAP—American Academy of Pediatrics
COI—conflict(s) of interest
IRB—institutional review board
DHHS—Department of Health and Human Services
DSMC—data- and safety-monitoring committee

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ing these studies and the need to protect children as research subjects is a challenge. This report provides a framework from which to guide and monitor the ethical conduct of studies to evaluate drugs in children.

THE NEED FOR ETHICAL GUIDELINES

Historically, ethical guidelines to protect human subjects of scientific investigation were developed in recognition of past exploitation of human subjects and the acknowledged need to protect individual human rights. Federal regulations governing the protection of human subjects were published in 1974 and revised in 2005.[2] The American Academy of Pediatrics (AAP) first published "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations" in 1977[3] and revised the document in 1995.[4] Federal regulations that specifically addressed research in children were published in 1978,[5] 1983,[6] 2001,[7] and 2005.[8]

In the landmark Belmont report of 1978,[9] 3 basic ethical principles for the protection of all human subjects were outlined:

1. Respect for persons
   - Individuals should be treated as autonomous agents.
   - Persons with diminished autonomy are entitled to protection.
2. Beneficence
   - Human subjects should not be harmed.
   - Research should maximize possible benefits and minimize possible harms.
3. Justice
   - The benefits and risks of research must be distributed fairly.

The conduct of research in children carries with it all the ethical obligations of research in adults as well as additional obligations and protections. Children are an especially vulnerable population, and respect for children is a critical guide for research in this population. This situation imposes special considerations when inviting participation in studies, assessing risks and benefits, and ensuring equitable participation in and benefits of clinical research.

RESEARCH-PROPOSAL DESIGN

Proposals for clinical investigation of drugs in children must include measures to protect the interests of children and must:

1. Be scientifically sound and significant, with value to children in general and, in most cases, to the individual child subject. Outcomes should be meaningful and measurable, with adequate control or normative data for comparison and there should be appropriate power analysis to ensure enrollment of an adequate number of subjects to answer the research question and strategies for dealing with potential problems with recruitment and retention.
2. Be directed by investigators who operate in a state of scientific uncertainty; that is, the investigators should have true uncertainty about which of the treatments being compared in the research study is superior.
3. Include a robust plan to monitor safety during the study.
4. Take into consideration the unique physiology, anatomy, psychology, pharmacology, social situation, and special needs of children and their families.
5. Minimize risk while maximizing benefit.
6. Take into account the racial, ethnic, gender, and socioeconomic characteristics of children and their parents and, when appropriate, include input from the community or appropriate advocacy representatives.
7. Conform to all local, regional, and national regulatory guidelines and laws.

Timing of Pediatric Studies

The timing of the initiation of pediatric studies should be governed by a risk/benefit analysis that incorporates all relevant information on the drug under study as well as considerations related to the disease that is targeted for treatment and the availability of alternative therapies. Because the large majority of compounds that enter phase 1 trials in adults never receive regulatory approval because of safety concerns and/or inadequate proof of efficacy, the risk/benefit ratio is high at that stage of development (Table 1). In general, drugs should be tested for safety, pharmacokinetics, and at least initial indications of efficacy in adults before being tested in children. It may often be appropriate to defer pediatric testing until adult testing has reached phase 3 or beyond, when substantial data are available on the safety and efficacy of a drug in adults.

The severity of a disease and the availability of alternative therapies may influence the risk/benefit analysis and, thereby, support the earlier initiation of pediatric studies. For example, for a disease that is severe or life-threatening in children and for which no alternative, proven therapy exists, it may be reasonable to initiate pediatric studies relatively early. Similarly, it may be appropriate to initiate pediatric studies relatively early for children with severe or life-threatening disease for whom all accepted therapies have failed.

When a pediatric disease has no close analogy in adults, as may be the case for some genetic/metabolic conditions that typically result in death before

TABLE 1 FDA Definitions of Phase 1, 2, and 3 Studies

Phase 1 clinical studies
Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies.
Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. These studies also determine which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects included in Phase 1 studies varies with the drug but is generally in the range of 20 to 80.
In Phase 1 studies, the Center for Drug Evaluation and Research (CDER) can impose a clinical hold (ie, prohibit the study from proceeding or stop a trial that has started) for reasons of safety or because of a sponsor's failure to accurately disclose the risk of study to investigators. Although the CDER routinely provides advice in such cases, investigators may choose to ignore any advice regarding the design of Phase 1 studies in areas other than patient safety.
Phase 2 clinical studies
Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.
Phase 3 clinical studies
Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase 2, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people.

www.fda.gov/Drugs/Development/ApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm176522.htm.

adulthood, it may not be possible to obtain adult efficacy data before the initiation of pediatric testing. However, the possibility of adult testing in analogous, if not identical, patients, such as heterozygote carriers of a metabolic disorder, should be considered. Even when there is no analogous adult condition, it may still be reasonable to obtain initial safety data in adults before the initiation of any pediatric testing.

Registering and Reporting the Results of Clinical Trials in Children

It is unethical to unnecessarily repeat clinical drug trials in children. Therefore, all clinical trials should be registered before initiation (www.clinicaltrials.gov), and any results (including negative findings) should be published or otherwise made available to all researchers and the public.

THE INVESTIGATOR

The investigator's competence and ethical conduct are the most important safeguards for the protection of the child as a research subject. The investigator must:

- have the qualifications and expertise to carry out the study to completion;
- understand the developmental and ethical issues involved in research with children;
- have scientific uncertainty with regard to the research question being asked;
- understand the pathophysiologic features of pediatric illnesses and how they evolve with age;
- understand the adverse effects of drugs, drug interactions, and pediatric drug formulations;
- strive to prevent bias from affecting the design, conduct, or reporting of the results of the research study;
- ensure adequate disclosure of all conflicts of interest (COI) related to the research to the subjects and their families;
- be an effective communicator and present a balanced view of the risks and benefits of the research when seeking participation in the study;
- vigorously guard against scientific misconduct; and
- maintain complete records and comply with all regulatory, legal, and ethical standards for research in children.

If the investigator is a junior investigator, there should be evidence of appropriate mentorship and oversight by a more senior investigator or oversight committee.

INSTITUTIONAL REVIEW BOARDS

The primary responsibility of the institutional review board (IRB) is to protect the rights of the research subject. This responsibility includes interpreting the federal guidelines and determining whether each study is designed ethically in compliance with the federal regulations, local and state law, and local IRB directives. Any individual or institution under whose auspices clinical research is conducted must ensure that the research protocol is reviewed by an appropriately constituted IRB. The specific regulatory criteria for IRB approval of research are listed in Table 2.

All IRBs that review proposals for investigations in children must include members with pediatric expertise who are knowledgeable about the special medi-

TABLE 2 Criteria for IRB Approval of Research

1. Risks to subjects are minimized. Are procedures consistent with sound research design used? Do procedures not unnecessarily expose subjects to risk? Whenever possible, are procedures already being performed for diagnostic or treatment purposes? Note: consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that participants would receive even if not participating in the research).
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and to the importance of the knowledge that may reasonably be expected to result. Consider only those risks and benefits that may result from the research and not possible long-range effects of the knowledge gained.
3. Selection of subjects is equitable. Consider the purposes and setting of the research, paying special attention to any vulnerable populations.
4. Informed consent will be prospectively obtained and documented (unless the IRB approves a waiver of this requirement).
5. Adequate provisions exist to monitor the data and ensure subject safety.
6, Adequate provisions exist to protect the privacy of subjects and maintain confidentiality of data.
7. The influence of payments on equitable selection and amount, method, and timing of compensation is not coercive or do not present undue influence to potential subjects. Also, consider whether completion bonuses are reasonable and do not unduly induce subjects to remain in the study when they otherwise would withdraw.
8. If some or all subjects are likely to be vulnerable to coercion or undue influence, additional safeguards exist to protect their rights and welfare.

cal, psychological, ethical, and social needs of child research subjects.[10] Members of the IRB are assumed to be reasonable individuals who act in the best interest of the prospective subjects.

The IRB should establish a mechanism to ensure that no child is enrolled in more studies than is consistent with his or her welfare. There may be reasons to enroll the same child in more than 1 study simultaneously. In most instances, this does not jeopardize the child's welfare or safety, but in some situations, the child's participation in more than 1 study may be detrimental to the child or may confound the scientific validity of the studies.

ETHICAL ISSUES OF PARTICULAR CONCERN IN DRUG INVESTIGATIONS IN PEDIATRIC POPULATIONS

Determination of Benefits and Risks

Federal law (Title 45, Protection of Human Subjects [21 CFR 50, Subpart D]) requires that IRBs review clinical investigations that involve children and approve only those that satisfy 1 of the following conditions[1]: clinical investigations involving no greater-than-minimal risk[7]; clinical investigations involving greater-than-minimal risk but presenting the prospect of direct benefit to clinical subjects[8]; or clinical investigations involving greater-than-minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subjects' disorder or condition.[7,8] If the proposed research does not satisfy 1 of these 3 conditions, there is a fourth condition of child research that includes research that is not otherwise approvable but presents opportunities to understand, prevent, or alleviate a serious problem that affects the health or welfare of children. Research that falls into this fourth category requires review and approval by the FDA and/or US Department of Health and Human Services (DHHS).[7,8]

The categories for approving research in children are presented in more detail in Table 3. Regulations stratify the levels of research risk for children into minimal and a minor increase over minimal. These risks include the known and predictable risks of the drug being studied as determined from previous animal and human studies in addition to the inherent risks of the research procedures themselves. In addition, there is always the risk of a heretofore unrecognized complication or adverse event from any drug being studied. Thus, all drug-study protocols in children must be scrutinized carefully for all potential risks, including those that are not necessarily a concern in adult studies. These risks include discomfort; inconvenience; fear; pain; separation from parents, family, or friends; effects on growth and development; and size and volume of biological samples being collected. The type and number of invasive tests must be minimized and scientifically sound, and creative methods to obtain needed information noninvasively must be sought.

With the growing number of pediatric drug studies, IRBs need to be familiar with the various research-design methods that minimize risk to the child. Examples include limiting research under some circumstances to pharmacokinetic and safety data, combining this approach with pharmacodynamic data, and minimizing the volume of blood withdrawn through the use of sensitive assays, pediatric-enabled laboratories, and population pharmacokinetic approaches.[11] The minimization of risk in pediatric studies also includes the requirement that those conducting the study be properly trained and experienced in studying the pediatric population, including in the evaluation and management of potential pediatric adverse events.[12] Minimizing risk requires careful design of pediatric studies. Every attempt should be made to minimize the number of subjects and procedures, consistent with good study design. Data-monitoring mechanisms should be in place for all drug studies in children to ensure that a study can be rapidly terminated should an unexpected hazard be identified.[10]

TABLE 3 Categories of Research

Category 1: Research not involving greater-than-minimal risk to children
- To approve this category of research, the IRB must make the following determinations:
  - the research presents no greater-than-minimal risk to the children; and
  - adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians

Category 2: Research involving greater-than-minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research
- To approve research in this category, the IRB must make the following determinations:
  - the risk is justified by the anticipated benefits to the subjects;
  - the relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches; and
  - adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians

Category 3: Research involving greater-than-minimal risk and no prospect of direct benefit to the individual child subjects involved in the research but likely to yield generalizable knowledge about the subject's disorder or condition
- To approve research in this category, the IRB must make the following determinations:
  - the risk of the research represents a minor increase over minimal risk;
  - the intervention or procedure presents experiences to the child subjects that are reasonably commensurate with those inherent in their actual, or expected, medical, dental, psychological, social, or educational situations;
  - the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the disorder or condition; and
  - adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians

Category 4: Research that requires a special level of DHHS or FDA review beyond that provided by the IRB
- Research that the IRB believes does not meet the conditions of the above-listed categories but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem that affects the health or welfare of children
- If the IRB believes that the research does not meet the requirements of the categories listed above but finds that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem that affects the health or welfare of children, it may refer the protocol to DHHS or FDA for review; the research may proceed only if, after consulting with a panel of experts in pertinent disciplines (eg, science, medicine, education, ethics, law) and after an opportunity for public review and comment, it is determined that either (1) the research, in fact, satisfies the conditions of category 1, 2, or 3 or (2) the following:
  - the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem that affects the health or welfare of children;
  - the research will be conducted in accordance with sound ethical principles; and
  - adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians

Data- and Safety-Monitoring Committees

Because children are a potentially fragile population, they deserve the highest standards for monitoring safety during a drug study. It is not possible to foresee all risks related to a drug study in children, and unexpected events can and do occur. Therefore, an independent data- and safety-monitoring committee (DSMC) should be created for all phase 3 drug trials conducted in children. A DSMC may also be necessary for some phase 1 and 2 trials as well, especially those that include blinding. In phase 1 and 2 studies without a DSMC, a robust data-monitoring plan must be in place.

Informed Permission/Consent/Assent

No drug research may be performed in humans without the informed permission/consent/assent of the subject and an individual who is legally qualified to act on behalf of the subject unless the need for permission/consent/assent is waived by the IRB. DHHS and FDA regulations are similar in their definition of parental permission. Subpart D of both regulations define permission as the agreement of parent(s) or guardian(s) to participation of their child or ward in research (DHHS) or a clinical investigation (FDA). A parent is defined as a child's biological or adoptive parent, and a guardian is defined as an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care. For a child to participate in a clinical study, parents or guardians must agree to (ie, permit) their child's participation in research.[11]

Permission Process

Parental permission is treated much the same as informed consent for adults, with the exception of some additional requirements.[7,8] All the general and required elements for adult consent apply to parental permission. Information provided to the subjects and/or parents must be written in language that is easily understood by the consenter, permission giver, and assenter. If the document is not written in an easily understood language, the information must be provided in a language that is understood, or an interpreter must be provided. The IRB must approve the procedure by which the prospective consenter, permission giver, or assenter is informed. Table 4 provides an outline of required content for written consent. In addition to obtaining permission from a parent or guardian, IRBs are required to determine that adequate provisions have been made for soliciting the assent of the child.[10] The requirement for permission is based on the premise of protecting a population whose mem-

TABLE 4 Required Contents of Written Consent Specified in DHHS Regulations

I. Basic elements of informed consent
- A. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- B. A description of any reasonably foreseeable risks or discomforts to the subject
- C. A description of any benefits to the subject or to others that may reasonably be expected from the research
- D. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
- E. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records
- F. For research involving more-than-minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, of what they consist or where further information may be obtained
- G. An explanation of whom to contact for answers to pertinent questions about the research and the rights of the research subjects and whom to contact in the event of a research-related injury to the subject
- H. A statement that participation is voluntary, that refusal to participate involves no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

II. Additional elements of informed consent: when appropriate, 1 or more of the following elements of information shall also be provided to each subject
- A. A statement that the particular treatment or procedure may involve risks to the subject (or the embryo or fetus, if the subject is pregnant or may become pregnant) that are currently unforeseeable
- B. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
- C. Any costs to the subject that may result from participation in the research
- D. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- E. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
- F. The approximate number of subjects involved in the study

bers may not be capable of protecting themselves. Research that involves children that falls in categories 3 and 4 as described in Table 3 requires permission of both parents.[7,8] The regulations allow an exception to this requirement if 1 parent is deceased, unknown, incompetent, or not reasonably available or when only 1 parent has legal responsibility for the care and custody of the child.

Waiver of Permission

There are 2 situations in which parental permission may be modified or waived entirely under the federal regulations that do not involve an FDA-regulated product. The first waiver is for research that involves only minimal risk, does not negatively affect the welfare of the subjects, and cannot be practically performed without the waiver. The second waiver is applicable when getting permission will not function to protect the child. If a determination is made by the IRB 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 (eg, neglected or abused children), it may waive the consent requirements. This situation is conditional, provided an appropriate mechanism for protecting the children who will participate is substituted, and the waiver is not inconsistent with federal, state, or local law. FDA regulations did not adopt this second waiver. The only waiver of parental permission that the FDA considers is for emergent and life-threatening situations (discussed in the next paragraph, "Emergency Research").[11]

Emergency Research

Federal regulations allow the conduct of research studies to test emergency treatments on patients with specific life-threatening medical conditions when patients cannot give informed consent because of their conditions and their family is not available to provide consent. Emergency research studies approved under this regulation must hold out the prospect of direct benefit to the subject. The exception for obtaining informed consent applies to emergency research that (1) involves human subjects who have life-threatening medical conditions for which available treatments are unproven or unsatisfactory, (2) involves subjects who, because of their conditions (eg, unconsciousness), cannot give informed consent, and (3) to be effective, must be initiated before consent can be obtained from the subject's legally authorized representative. An investigational new drug (IND) application or investigational device exemption (IDE) is required. Studies that involve an exception from the informed-consent requirements may proceed only after a sponsor has received previous written authorization from the FDA and the IRB has found and documented that the specific conditions have been met. Additional requirements for emergency research studies include developing and implementing a plan for community consultation and public disclosure before the start of the study and a mechanism for contacting and providing information to the subject's legally authorized representative or family member within the therapeutic window or at the earliest feasible opportunity. If subjects are

enrolled before consent is obtained, there must be an opportunity for family members to object to a subject's continued participation in the study.

Permission for Studies With Life-Threatening Illness

The study team and IRB need to carefully evaluate studies that require parents to make decisions when their child has a life-threatening illness. This situation creates dilemmas for parents when they are required to make emotionally charged decisions related to their child's health. It is important for the study team to acknowledge the parents' emotional state, lack of medical knowledge, and inexperience with clinical trials. During the initial consent process and throughout the study, clinical research staff who obtain consent from parents should educate them about their child's disease and how clinical trials work. They should clearly explain all potential risks and not overstate potential benefits. They should also outline in detail any potential financial costs that may be associated with the study.

Assent of the Child

Age of Assent

According to federal regulations, assent is defined as a child's affirmative agreement to participate in research, and further clarification is given that "mere failure to object should not, absent affirmative agreement, be construed as assent."[8] Federal regulations do not specify an age at which assent ought to be possible. The AAP recommends that active agreement by a minor (not qualified to give consent) to participate in a research study generally applies to children who have reached an intellectual age of at least 7 years. More recently, it was suggested that assent is generally applicable to developmentally normal children between 8 and 14 years of age.[12] It is up to the IRB to determine if children are capable of assent. Regulations state that adequate provisions are needed for soliciting assent when the child is capable, but little guidance exists to determine this capacity other than evaluating the child's age, maturity, and psychological state; as a practical matter, many IRBs require assent for children older than 7 years. The IRB can waive the requirement for child assent if the capability of some or all of the children is so limited that they cannot reasonably be consulted, if the intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research, or if the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults.[11] For example, this waiver could be used in research with infants, children with illnesses that require mechanical ventilation, or children with severe developmental delay.

Delivery of Assent

The assent process for children requires ongoing discussion and evaluation throughout the trial. In situations in which children either do not give initial assent or withdraw assent for participation, researchers should not ignore a child's wishes.[13] If the IRB has determined that assent is required for a study and the child dissents from participating in research, the child's decision prevails even if his or her parents or guardian have granted permission.

The Consenting Minor

Generally, adolescents are considered to be between 12 and 18 years of age (dependent on region).[10] When obtaining assent from older adolescents, it is reasonable to assume that an adequate assent process would be viewed the same as the informed-consent process for adults, although parental permission is still required. The legal definition of adolescents groups them with children. Federal regulations define children as persons who have not attained the legal age for consent to treatments or procedures under the applicable law of jurisdiction in which the research will be conducted.[8] Under this definition, not all adolescents who are under the legal age of majority are defined as children. In common practice, the applicable law of the jurisdiction is state law, but it could include federal statutes. Childhood is not defined by age but by local laws that govern medical treatment, age of majority, and emancipation status.

Emancipated and Mature Minors

Because there is precedent that allows emancipated minors, and in some cases mature minors, to consent to clinical research, it is important that this group of youth be defined. Emancipation is governed by individual state law. Typical conditions that states use to establish the status of an emancipated minor are marriage, military service, parenthood, runaways who refuse to identify themselves, or court order. Therefore, for purposes of pediatric clinical research, emancipation, whatever the causal event, is taken to mean that the child becomes an adult in the eyes of the state; that is, all rules that govern parental custody or control are severed, which could include parental permission for research participation, to the extent that states follow a broader range of emancipation effects.[14] Investigators and IRBs considering recruitment of adolescents into research studies can obtain consent from only those adolescents considered adults, for all purposes under state law, as emancipated minors. Emancipated minors may give permission for their children. In research that involves an emancipated minor or a mature minor, the investigator and the

local IRB must be careful to protect the welfare of the minor subject. In cases in which minors are legally authorized to provide independent consent for particular treatments, parental permission is not required.

An emancipated minor is effectively an adult in the eyes of the law and is, therefore, capable of partaking in any medical research that would otherwise include adults. The capacity of the mature (but not emancipated) minor to partake in medical research depends on individual state laws, the type of research, and the risk/benefit ratio. The risk should be minimal, and answers to the scientific questions being asked must not be obtainable by using another group of adolescents whose parental permission and involvement are required. The research must be aimed at preventing or treating the medical condition for which the adolescent can legally give consent. For example, a researcher may investigate drug compliance in mature minors being treated for sexually transmitted diseases. Whether there are ethical reasons not to allow such research to proceed with adolescent consent would need to be addressed on a case-by-case basis. The investigator should determine if the parents can be informed by asking the minor's permission to involve the parents.

Withdrawal of Consent

The parent, emancipated minor, or mature minor has the right to revoke permission/consent at any time during the study. The child who gave assent also has the right to withdraw assent. If the investigator identifies reluctance in the parents or child about continued participation in a research protocol, the child's continuation in the study should be reevaluated. The same principles that govern permission/assent/consent also govern its withdrawal.

Institutionalized Children

Children who are institutionalized because of special care requirements or under the supervision of a court or social welfare agency acting in lieu of a court should rarely be considered for inclusion in research studies, because institutionalization may deprive them of some of the safeguards necessary for the conduct of ethical investigations. In general, these children should only be involved in studies of special conditions unique to them or to the type of institution in which they reside. They should have access to experimental drug therapy when the research therapy is the only treatment available for the illness that affects them. Access to experimental therapy may be allowed under a compassionate use protocol.

SPECIFIC ASPECTS OF PROTOCOL DESIGN

Advocate Group

Extra measures to protect the rights of special populations, such as institutionalized children or children with chronic progressive or lethal diseases, may involve special advocacy groups. Such groups may include parents of children in the institution at which the study is being conducted, health care professionals, lawyers, clergy, and other community representatives as appropriate. An advocacy group may assist in the overall design of the study as it relates to the rights, clinical condition, and needs of the targeted special population. Such a group could also facilitate communication with the subjects and their parents to help ensure that they understand the more complex or difficult aspects of the study, such as the implications of a randomized, controlled trial. The advocacy groups, however, must not act as a coercive influence on the subject or parents.

Distributive Justice

Insofar as possible, subjects enrolled in clinical investigations should represent a cross-section of society. A study should not rely exclusively or disproportionately on any socioeconomic, racial, gender, or ethnic group unless this type of selection is a necessary part of the investigation, such as in a study of sickle cell anemia. The distribution of risks, inconveniences, and benefits from research studies must be equitable throughout societal groups. This equity is important from both an ethical and scientific standpoint, because data obtained from 1 ethnic or socioeconomic group may not be applicable to other populations.

Recruitment

Payment of Providers

Recruitment of subjects to participate in a clinical research protocol often is vital to the successful completion of a study and involves identifying potential research subjects. Potential research subjects frequently are identified and recruited by health care workers who are providing their care. However, providing staff members or hospital personnel with a direct financial incentive for enrolling a research subject has the potential to add a strong element of undue influence or coercion to the recruitment and consent process. Therefore, a monetary "finder's fee" or other financial incentive for recruiting or referring children to clinical investigations should be prohibited.

Advertisements

Advertising for volunteers to enroll in a study may be necessary for recruitment. The content of an advertisement as well as the proposed distribution of the advertisement should be reviewed by the IRB before its dissemination. Advertisements should not explicitly or implicitly misconstrue the risks and benefits from participation in a study.

Payment for Participation of Children in Research

Compensation for participation in research is a common practice for research studies that involve both children and adults. A number of different types of compensation are used in clinical studies, including material or monetary compensation such as reimbursement for travel, parking, food expenses, overnight lodging, telephone calls, child care that a family might incur because of research participation, or inconvenience. IRBs are required to review proposals to pay research subjects with minimal guidance from federal regulations, which do not specifically address the issue of payment to research subjects. The amount paid to study subjects varies tremendously from site to site, even for the same multisite studies. It also varies from study to study, even at the same institution for similar tasks.[15]

Offering payment in studies that enroll children requires parents, investigators, and IRBs to weigh the importance of several competing values.[16] Incentive payments may be essential to the recruitment and retention of pediatric study subjects. In addition, prohibiting payments might jeopardize some important research. Finally, the obligation to treat all patients fairly might include compensating them for their time, effort, and discomfort and for their contribution to the social good. These objectives are all important and need to be balanced between the need to protect children from the potential harms of clinical research and to ensure that parents remain free from influences that might tempt them to enroll a child in a research protocol that is not consistent with the best interests of the child.[14,17] Payments to parents for their child's research participation could potentially sway parents to decide in favor of participation, because there is no personal risk to them.[18] This problem can be mitigated by keeping payments reasonable and minimal.[15] The investigators and the IRB must be certain that the compensation offered is fair and does not become an undue inducement for participation of the child subject.

When untoward medical events occur as a result of participating in a study, the institution and its investigators are obligated to provide emergency care. The extent to which emergency care and subsequent medical care will or will not be provided free of charge must be clearly stated in the consent form.

COI and Disclosure

Given the current efforts to increase the number of children in clinical research studies, it is critical that research be conducted ethically so that the outcomes provide adequate labeling of new medicines for children and that evidenced-based medicine will not be overshadowed by COI. The Office of Research Integrity (ORI) has provided a simple definition of COI: a situation in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity.[19] These considerations include relationships with pharmaceutical companies or other entities that have an interest in the product (drug or device) under investigation.

Institutions that perform drug research in children should consider the appointment of COI committees that are independent of IRBs. These committees can require that clinical studies be reviewed for conflicts before submission to the IRB. COI committees govern a variety of activities at universities, including research. They are charged with reviewing conflicts in clinical studies and, if a conflict is present, determine how that conflict can be managed, reduced, or eliminated. Options include public disclosure of significant financial interests, independent monitoring of research, modification of the research plan, blinding of data or those who analyze the data, monitoring of the research by independent reviewers, conduct of all or part of the research by another nonconflicted member of the research team or by a third party, divestiture of financial interests that present COI, or severance of relationships that present COI.

Until recently, there has been little guidance available on how to appropriately disclose COI. The Conflict of Interest Notification Study (COINS), funded by the National Heart, Lung, and Blood Institute, was initiated to provide data to IRBs, COI committees, and other policy makers to assist them in deciding how, when, and what to disclose to potential research subjects. The study group developed disclosure language concerning different financial interests commonly found in clinical research.[20] The generic disclosure language states: "The person leading this medical research study might benefit financially from this study. The Institutional Review Board and a committee at ABC University have reviewed the possibility of a financial benefit. They believe that the possible financial benefit to the person leading the research is not likely to affect your safety and/or scientific quality of the study. If you would like more information, please ask the researchers or the study coordinator."

The new model language also includes specific language for situations in which there may be risks to the study subjects. The Conflict of Interest Notification Study team categorized this additional language by the 9 types of financial interests that are most commonly encountered in the clinical research setting: salary support; money received outside of the study; payment for each subject enrolled;

finder's fees restricted to research uses; unrestricted finders' fees; researchers holding a patent; university holding a patent; researchers owning equity; and university owning equity. Contractual agreements between sponsors and investigators should ensure that reports and publications of research results accurately and objectively represent the results and will not be constrained by any proprietary interests of the sponsor.

Placebo and Control Groups

Placebo and control groups can be used in pediatric studies if their use does not place children at increased risk. The conditions under which placebos may be ethically used in drug research in children include the following:

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

Long-term Prospective Studies of the Safety of a Drug

When investigational drugs are administered to children, the effects may be latent and may not be predicted from any previous studies. This concern is not unique to children; it also applies to studies of investigational drugs in adults. Thus, studies of certain drugs given to pediatric patients may require a mechanism for follow-up of the research subjects.

CONCLUSIONS

This report is intended to provide a format that allows for the participation and protection of child subjects in drug research. Research that involves children carries with it additional responsibilities for the investigator, IRB, and sponsor. The additional responsibilities should not be reasons for the pharmaceutical company or other sponsor, IRB, or the investigator to exclude children from drug research and its potential benefits.

The AAP believes it is unethical to deny children appropriate access to existing and new therapeutic agents. It is the combined responsibility of the pediatric community, pharmaceutical industry, and regulatory agencies to design, approve, and conduct high-quality studies in children. It is the responsibility of the general public to support the necessary research to ensure that all children have access to important medication and receive optimal therapy.

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