Pediatric Informed Consent
Challenges for Investigators

M. Renee Simar and Virginia A. Johnson

Being certain that your pediatric trial subjects and their parents are making informed decisions requires a unique consent process.

Ethical standards for patient informed consent appeared on the horizon of medical research more than half a century ago following the Nuremberg trials. More recently, expectations have evolved regarding consent issues in research with children. Children are counted as members of a vulnerable population at risk for exploitation and are afforded special protection in clinical research. Soliciting a child’s willingness to volunteer is recognized as ethically appropriate and essential to the overall success of pediatric clinical trials. In pediatric trials, just as in adult trials, materials in an understandable language, opportunities to discuss the trial, and freedom to withdraw without penalty must be provided to potential subjects.

A myriad of guidance documents from governments and professional organizations have generally agreed that consent in pediatric research involves a “consent dyad”—informed permission from parents and assent from children. Distinguishing characteristics of the dyad compared with adult informed consent are shown in Table 1. Complexities surrounding the regulations on pediatric consent often present uncertainties to entities charged with compliance. Differences in interpretation may lead to delays in studies as regulators and researchers negotiate agreements, while subject rights regarding informed participation may be compromised.

Investigators are ultimately held responsible for ensuring adequate informed consent. More than two decades of inquiry into the process of consent have shown that adults are less than adequately informed about risks, benefits and participation in research.1–4 The process is even more problematic for research involving individuals with limited abilities in decision-making. The evolving psychological and emotional development of children and adolescents presents challenges to pediatric investigators not encountered when dealing with adult subjects.

Developing consent forms for school-age children versus adolescents, respecting differences in attitudes on parenting, and evaluating capacity to understand by parent and child are a few of the unique intricacies associated with the pediatric consent process.5 Attempts to achieve the objectives for informed consent may be well intentioned, but empirical evidence is lacking on the means to ensure success in comply-
ing with ethical standards. Moreover, strict adherence to pre-
cepts for the consent process does not guarantee comprehen-
sion. Especially lacking are data on tools to evaluate whether
agreement to participate fully meets the conditions of informed
consent.

This article addresses the consent challenges encountered
by investigators conducting pediatric clinical trials and offers
solutions for ensuring compliance with consent mandates. The
scope is limited to non-institutionalized children and adoles-
cents living with parents or legal guardians. Beginning with an
overview of guidance principles and regulations, we have identi-
fied controversial topics on consent in pediatric research involv-
ing evaluation of pharmaceutical products. Viewpoints on
capacity for understanding, confidentiality, and financial com-
ensation provide a framework for the discussion on practical
solutions for pediatric investigators.

Principles of pediatric consent

Protections for children in research have markedly advanced
since the 18th century when Edward Jenner injected smallpox
into a young boy.6 Although children were once viewed as prop-
erty, international principles now grant them limited autonomy
in decision-making for matters on their own behalf.7 Important
features of autonomy include intentionality (making decisions
based on the goals and values to which the individual is commit-
ted) and voluntariness (decision-making, free of excessive, inap-
propriate external influences) based on an understanding of rel-
vant information.8 Most ethicists and legalists have dismissed
the notion of proxy consent in which adults process medical infor-
mation and provide willingness to consent on behalf of their chil-
dren. Consent cannot be given for another person, leading to the
current approach of informed permission and assent in both pedi-
atriatric clinical practice and medical research.9 In most cases, par-
ents undergo a consent process, and then may grant informed
permission for their child to participate. In parallel, a willingness
to participate, or assent, is solicited from children following an
age-appropriate information process. Assent supports the tenet
of subject respect described in the Declaration of Helsinki10 and
the Belmont Report,11 under which a person should be treated
as an autonomous being and given the right to agree or not

### Table 1: Adult and pediatric consent compared

<table>
<thead>
<tr>
<th>Adult informed consent</th>
<th>Informed permission</th>
<th>Pediatric consent dyad</th>
<th>Assent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Parental agreement for one’s child to participate in research</td>
<td>Child’s affirmative agreement to participate in research</td>
<td></td>
</tr>
<tr>
<td><strong>Assumptions</strong></td>
<td>Capable of full understanding—processing information and agreeing to participate</td>
<td>Capable of limited understanding according to developmental age—processing some of the information and agreeing to participate</td>
<td></td>
</tr>
<tr>
<td>Subject is at least 18 years old or an emancipated minor</td>
<td>Parent is at least 18 years old or an emancipated minor</td>
<td>Subject is at least 7 years old</td>
<td></td>
</tr>
<tr>
<td><strong>Process</strong></td>
<td>Ongoing, interactive discussions between researcher and adult volunteer</td>
<td>Ongoing, interactive discussions between researchers, parent, and pediatric volunteer</td>
<td>Ongoing, interactive discussions between researchers and pediatric volunteer</td>
</tr>
<tr>
<td>Materials provided in a language understandable by the subject</td>
<td>Materials provided in a language understandable by the parent</td>
<td>Materials are age- and developmentally appropriate and in a language understandable by the subject. The form is of a simple format and short length.</td>
<td></td>
</tr>
<tr>
<td><strong>Documentation</strong></td>
<td>Witnessed signature on a consent form</td>
<td>Witnessed signature on an informed permission (consent) form</td>
<td>Witnessed signature on an assent form</td>
</tr>
</tbody>
</table>

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"The term is often used interchangeably with “parental consent.”

Parent or legal guardian. Local ethics board determines whether one or two parents’ signatures will be required.

Age varies by local standards.

Assent from children as young as 5 may be required by some ethics boards.

In place of the assent form, ethics boards may allow use of the parental consent form for adolescents."
agree to participate. These precepts emphasize that special protection be provided to groups with limited autonomy, generally referred to as “vulnerable” populations. Application of these principles to pediatric consent is guided by undertakings over the last two decades to ensure special protections for children and other vulnerable research subjects.

Standards on participation by pediatric subjects address general protections, as well as specifics on the consent dyad. Details are set forth in the U.S. Common Rule, a regulation on human research protection involving most federal agencies supported by public funds. Subpart D of the Common Rule links the requirement for consent and assent to the degree of risk involved in the research. Controversy surrounds assignment of risk, due to the contextual experience of risk for each child. However, the Rule permits studies involving minimal risk in children, with the provision that permission from parents and assent from subjects are obtained. Research involving greater than minimal risk, but providing potential direct benefit to the child, is also permitted with the same provision. Exceptions to the requirement for assent and consent are also given (Figures 1 and 2). Assent is not necessary for research expected to directly benefit the child. Parental consent may be waived if the research is not a reasonable requirement to protect the child, as in cases of child abuse or neglect. The interim rule released in 2001 by the Food and Drug Administration (FDA) supports the Common Rule: Subpart D, except for the parental consent waiver. This distinction has given rise to public comment on the interim rule regarding the likelihood of constraints on certain types of research in adolescents (see the discussion of confidentiality that follows).

Increasing support on rights associated with the consent dyad is evident in statements from other regions and global organizations (Table 2). The International Conference on Har-

**Figure 1.** Algorithm for pediatric assent: U.S. regulations. (CFR 45, Part 46, Sections 404–408)

**Figure 2.** Algorithm for parental permission: U.S. regulations. (CFR 45, Part 46, Sections 404–408)
and individually. Psychological and psychosocial development contributes to a young person’s understanding and choice to participate in health-care research.21 The ability to process information on research begins with concrete approaches in early years, relies on increasing life experience as the child matures through preadolescence, and eventually involves abstract thinking and hypothetical evaluations.22 Children who are chronically ill may understand less (or more) than healthier children.23 Unless opposing evidence is identified, capacity to understand and provide informed consent has long been assumed in adults. The assumption has not been applied to children,21 but results from studies in healthy and sick children suggest that they do, in fact, have this capacity. Several investigators have evaluated the degree to which minors from school age through adolescence are capable of providing assent. Even very young children demonstrate inquisitiveness about the proposed research,24 and by age nine children can understand purpose, risk, and right to withdraw.25–27 Even children as young as seven years can understand purpose,28 supporting the requirement by most ethics boards that assent be obtained in children by age seven. On the other hand, comprehension on abstract information regarding scientific versus therapeutic purpose for the research and alternative treatment was not well understood in a hospitalized group of 7- to 20-year-old subjects.29 Overall, these findings suggest that pediatric subjects can provide an informed agreement to participate, although individual differences should be considered. Implicit to the findings is that the assent process should be conducted using discussions that encourage questions, along with a comprehensible assent form and other materials to enhance understanding.

The corollary to the assent process is informed permission required of parents or legal guardians. Information is provided and parental permission is given prior to conducting any study procedures in the child. As for adult trials, it is presumed that the parent has the capacity to understand, although surveys have shown that parental understanding of research purpose and risk for their children may be inadequate.30 Much attention has been given to the research vulnerability of children, yet parents share this vulnerability because they are making a decision under stressful conditions. Emotional complexity enters the process when parents must decide on entering their child into a research protocol while coping with critically sick offspring.31 Clinical urgency to initiate research treatment may preclude adequate consent.32 Not only does stress have an effect on choice, but also parents may rely on their relationship with health-care providers for decision-making. Influenced by trust in the medical system and allegiance to physicians, parents may give permission without fully considering protocol expectations. At least one study has shown that a significant proportion of parents with children enrolled in a trial for asthma medication were unaware of the right to withdraw consent.33 Investigators must encourage equal awareness by parents and children regarding the proposed research.

### Authoritative relationships

A salient feature of obtaining assent in pediatric clinical trials is the influence of individuals with authority, including parents, teachers, counselors, and health-care providers. The degree of self-actualization and independence often is a reflection of the parent-child relationship. A child with minimal autonomy displays deference to parents for

### Table 2  Sample guidance documents that refer to pediatric research

<table>
<thead>
<tr>
<th>Guidance title</th>
<th>Year</th>
<th>Scope or origin</th>
<th>Are specifics included on the pediatric consent dyad?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH E6: Good Clinical Practice</td>
<td>1997</td>
<td>International</td>
<td>No</td>
</tr>
<tr>
<td>ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population</td>
<td>1999</td>
<td>International</td>
<td>Yes</td>
</tr>
<tr>
<td>WMA: Declaration of Helsinki</td>
<td>2000</td>
<td>International</td>
<td>Yes</td>
</tr>
<tr>
<td>WHO: CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (draft)</td>
<td>2002</td>
<td>International</td>
<td>Yes</td>
</tr>
<tr>
<td>EMEA: CPMP: Note for Guidance on Clinical Investigation of Medicinal Products in Children</td>
<td>1997</td>
<td>Europe</td>
<td>Yes</td>
</tr>
<tr>
<td>EP: Directive on Good Clinical Practice 2001/20/EC</td>
<td>2001</td>
<td>Europe</td>
<td>Yes</td>
</tr>
<tr>
<td>Report of the Working Party on Registration of Drugs in Children</td>
<td>1997</td>
<td>Australia</td>
<td>Yes</td>
</tr>
<tr>
<td>Bulgarian Medicines Act: Law of Medicinal Products and Pharmacies in Human Medicine</td>
<td>1995</td>
<td>Bulgaria</td>
<td>Yes</td>
</tr>
<tr>
<td>Therapeutic Products Directorate Guidelines: Inclusion of Pediatric Subjects in Clinical Trials (draft)</td>
<td>1997</td>
<td>Canada</td>
<td>Yes</td>
</tr>
<tr>
<td>Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans</td>
<td>1999</td>
<td>Canada</td>
<td>Yes</td>
</tr>
<tr>
<td>National Commission: Research Involving Children</td>
<td>1977</td>
<td>US</td>
<td>Yes</td>
</tr>
<tr>
<td>45 CFR 46: Additional Protections for Children Involved as Subjects in Research</td>
<td>1991</td>
<td>US</td>
<td>Yes</td>
</tr>
</tbody>
</table>
important decisions. Parental attitudes toward research have been shown to influence children’s willingness to participate in medical research, suggesting that investigators need to be attuned to family dynamics. Promoting informative discussions without parental coercion can be achieved by careful observation and guided conversations.

The child–physician bond is the other key relationship likely to influence a child’s willingness to participate. Physicians assuming the role of investigator in adult trials are challenged with objective presentation of the protocol. The inherent responsibility for a neutral discussion with an adult patient becomes increasingly arduous with children, particularly when the child is markedly ill or has a long-standing relationship with the physician. Well-intentioned persons with authority over children often purposely influence juvenile choices to safeguard them. A moral dilemma arises when the authority figure is obliged to solicit and facilitate an autonomous decision on a clinical trial. Just as their parents place their trust in health-care providers, children may simply rely on the physician’s recommendation about the trial. However, the investigator is obligated to present the protocol without swaying the child’s choice—a notion unlike typical expectations for guiding children.

Involvement of a neutral person may minimize authoritarian influence on consent. The approach involves removing the physician-investigator from the consent process and enlisting another individual independent from the child’s medical care. For example, a partner in a pediatric practice, other than the investigator, could conduct the process. The individual should be knowledgeable about the therapeutic area and protocol to ensure that information is accurate. The impartiality is likely to enhance consent protections for both the child and parent.

Confidentiality. Research in therapeutic areas for which a minor can obtain medical treatment without parental consent may be difficult for enrolling adolescents (for example, family planning, drug abuse, communicable disease, and mental health). The requirement for involving parents in the decision may encroach on the rights to confidentiality for sensitive health issues. The 1977 U.S. National Commission for the Protections of Human Subjects recommended a parental consent waiver for research areas in which the subject could legally receive treatment without parental consent. The waiver was not adopted in the Common Rule, thereby disallowing subject privacy for adolescents in some cases. The incongruity between allowing access to clinical treatment for sexually transmitted disease without parental awareness while requiring the same parent to consent for medical research has been denounced by a number of experts. The outcome is that adolescents may decline to participate, resulting in a paucity of data for certain conditions. The problem may be surmounted in some research by support of local standards that permit research physicians to maintain privacy on some issues, although full disclosure to parents may be required in other cases.

Uncertainty on allowable privacy is evident from a survey on adolescent research involving more than 150 ethics boards. Results on the requirement for parental consent in a hypothetical research protocol with an experimental AIDS drug in 16-year-olds revealed that only 58% of the ethics boards agreed consent would be necessary. The percentages in favor of regulatory changes to allow minor consent depended on whether the drug was labeled for pediatric use. In support of change were 57% for pediatric and 35% for adult medications. These data, along with opposing public comment on the requirement for parental consent in the interim FDA ruling on subject protection, suggest the need for further evaluation. Notwithstanding disagreement over a sensitive issue, respect for the rights of adolescent research volunteers should be preserved. Soliciting opinions from adolescents and parents, as well as expert consensus, will be key to safeguarding adolescents’ interests in the ongoing development of consent standards.

Few subjects between the ages of 7 and 12 years believed their responses to a psychological survey would be confidential.

Concerns over confidentiality extend to younger children. Few subjects between the ages of 7 and 12 years believed their responses to a psychological survey would be confidential. Fearful that parents may be privy to interviews, children may provide inexact responses, leading to inaccurate data. Trust can be engendered by truthful discussions on confidentiality expectations and constraints. Some commentators believe that confidentiality statements regarding conveyance of information to parents should be cited in consent forms. If the parent and child are promised complete confidentiality, then parents can be advised to discuss sensitive topics directly with the child. Specifics on the terms of confidentiality should be discussed with pediatric subjects of all ages to protect rights on disclosure and promote accurate data collection.

Consent withdrawal. Guidance on assent emphasizes that “mere failure to object” does not equate to voluntary participation by a child. The AAP has stated that refusal to assent (disent) is binding in most cases, especially for non-therapeutic research (for example, pharmacokinetic safety studies). The investigator may be challenged with arbitrating between parents and children when conflicts arise over participation to enter the trial or withdraw once treatment is underway. Awareness of parent-child interactions will enable the investigator to facilitate discussion. Preparing the child for anticipated discomfort and inconvenience during the consent process is often the most effective means for minimizing dissent. Thorough discussions not only uphold the ethics of assent but also contribute to retention by empowering children to view their role as a partner in the research.

Careful consideration should be given to the child or adolescent voicing complaints about participation. Encouraging dialogue about the research may alleviate fears underlying desire to withdraw, but the discussion should be without coercion to remain in the trial. In younger age groups, dissent may be displayed by antagonism toward research procedures. For example, if a child displays distress over blood collection, the investigator is obligated to address the concerns and offer alternatives whenever possible.
The FDA caveat for overriding dissent involves research with
the prospect of direct benefit that is not available through other
medical treatments. Although some might argue that dissent
should always be respected, the limitation is supported by the
ICH, European Parliament, and AAP. The often-cited exam-
ples are cancer treatment, in which the only opportunity for poten-
tially life-saving medications may involve experimental drugs.
The parental choice for participation may outweigh child dis-
sent, but the investigator should continue to acknowledge the
concerns of the pediatric subject with ongoing efforts to obtain
assent during the trial.

Financial compensation. Divergent views regarding payment of
human subjects to participate in medical research exist for all
types of protocols, and pediatric trials are no exception. In
pediatric clinical trials, financial incentives for subjects can
range from reimbursement for travel and meals along with nov-

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medical research exist for all types of protocols, and pediatric trials are
no exception.

eelry items such as a T-shirt or stuffed animal, to more elaborate
incentive programs where, in studies involving multiple visits,
the child may accumulate points or coupons for gifts or toys as
visits are completed, or have use of a laptop computer during the
study, in addition to a monetary payment. Many feel that these
types of incentives are necessary to encourage enrollment and
completion of pediatric clinical trials, especially long-term ones.
On the opposite end of the spectrum, there are both sponsors and
investigators who believe that no incentives should be
offered, especially in trials where subjects are receiving a study
drug for a therapeutic indication at no charge.

The use of financial incentives in the form of monetary pay-
ment and gifts in pediatric trials is complicated by the fact that
both the parent and the child may be the recipient of the finan-
cial incentives. Some investigators feel that it is prudent to reim-
burse parents for time taken away from work in order for their
child to participate in the study. In the presence of substantial
financial remuneration, parents’ ability to assess the risk of the
study and make sound decisions about their child’s participation
may be jeopardized. On the other hand, the child’s desire to
receive money or toys might ultimately have influence in the
decision of a parent to grant permission for the child to partici-
pate in the study. Similarly, these incentives may have a comp-
pelling effect in gaining assent from the child or adolescent to
become involved in the research study. Because the degree of inducement is relative and subjective, care must be exercised to
avoid conditions in which the subject and the parent may be
“unduly influenced.”

According to the FDA, the amount and schedule of payments
to research subjects is part of the ethics board process and
should be presented to the board at the time of initial review.

In this manner, the ethics board serves as a guard against the
presence of undue influence from financial incentives, which are
proposed in the study as payment to the subject. Additional pro-
tection can be afforded by investigators who remain knowledge-
able and aware of incentive issues during the recruitment pro-
cess, in obtaining consent and assent, and throughout the
remainder of the study. In some countries, participation is seen
as an obligation to society and no compensation is expected,
although that does not appear to be an opinion held by many in
the United States.

Practical approaches

Investigators conducting pediatric trials can avoid the obstacles
mentioned above by carefully attending to certain areas in the
design and execution of a study.

Assent and consent process. The process should begin with
informed permission from the parents to shield the child from
unnecessary interviews about their illness if the parent declines.
The process for informed permission should follow consent pro-
cedures for adult trials, such that the investigator describes
the protocol and encourages discussion. Most guidelines require
that permission for the child to participate then be solicited from
the parent. A slightly different interpretation, notable in the EP
Directive 2001/20, states that parents represent the minor’s pre-
sumed will. Regardless of these distinctions, parental agree-
ment is generally required.

Whether the investigator should then discuss the protocol
with the potential subject in the presence or the absence of the
parent has not been addressed in guidance documents. Sup-
porters of complete privacy for adolescents would be inclined to
have independent discussions with the adolescent. Others
might argue about the risk for coercion by the investigator if
assent is solicited without parents. As mentioned previously,
local clinical standards often serve as the framework to guide
investigators. Variations for the process have been identified in
preliminary findings of a survey to 31 pediatric investigators.
When asked whether consent is conducted with both the parent
and pediatric subject, 64% of the investigators responded affir-
matively. Nineteen percent of the investigators indicated that
they interview adolescents separately from parents when dis-
cussing sensitive topics, and the remaining 16% always conduct
interviews separately. Clearly, further discussion is needed to
ensure uniform approaches and appropriate protections.

Investigators are expected to facilitate independent decision-
making by the pediatric subject. The goal can be accomplished
by ongoing discussion. Children and adolescents can be empow-
ered with information relative to age, maturity, and psychologi-
ical state. Attention to the child encourages partnership and
enhances self-worth. Perceptions of being an active contribu-
tor to the research enhance compliance to drug intake and pro-
cedures, the quality of self-reports, and accurate reporting of
adverse effects.

The responsibility for investigators to promote competent
decision-making involves assessment of understanding. Recom-
pendations for using written assessments in adult trials may
be applicable to pediatric trials. Open-ended inquiries during the
oral presentation of the protocol are more likely to ensure
understanding, rather than asking questions with yes/no
answers. For example, subjects and parents can be asked to describe study procedures in their own words. Allow the answer to guide further probing of understanding. Use repetition and simplify complexities of the protocol by defining terminology. Each packet of information should be followed with additional open questions. A child of seven generally grasps more rudimentary concepts than an adolescent, so mindfulness of developmental age should guide an investigator’s efforts to access understanding.

Along with understanding, intentionality is another criterion for consent. The concept implies that the subject reasons about participation based on information applied to personal situations. In other words, voluntary choice should meet with personal goals or beliefs. Some children may volunteer to avoid reprisal or neglect, suggesting that the investigator should be alert to a fearful child who displays undue eagerness to participate. An investigator cannot determine with certainty that the criterion of intentionality is met, but diligence to the objectives of consent are expected.

It is important to recognize that decisional processes are augmented or diminished by altering the context for presenting the information. Approaches to facilitate rational judgment on participation involve both environment and timing for presentation of information. First, present materials in a supportive atmosphere. A private area with minimal risk of interruptions should be utilized whenever possible. Second, conduct interviews at times convenient to children’s daily routines, along with opportunities for multiple discussions to meet their relatively short attention span. For example, soliciting participation with a hungry or tired young person may not be conducive to the assent process. Importantly, each investigator’s standard consent process should include additional means for addressing uncertainties. More than one interview will ensure that pediatric subjects and their parents are not pressured into hasty, uninformed decisions. Fortnight discussion during initial consent and throughout the trial will contribute to safeguarding the process.

**Forms and supplementary materials.** The process of pediatric consent must be documented by signature of parents on a consent form and by children on an assent form according to applicable regulations. The overall process should be noted in the medical record by the investigator. A source of ongoing debate by clinical research stakeholders is the issue of consent form readability. Ethics boards are charged with final acceptance of forms prior to implementation in a trial. Standards require that material be in a language understandable to the potential subject and certain elements be included. Using nontechnical language in consent documents, difficult enough when writing for adults, is even more perplexing for assent forms tailored to children. The depth of the problem in pediatrics research was demonstrated in a readability evaluation of 238 forms over a 10-year period. The readability scores revealed forms were written at a college graduate level, although ethics guidelines suggest that information should be at a middle-school level. Readability analysis can be helpful in developing forms, but a more reliable measure may involve using focus groups or similar audiences to preview the form.

Companion brochures to accompany the consent form are reported by investigators and parents to markedly enhance understanding. Handouts describing the study plan and subject visits ensure that both children and parents are informed about procedures and time commitments. As for the consent documents, the materials should be age-appropriate. Videotapes for consent have been used effectively in adult trials, and parents of children expressed appreciation of videotaped information in a pediatric oncology trial. Another suggestion applicable to pediatric trials is the consent interval recommended in psychiatric trials for individuals with limited decision-making. Tapes or other supplementary materials lend themselves to review during a waiting period between initial discussion and actual consent.

**Opportunities for improvement**

In the past 15 years, considerable progress on subject protection in pediatric trials has materialized through guidelines on pediatric data requirements, safety considerations, and ethical approaches to protocol design. A few precepts have ventured into the unique aspects of the pediatric consent dyad, but agreement on specifics is lacking. As global development for pediatric medication accelerates, diligence to established standards on pediatric assent and parental permission is crucial. We have highlighted unresolved issues in this article, and discourse on practical implementation should persist. Additional mandates and consensus statements are needed from all concerned, including subjects and their parents. Improving assent documents and developing tools to assess understanding will enhance compliance to ethical principles and promote safeguards for voluntary participation. Taken in its entirety, the approach will require continuous reevaluation of the consent process in pediatric clinical trials.

**References**


43. National Cancer Institute, Protections for Participants in Clinical Trials: Children’s Assent to Clinical Trial Participation: Special Considerations (1999), www.cancer.gov.


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M. Renee Simar, PhD, is senior director, scientific affairs at INC Research, CNS Division, Pediatric and Adolescent Services, 3321 Bee Caves Road, Suite 300, Austin, TX 78620, (512) 327-7333, fax: (512) 327-6996, email: rsimar@incrsearch.com. Virginia A. Johnson, MS, is an instructor in the Department of Pediatrics, Section on Clinical Pharmacology and Regulatory Director, Pediatric Pharmacology Research Unit at the Louisiana State University Health Sciences Center-Shreveport.