**Industry and Patient Perspectives on Child Participation in Clinical Trials:
The Pediatric Assent Initiative Survey Report**

**Abstract**

**Background**: Obtaining assent from children participating in clinical trials acknowledges autonomy and developmental ability to contribute to the consent process. This critical step in pediatric drug development remains poorly understood, with significant room for improving the clarity, efficiency, and implementation of the assent process. Beyond ethical necessity of informing children about their treatment, the assent process provides the advantages of including children in discussions about their diagnosis and treatment – allowing greater understanding of interventions included in the study. A formalized assent process acknowledges the child as a volunteer and provides a forum for questions and feedback. Legal, cultural, and social differences have historically prevented the development of clear, concise, and accessible materials to ensure children understand the clinical trial design. Published guidelines on obtaining pediatric assent are vague, with many decisions left to local institutional review boards and ethics committees, underscoring the need for collaboratively designed standards. To address this need, 2 surveys were conducted to quantify perspectives on assent in pediatric clinical trials.

**Methods**: Two digital surveys were circulated in the United States and internationally (October 2014 to January 2015). The first survey targeted children, parents, and/or caregivers. The second polled clinical trial professionals on their organizations’ experience and policies regarding pediatric assent.

**Results**: 45 respondents completed the child and parent/caregiver survey; 57 respondents completed the industry survey. Respondents from both surveys detailed experiences with clinical trials and the impediments to securing assent, offering potential solutions to attaining assent in pediatric patients.

**Conclusions**: An important opportunity exists for standardized practices and tools to ensure pediatric patients make well-informed decisions regarding their participation in clinical trials, using materials appropriate to their level of understanding. These tools would establish a baseline standard for the assent process and be made available to researchers, improving their ability to secure assent from young patients.

**Keywords:** pediatrics, pediatric assent, clinical trials, consent, survey

**Introduction**

Children cannot provide true *informed consent*, in the legal sense,until they reach the specified age at which the law recognizes their ability to give consent but are often asked to agree (provide assent) to participate in clinical trials while they are minors. Although pediatric assent is not required by law in all countries, institutional review boards (IRBs) and ethics committees, academic institutions, and clinical trial organizations increasingly require assent be obtained from pediatric patients before participation in a clinical trial. Securing assent is explicitly outlined in the Declaration of Helsinki.1 Because there is no universal guidance for securing assent—or agreement on the age at which assent for pediatric patients is mandatory—assent procedures vary significantly among countries or even between IRBs/ethics committees within a country.2 The US Food and Drug Administration (FDA),3 World Health Organization (WHO),4 European Commission,5 Australian National Research Council (ANRC),6 National Cancer Institute (NCI),7 American Academy of Pediatrics (AAP),8 and United Nations (UN)9 have all published guidance on the importance of ensuring assent from pediatric patients is attained prior to their participation in clinical trials. While assent guidelines from these organizations vary in nature and context, all emphasize the importance of obtaining assent prior to clinical trial participation whenever possible. Other consistent themes include the need for parental informed consent before a child can be enrolled in a clinical trial, the need for both parents to give informed consent unless only one parent is available and for the clinical research team to fully explain the trial procedure to the child in a language that they can understand, including what participation entails and what the child may experience during the treatment.4,7,10,11 All government and organizational guidance documents include language pertaining to the withdrawal of parental consent at any time.

Overall, however, regulatory guidance on the topic of securing pediatric assent is vague. Recent regulation from the European Parliament and of the Council on clinical trials on medicinal products for human use allowed participation in pediatric clinical trials in the event of informed consent, with the provision pediatric patients receive information about the procedure “in a way adapted to their age and mental maturity” from investigators trained or experienced in working with children.11 This regulation respects the legal requirement for assent in some Member States and the lack of such a requirement in other Member States.11 The WHO similarly instructs clinicians and scientists to use age-appropriate language when securing pediatric assent for clinical trial participation but does not provide specifics as to content or delivery method.4 FDA guidance instructs researchers to secure pediatric assent via a separately designed, written document, which should be signed and dated by the child participant if they demonstrate the “appropriate intellectual maturity” for understanding the assent process.3 The age at which assent can be realistically obtained varies; the WHO instructs researchers to obtain assent in children 7 years and older.4 Guidelines from the ANRC concede the difficulty of assigning appropriate ages for pediatric assent, which vary from child to child.6 The timing and length of assent are similarly inconsistent. The ANRC’s National Statement on Ethical Conduct in Human Research includes a provision for “standing parental consent,” in which parents give consent to their child’s involvement in research activities and are notified of changes in study protocol but are not required to reaffirm their consent throughout the year.6 The WHO, UN, and EMA leave this decision to the discretion of investigators. Inconsistencies among government and health agency documents are reflected at an institutional level. Kimberley et al found considerable variability in IRB policies and procedures regarding pediatric assent at 55 centers across the United States.12

Guidance documents discuss the ethical and clinical importance of attaining assent from pediatric patients entering clinical trials, but they offer little practical instruction on how investigators should implement the assent procedures. The importance of understanding the language that informs assent procedures is a recurring theme in guidance literature, though no peer-reviewed guidelines exist to provide exact information on what understandable language entails in this context. Although all identified guidelines have a provision for pediatric patients to be engaged in discussions about the research in which they participate, the exact requirements for pediatric assent remain undefined. Furthermore, no identified guideline provided any direction as to the practicalities of obtaining assent from a pediatric patient; verbal confirmation is insufficient, but a child’s signature on a consent form carries little legal weight.10,13

In light of these inconsistencies, the Institute for Pediatric Innovation (IPI) identified a need for consensus in the operational practicalities of obtaining assent from pediatric patients participating in clinical trials. To better understand the prevailing attitudes and policies governing pediatric assent, the Global Alliance for Pediatric Therapeutics (GAPT, “The Alliance”), commissioned 2 Internet-based surveys: a survey of children and their caretakers and a survey of the wider pediatric research community, including academicians, IRB representatives, hospital administrators, and biopharmaceutical company employees. The Alliance is a consortium of biopharmaceutical industry, clinical, and pediatric advocacy groups convened by the IPI to address the growing need for establishing best practices in pediatric therapeutics. The Alliance has previously conducted surveys and literature analyses on tools for evaluating the palatability and swallowability of pediatric drug formulations.14,15 The 2 surveys were conducted under the aegis of The Alliance with support and assistance from Pfizer Inc and Shire LLC.

**Survey Populations**

The survey of parents and children was conducted in cooperation with the International Children’s Advisory Network (iCAN; [http://www.icanresearch.org)](http://www.icanresearch.org/%29). iCAN is a global consortium of children’s advisory groups working together to provide a voice for children and families in health, medicine, research, and innovation through synergy, communication and collaboration. An Internet-based survey was developed and distributed to the total iCAN membership (n = 37 children and their parents / caregivers) to collect the perspectives from children and their parents/caregivers on the process of attaining assent in clinical trials.. A total of 21 multiple-choice questions were asked of both parents and children, using various yes/no, 5-point Likert scale, and open-discussion question design. The survey was distributed through the iCAN with a direct link to the Internet survey through iCAN’s normal communication process. Complete responses were received from 20 children (54% response rate) and 25 parents / caregivers (68% response rate).

The second survey polled clinical trial professionals from the academic, pharmaceutical, and medical device communities on their perspectives and experiences with securing pediatric assent. The professional survey targeted medical and scientific directors, hospital administrators, IRB/ethics committee members, and academic researchers through membership of the Clinical and Translational Science Award (CTSA) program. Seventy-nine multiple-choice questions were asked of all respondents, employing various yes/no responses, 5-point Likert scale, and open-discussion question design. The survey was translated into Japanese and Korean for local implementation, with data collection and analysis currently under way; the findings from the 2 Asian surveys will be published subsequently. The survey was distributed to 83 clinical trial professionals via personal e-mail communication with a direct link to the Internet survey, with n = 57 compete responses [69% response rate]).

**Pediatric Patient/Caregiver Survey Results**

A total of 45 complete responses were received from parents (n = 21), caregivers (n = 4), and children (n = 20; mean age: 16 years) (Table 1). A total of 78% (n = 35) of all respondents resided in the United States at the time of the survey; 9 (20%) lived in Canada and 1 respondent (2%) lived in Scotland. Exposure to clinical trials was limited, with only 29% (n = 13/45) of respondents reporting they had previously participated in a clinical trial and 9% (n = 4/45; all children) reporting they were unsure. Of the 13 respondents with clinical trial experience, 77% (n = 10/13) stated they believed the assent process was clear and understandable.

*Cultural Perspectives*

A majority (69%; n = 31/45) of all respondents believed cultural issues such as race, religion, socioeconomic status, and country influenced the assent process. When separated, 84% (n = 21/25) of parents and caregivers believed these cultural differences influenced the assent process, compared to an even (50%; n = 10/20) distribution among polled children. Respondents cited cultural distinctions including male-dominated society, societal mistrust of health care and health care workers, language barriers, religious restrictions, and the place of the child in the family and societal hierarchy as potential issues that could influence the assent process. The majority of respondents (80% of caregivers [n = 20/25] and 75% of children [n = 15/20]) did not indicate that the gender of the child influenced the ability to obtain assent.

*Therapeutic Perspectives*

A large majority (92%; n = 23/25) of parents and caregivers reported certain diseases or symptoms, including cancer, diabetes, or asthma, could influence their approach to assenting to a clinical trial; 45% (n = 9/20) of children believed these factors played a role. Both groups cited exposure to health care as a factor, with children repeatedly exposed to treatments such as chemotherapy considered more receptive to the assent process. Disease severity and child maturity were also cited, with older children and children with life-threatening diseases believed to have a greater understanding of the assent process.

Opinions varied between the 2 groups regarding whether assent procedures should differ if the trial is for a medical device rather than for a medicine or vaccine, with 20% (n = 5/25) of parents and caregivers believing the process should depend on the therapy, compared with 60% (n = 12/20) of children.

*Age, Timing, and Renewing Assent in a Pediatric Clinical Trial*

Of the 25 parents and caregivers who answered, 80% (n = 20/25) believed that pediatric patients should renew their assent over the course of the trial; 65% of child respondents (n = 13/20) agreed. Parents/caregivers and children agreed that it would be appropriate to renew assent if the study design changed, a new treatment was introduced, or new safety information became available, and 31% (n = 5/16) of parents and caregivers and 35% (n = 5/14) of children believed assent should be renewed at least once annually. Perceptions on the age by which assent could reasonably be obtained were similar between the 2 groups, with 44% (n = 11/25) of parents/caregivers and 45% (n = 9/20) of children stating between the ages of 7 and 10 years to be appropriate (Table 2, Supplemental Figure A).

*Means of Securing Assent*

Of the 45 total respondents who answered, 89% (n = 40/45) believed a suite of tools to help researchers attain assent would be useful; 92% (n = 23/25) of parents and caregivers and 85% (n = 17/20) of children believed these tools would be beneficial. Both groups called for visual aids that clearly explain the procedure and hold the child’s attention. Each group (80% [n = 20/25] of parents/caregivers and 70% [n = 14/20] of children) also strongly preferred computer-based tools such as tablets or smart-phone applications to paper-based tools for securing assent (Supplemental Figure B). Respondents from both groups cited the technology savviness of young patients and the ability to quickly update digital materials as factors in their decision. When polled on which materials would be the most helpful to a child making an informed decision about assent, 88% (n = 22/25) of parents/caregivers and 80% (n = 16/20) of children selected tablet or smart-phone applications (Supplemental Figure C). Respondents from both groups believed assent materials should be reviewed by children before materials are used in a study (96% [n = 24/25] of parents and caregivers, 85% [n = 17/20] of children).

**Industry/Academic/Professional Survey Results**

*Organizational Perspectives and Experience with Pediatric Trials*

A total of 57 complete responses (47 from academic or hospital centers and 10 from biopharmaceutical companies) were received from the 58 participants who started the survey, with 42% (n = 24/57) of respondents occupying their current position within the organization for more than 10 years. Slightly more than half (50.8%;n = 29/57) of respondents in the industry and academic survey were from the United States, followed by 45.6% (n = 26/57) from Europe and 1 each (1.7%) from Canada, Japan, Australia, and South Korea. Forty-two percent of respondents (n = 24/57) reported their organization participated in more than 30 clinical trials within the previous 5 years; 25% (n = 14/57) reported participation in between 10 and 20 trials, followed by 16% (n = 9) in fewer than 10 trials, and 7% (n = 5) in between 20 and 30 trials, with 10% (n = 6) unable to answer. With regard to investigational drug studies during that time, 39% (n = 22/57) of respondents said their organization participated in more than 30 such trials, followed by 26% (n = 15/57) of respondents whose organization participated in fewer than 10, 18% (n = 10/57) between 10 and 20, and 3% (n = 2/57) between 20 and 30. Organizations were split regarding availability of a dedicated research unit, with 51% (n = 29/57) reporting that a dedicated unit was available for conducting trials in pediatric patients.

When asked about how they conduct clinical trials, 47% (n = 27/57) of professionals said their organization participated in an equal distribution of internal and external resources to conduct pediatric clinical trials; 19% (n = 11/57) and 7% (n = 4/57) used mostly internal or external resources, respectively; 18% (n = 10/57) used exclusively internal resources to conduct pediatric clinical trials; 9% (n = 5/57) were unable to answer. Eighteen respondents (31%) listed clinical research organizations (CROs) as their partner when their organizations collaborated externally on pediatric research. Other external partners included pharmaceutical companies, regional or city governments, designated pediatric centers, university-based medical centers, data coordinating centers, and law firms (for contracts and agreements). Eighty-four percent of professional respondents (n = 48/57) reported their organizations conducted clinical trials in pediatric patients of all ages. Eighty-six percent (n = 49/57) conducted pediatric trials across a variety of therapeutic categories.

The majority (78%; n = 46/57) of those polled believed ethics committee requirements regarding assent differed from country to country, with 17% (n = 10/57) unsure. Respondents cited variable assessments among countries’ laws and customs as a reason for this belief. At least 3 respondents reported from their experience that IRB or ethics committees often work within a single country and are therefore more knowledgeable about local cultures, values, and beliefs. Multiple respondents reported these IRBs and ethics committees to be aligned to the legislative framework of the countries in which they perform their duties. Respondents reported the mechanisms for securing assent, including determinations on the legal age at which assent must be given, how many parents must be present, and whether and when assent should be re-obtained, can vary significantly among countries. When asked if they believed assent practices differed among hospital-, academic-, and pharma-sponsored clinical trials, 39% (n = 22/57) of respondents said no, 33% (n = 19/57) said yes, with 30% (n = 17/57) stating they did not know.

*Organizational Perspectives on Pediatric Trial Design*

Language barriers were frequently cited as a challenge to securing assent, with 38% (n = 22/57) of organizations polled reporting they provided a translation service. Translational challenges remain, with 54% (n = 31/57) of academic or industry respondents reporting their organization did not translate assent materials. Of the organizations that did translate, 41% (n = 23/57) of translations were out-sourced; only 19% (n = 11) of outsourced translations were validated internally after translation. Several respondents expressed concerns that translated versions may not represent the concept of assent as defined in the original document.

The majority (75%; n = 43/57) of academic or industry respondents reported they believed there are significant differences across therapeutic areas for obtaining assent. When given the option to elaborate in the survey, multiple professional respondents reported an inverse relationship between disease severity and the ease of securing assent: critical conditions do not face serious challenges from parents or children. In instances where a clinical trial is the only option for therapeutic benefit or when that treatment offers a prospect for direct benefit critical to the health or well-being of the pediatric patient—as is common in oncology—parental permission alone is sufficient. Multiple respondents stated that in cases where the child cannot physically assent, as “when the child is intubated or in a trauma management setting,” parental consent alone is sufficient from an immediate clinical and ethical perspective.

Oncology was viewed by many respondents (63%; n = 36/57) as a special circumstance. When prompted to elaborate, professional respondents noted that cancer is often a difficult concept for young children to comprehend and that the side effects of radiation or chemotherapy may cause these patients to object to treatment even if treatments are beneficial. In these instances, parental consent was viewed as the only necessity prior to clinical trial enrollment. However, several respondents note that in chronic diseases, including oncology, the concept of assent may be better understood by patients and their families due to more frequent and prolonged exposure to medical procedures. Understanding of patients’ diseases and knowledge of medical procedures vary among therapeutic areas. According to one respondent, patients with HIV, psychiatric disorders, and cancer “frequently report a deeper understanding of medical procedures” and their attendant consequences and are correspondingly more comfortable assenting to treatment.

*Age, Timing, and Renewing Assent in a Pediatric Trial*

When polled about renewing assent as the study progressed, the majority of respondents in the Professional Survey (68%; n = 39/57) responded positively (Table 4). However, 61% (n = 34/57) of respondents reported their organizations did not obtain assent more than once per clinical trial. Assent and consent were cited by multiple respondents as ongoing processes that assume greater significance as the child matures and becomes familiar with the study. Several respondents believed renewing assent would be contingent upon the length of the study and stated that assent should be renewed at least on an annual basis. Others said renewing assent is necessary only in the event of significant protocol changes. When responding via free text, respondents identified several risks associated with renewing assent in the middle of an ongoing trial, including children choosing not to continue participating if given the option. There was near universal agreement that young patients should be given an opportunity to renew consent if they attain their legal majority (as defined by local laws) during the course of the study. One participant suggested assent should be verbally obtained at each visit for the long-term interventional studies common in oncology. Among professionals who answered *no* to renewing assent during the clinical trial, several (39%; n = 22/57) considered renewing assent unnecessary unless substantial changes were made to the study protocol. Multiple respondents replied that many pediatric trials do not last more than 1 year and were skeptical about whether asking patients to assent to treatment at each visit is a worthwhile use of constrained time. One European investigator reported that assent is obtained only once by their country’s laws but that a parent can stop their child’s participation at any time, obviating the need for reconfirming assent.

When asked their opinion on when in the clinical trial process assent should be obtained, 57% (n = 33/57) of professionals said *At Recruitment*, followed by *At Screening* (33%; n = 19/57), *At First Visit* (8%; n = 5/57), and *At Randomization* (2%; n = 1). Respondents were asked at what age they believed a pediatric patient could feasibly acknowledge assent. This refers to the age at which the child is able to understand the trial, understand what participation in that trial entails, and agree to participate. More than a third (38%; n = 22/57) of respondents reported 7 to 8 years to be appropriate, followed by 11 and over (28%; n = 16/57) and 9 to 10 (21%; n = 12/57). Surprisingly, 17% of respondents (n = 10/57) felt children aged 6 and under were capable of providing assent. These findings were not universal and many respondents were reluctant to apply an age limit to securing assent, citing differences in individual maturity levels, disease areas, reading ability, and location. Thirty-seven percent (n = 21/57) of respondents reported a minimum age for securing assent was never requested by regulators or IRBs/ethics committees (Supplemental Figure D), with 30% (n = 17) of respondents reporting regulators required assent by age 7.

*Variability Among Processes for Securing Assent*

Altogether, 53% (n = 30/57) of professionals reported their organization developed its own internal standards for attaining assent in pediatric clinical trials. Of these, 87% (n = 26/30) stated the guidelines aligned with their state’s guidance on pediatric assent. Such an alignment suggests legislative influence as an important factor in assent guideline development. Slightly more than half (52%; n = 29/56) of organizations developed their own modules or internal templates for attaining assent. A total of 32% (n = 18/57) of respondents from these organizations expressed a willingness to share these materials, pending organizational approval, and 5% (n = 3) said these templates were available via their company’s website.

Age was the most significant mitigating factor for differences in the assent process. When asked which factors affect the assent process for pediatric clinical trials, 82% (n = 47/57) of respondents said age was the most important variable, followed by clinical trial design (46%; n = 26/57), underlying disease state (44%; n = 25/57), culture (23%; n = 13/57), ethnicity (12%; n = 7/57), and gender (7%; n = 4/57). There was little difference between assent protocols for various clinical interventions. Assent protocols differed from standardized assent forms most for nonpharmacological therapy (7%; n = 4/57) and placebo-controlled studies (5%; n = 3) (Supplemental Figure E). Several respondents reported using one template as a basic assent protocol, which was then tailored for specific interventions.

*Areas for Improvement*

When asked for ways to improve the process for securing assent for pediatric subjects in clinical trials, respondents favored consistency in both assent materials and procedures. An overwhelming majority (93%; n = 52/57) of professionals surveyed reported that a comprehensive/novel suite of tools or methods could be developed to assist in attaining assent in pediatric clinical trials. Multiple respondents echoed one respondent calling for “*standardization across institutions for age, signatures, verbal and written assent procedures*” within countries, followed by global standardization, wider use of verbal rather than written assent, and translation services. Multiple respondents expressed a need for assent materials that target specific age ranges, developmental levels, cognitive capacities, or geographic regions that could be distributed among research institutions. Several respondents called for interactive/digital templates—such as a computer game, photo array, or video series—to be used across organizations and countries. Use of such tools remains stratified by age group, with assent from adolescents (aged 13–17 years) secured primarily (61%; n = 35/57) via comprehensive written forms only or with comprehensive written forms with some visuals (35%; n = 20/57) (Supplemental Figure F). School-aged children (aged 6–12 years) are more frequently presented with concise written forms with some visuals (46%; n = 26/57). Procedures to obtain or review assent from preschoolers (aged 4–5 years) are not attempted 53% (n = 30/57) of the time.

With regard to developing high-quality visuals or electronic media to attain assent, respondents said it should have several attributes, notably development by a multidisciplinary team (potentially including minors), interactivity, user-friendliness, low cost (or free), age-appropriateness for several age levels, availability in multiple languages (or easily translated), and multicultural in scope.

A total of 74% (n = 42/57) of organizations had never received feedback in the form of criticism, questions, or recommendations from patients, caregivers, or regulators on the assent process. The majority (86%; n = 49/57) of respondents reported their organization’s assent processes were never validated and 91% (n = 52) reported never facing challenges from regulatory authorities related to the assent process. Similarly, only 23% (n = 13) of respondents received any feedback on their assent procedures, most of which related to translational difficulties or age-appropriateness of material. Collaboration on pediatric assent processes is rare, with 84% (n = 48) of respondents reporting they were not aware of assent processes employed by other organizations.

*Method of Delivery of Assent Forms*

The majority of respondents (74%, n = 42/57) indicated that their consent/assent forms were designed for both parents and pediatric patients to complete as a single process. A greater majority of respondents (89%; n = 50/57) had forms exclusively focused on obtaining consent from the parent/caregiver if the pediatric patient was unable to provide assent. Over 79% (n = 45) of respondents also had assent forms addressed specifically to pediatric patients. Fewer than half (42%; n = 24/56) of the respondents considered videos an appropriate tool for educating children and their families about assent/consent, with a small majority (51%; n = 29) unsure of their applicability. Multiple respondents favored making educational videos widely available via websites or preloaded on tablets at the trial site to help explain potential procedures, pending organization approval. Among respondents who were unsure regarding the usefulness of video aids, most cited unfamiliarity with suitable videos rather than an unwillingness to adopt them.

**Discussion**

We present a unique overview of assent in pediatric trials by comparing responses from 2 perspectives. Respondents from both the professional and child/caregiver surveys overwhelmingly reported respecting children’s best interests to be an essential part of the clinical trial process and that there is a place for assent achieving this goal. By cataloging and presenting the views of both groups in this study, we get insight into the realities of the assent process in pediatric clinical trials. These include inconsistent definitions of assent, maturity, and personal agency; legal nuances unique to individual countries; and strong cultural norms that influence pediatric care. These insights provide a framework for standardization of assent materials required to address these inconsistencies.

 Cultural and legal differences were cited as the most difficult obstacles for securing assent in pediatric patients. Laws on pediatric clinical trials can differ significantly between countries. Placebo use, study duration, poor-responder management, potential burdens or side effects of treatment, and the types of disease treated by clinical trials in young patients are subject to different laws even within countries. Privacy laws regarding children are similarly nuanced and can vary widely among countries, with respondents citing their organization’s need to amend assent protocols in some cases. Whether a young patient’s parents should be informed if their child has HIV or takes birth control or is pregnant, for instance, varies around the world. Legal and cultural views of when a child has the autonomy to assent to clinical intervention vary, according to data in these surveys. In some countries, parents may wish their children to be part of that decision-making process, but this is not universal. Parental decisions may override a child’s unwillingness to participate in a clinical trial. Respondents from both surveys reported in some cultures children cannot truly assent because they are not speaking for themselves. This situation can be especially true for girls and young women, who may not be permitted to speak without a father, brother, or other male family member present. Some cultural issues are so pervasive that several respondents in the professional survey reported their organizations no longer operate in some regions because these cultural forces prevent them from conducting ethical research as outlined by the Declaration of Helsinki.

The practical nature of securing assent is different across cultures as well. Although many organizations secure assent via a signature, the legal status of a child’s signature varies between countries. In some countries, where signatures are associated with police or criminal activities, legal guardians have declined to sign an assent document, according to one respondent.

Data from the professional survey strongly suggests the concept of community assent is largely unknown in the United States but may arise internationally. Medical decisions for some families may be made by one parent or may be made collectively. Some cultural differences on privacy or data collection color the assent process. Several respondents reported paperwork to be too long or descriptive for people of some cultures to be comfortable.

Respondents in both surveys considered language barriers a significant issue. The differences between consent and assent are nuanced even in English, and the concepts may be wholly alien to some cultures. These differences are compounded in children. More than half (54%; n = 31/57) of polled organizations said their pediatric assent materials were *not* available in a language other than the original.

Willingness to participate in clinical trials may be higher in oncology or diabetes, but more difficult in neonatology, according to respondents. It may be easier to secure assent when studies are not interventional or are performed in addition to the standard of care. Several respondents stated their belief that pediatric specialties are generally less research-active than other areas and may require less stringent assent processes.

Professional respondents cited several reasons why assent may not be achieved in pediatric patients. These include dissent or the child’s right to actively refuse, particularly if the clinical trial might cause pain or distress. However, respondents stated strongly that assent should not be required when the well-being of a child is in question, as with a young patient undergoing a difficult cancer treatment. Understanding of the risks associated with the trial or intervention should be considered a factor, as patients may be unlikely to assent to a treatment if they are unaware of the risks associated with the intervention. Disease awareness is another factor to be considered. Both pediatric and parental knowledge of the disease or attitudes about treatment specifically or health care in general were cited. Some parents, skeptical of health care workers or unproven treatments, are unwilling to consent for fear their child will be a “guinea pig”; this rationale was cited more than once. Educational and economic factors play a role, with low education levels among parents or economic conditions at some clinical sites preventing assent from being secured.

Many respondents in the professional survey reported the practicality of securing assent prevents it from being attained at all, particularly outside the United States. When assent is secured, respondents reported the process was not standardized and was inefficient and incompletely understood by children and their parents. Forms that were badly written or not age-appropriate for the audience were cited, as were the poor skills of the person obtaining assent. Staff might overlook some patients or not know the required age of assent for young patients and fail to secure it. One respondent discussed the difference between challenges to achieving assent (ie, fear, cultural differences, burdens associated with the trial, or complexity of the assent procedures) and attaining assent (ie, lack of knowledge about ethical requirements, cultural differences, or the nature of the underlying condition). Most professionals polled cited inexperience with e-tools rather than a reluctance to adopt them. E-based tools can obviate challenges posed by a language barrier by providing interactive visual aids, but the costs and logistics of using e-based tools may be prohibitive, particularly in the developing world. A suite of low-cost, collaboratively designed, standardized, and flexibly tailored tools to attain assent from pediatric patients would mitigate or eliminate many of the issues cited in both surveys. Such tools could remove much variability and nuance that plagues the pediatric assent process.

There are limitations to the survey, and conclusions drawn from responses come with a caveat. The overwhelming majority of respondents from the patient/caregiver survey resided in the United States and their comments are necessarily viewed through the prism of the American health care system. Similarly, more than half (51%) of the professional and academic responses came from the United States. Differences in health systems, regional views of pediatric medicine, drug development processes, and regulatory structures among international communities may impact how respondents approached and answered questions included in the survey. Versions of the professional survey were translated into Japanese and Korean and data analysis is under way, the results of which will provide valuable insights into perspectives of pediatric assent in Asia.

**Conclusions**

Pediatric assent remains a nuanced and inconsistently applied aspect of clinical trial design. Respondents in both surveys identified multiple challenges related to the attainment of pediatric assent in a clinical trial setting, including a lack of global consistency, varying age requirements, timing of initial assent, and the process for re-obtaining assent after it is initially secured. Respondents also cited regional differences in concepts of maturity, age appropriateness, and cognitive capacity as obstacles, underscoring the need for consistent global guidance and tools.

Cultural differences also impede consistency. Respondents cited distrust of health care workers, parental limits on understanding of intervention, unwillingness to seek treatment for sick children, and cultural perspectives on health care in general as obstacles for securing assent. Legal and ethical questions remain as well, such as the procedures for obtaining consent from divorced or separated parents, the role of legal experts in the assent process, and the usefulness of legal language when treating patients.

A precise definition of what constitutes assent in a clinical context remains elusive for patients, parents, and professionals. Respondents reported insufficient understanding of the concept of assent and were not universally clear on when assent is needed or how assent differs from informed consent in real-world scenarios. A need therefore exists for detailed procedures to obtain assent for medical interventions and clinical trial types that can be used across institutions and therapeutic areas. Researchers, clinicians, and organizations would see benefit in a set of validated, age-appropriate materials that serve to explain clinical procedures and potential risks and adverse events to children and their parents and secure their assent and, as far possible, judge their understanding of the trial in which they are enrolled. Many practitioners and health care providers would welcome access to a curated and expert-approved set of exemplary assent materials, which could be tailored to the needs of their pediatric patients.

*The views presented in this correspondence are those of the authors and should not be understood or quoted as being made on behalf of the European Medicines Agency or its scientific committees.*

**References**

1. World Medical Association (WMA). Declaration of Helsinki: ethical principles for medical research involving human subjects. World Medical Association (WMA). 2013. <http://www.wma.net/en/30publications/10policies/b3/>. Accessed 5/10/2016.

2. Frakking F, van der Lee T., Klassen T, et al. Survey of current guidance for child health clinical trials. 2009:1-37. <http://www.who.int/childmedicines/publications/GUIDANCECHILDHEALTH.pdf>. Accessed 12/2/2016.

3. US Food and Drug Administration. Guidance for industry E11 clinical investigation of medicinal products in the pediatric population. Rockville, MD: U.S. Department of Health and Human Services; 2000: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073143.pdf>. Accessed 12/2/2016.

4. World Health Organization Research Ethics Review Committee (ERC). The process of seeking informed consent 2009. [www.who.int/rpc/research\_ethics/Process\_seeking\_IF\_printing2.pdf](http://www.who.int/rpc/research_ethics/Process_seeking_IF_printing2.pdf). Accessed 12/2/2016.

5. European Union. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. *European journal of health law.* 2008;15(2):223-250.

6. Australian Government National Health Medical Research Committee. National statement on ethical conduct in human research (2007) - Updated May 2015. 2016. <https://www.nhmrc.gov.au/guidelines-publications/e72>. Accessed 12/2/2016.

7. National Cancer Institute. Children's assent. 2016. <https://www.cancer.gov/about-cancer/treatment/clinical-trials/patient-safety/childrens-assent>. Accessed 12/2/2016.

8. Shaddy RE, Denne SC. Clinical report--guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics.* 2010;125(4):850-860.

9. Children's Rights Alliance. Summary of the UN Convention on the rights of the child. 2013. <http://www.childrensrights.ie/sites/default/files/information_sheets/files/SummaryUNCRC.pdf>. Accessed 12/2/2016.

10. Gill D, Crawley FP, LoGiudice M, et al. Guidelines for informed consent in biomedical research involving paediatric populations as research participants. *Eur J Pediatr.* 2003;162(7-8):455-458.

11. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance. 2014. <http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32014R0536&qid=1480707497130>. Accessed 12/2/2016.

12. Kimberly MB, Hoehn KS, Feudtner C, Nelson RM, Schreiner M. Variation in standards of research compensation and child assent practices: a comparison of 69 institutional review board-approved informed permission and assent forms for 3 multicenter pediatric clinical trials. *Pediatrics.* 2006;117(5):1706-1711.

13. Ungar D, Joffe S, Kodish E. Children are not small adults: documentation of assent for research involving children. *J Pediatr.* 2006;149(1 Suppl):S31-33.

14. Squires LA, Lombardi DP, Sjostedt P, Thompson CA. A systematic literature review on the assessment of palatability and swallowability in the development of oral dosage forms for pediatric patients. *Therapeutic Innovation & Regulatory Science.* 2013;47(5):533-541.

15. Thompson CA, Lombardi DP, Sjostedt P, Squires LA. Industry survey on current practices in the assessment of palatability and swallowability in the development of pediatric oral dosage forms. *Therapeutic Innovation & Regulatory Science.* 2013;47(5):542-549.