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Empirically-derived Knowledge on Adolescent Assent to Pediatric Biomedical Research

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Abstract

Background—There has been a recent growth in empirical research on assent with pediatric populations, due in part, to the demand for increased participation of this population in biomedical research. Despite methodological limitations, studies of adolescent capacities to assent have advanced and identified a number of salient psychological and social variables that are key to understanding assent.

Methods—The authors review a subsection of the empirical literature on adolescent assent focusing primarily on asthma and cancer therapeutic research; adolescent competencies to assent to these studies; perceptions of protocol risk and benefit; the affects of various social context variables on adolescent research participation decision making; and the inter-relatedness of these psychological and social factors.

Results—Contemporary studies of assent, using multivariate methods and updated approaches to statistical modeling, have revealed the importance of studying the intercorrelation between adolescents' psychological capacities and their ability to employ these capacities in family and medical decision-making contexts. Understanding these dynamic relationships will enable researchers and ethicists to develop assent procedures that respect the authority of parents, while at the same time accord adolescents appropriate decision-making autonomy.

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Conclusions—Reviews of empirical literature on the assent process reveal that adolescents possess varying capacities for biomedical research participation decision making depending on their maturity and the social context in which the decision is made. The relationship between adolescents and physician-investigators can be used to attenuate concerns about research protocols and clarify risk and benefit information so adolescents, in concert with their families, can make the most informed and ethical decisions. Future assent researchers will be better able to navigate the complicated interplay of contextual and developmental factors and develop the empirical bases for research enrollment protocols that will support increased involvement of adolescents in biomedical research.

Keywords

Assent; Pediatric Biomedical Research; Research Ethics; Informed Consent; Research Participation Decision-making

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There is general agreement about the ethical principles that govern research with pediatric populations, but only recently has empirical research been used to hone these philosophical and regulatory principles into effective evidence-based practices. Using empirical studies to inform research ethics is especially critical in the case of research with children and adolescents (Sieber 2008). For more than a decade, it has been recognized there is insufficient biomedical research to guide medical intervention in pediatric populations and there have been calls for expanded participation of children and adolescents in biomedical research (National Institutes of Health 1998; Pediatric Research Equity Act of 2003; U.S. Food and Drug Administration 2001). At the same time, children and adolescents are recognized as a protected population for research purposes, and there is increased national attention and concern over the ethics and potential abuses of human research subjects (Code of Federal Regulations 1994; Lederer and Grodin 1994; Nelson 2005).

Empirical studies of the pediatric research participation process are providing data that can be used by pediatric biomedical researchers in their efforts to design ethically appropriate studies that are sensitive to the capacities of their research participants. This is particularly true in the area of adolescent assent and parental permission to participate in pediatric biomedical research. Assent scholars have turned to the cognitive, social, family, and developmental psychological sciences to address a diverse set of questions, including what decision-making heuristics individuals use when deciding whether to participate in research, what social and familial pressures influence research decision making, and how each of these issues are moderated by developmental maturity.

The objective of the following review is to discuss the progress and limitations of the psychological studies on adolescent assent to biomedical research. A comprehensive review of the legal, ethical, and biomedical literature on pediatric assent across developmental stages is needed, but would exceed the limitations of this venue. Instead, this article will focus on the content and process of attaining assent from adolescents, which involves important and controversial themes due to the ambiguity inherent in adolescents' capacities to participate in the research participation decision-making process. In particular, we review the research on several factors salient to adolescent decision-making for biomedical research participation, such as risk and benefit appraisals, the effects of authority figures such as parents and physicians, the influence of financial compensation, how these factors inter-relate, and how they are used to develop assent procedures. Based on the research reviewed, we conclude with directions for future studies that more fully appreciate the complexity of the psychology of research assent and provide some general guidelines for translating empirical results into the practice of obtaining parent permission and adolescent assent.

The State of the Art of Assent to Pediatric Research

There is now a more than 30-year history of empirical studies to draw upon on the issue of child and adolescent competencies to understand and assent to biomedical research. Assessing what is known from empirical studies of assent requires an appreciation of the research methods used by assent researchers, the methodological predicaments they face (Miller, Drotar, and Kodish 2004; Sachs et al. 2003), and how these issues affect external validity and the translation of research into practice.

The use of varied research design strategies

Synthesizing the body of assent research is complicated by the variety of research methods employed to study the phenomenon (Miller et al. 2004; Sachs et al. 2003). Some researchers have utilized qualitative methods, often designed as "piggy-back" studies in which people are observed providing assent to a clinical trial and asked to retrospectively reflect on the assent process. The data from these studies have provided insight on the consent process *in vivo*. However, this method does not allow for manipulation of experimental variables, often employs small samples that may have limited generalizability, and depending on the nature of the study and what family and/or physician-investigator discussions have preceded the observations, may not be an accurate reflection of the actual family research participation decision.

Quantitative studies have been mostly quasi-experimental in nature. In these studies, participants are typically asked to respond to hypothetical vignettes that pose research participation decision-making dilemmas in which key elements of the research endeavor (e.g., risk, benefit, compensation) are independent variables that can be manipulated to discover how they impact research participation decision-making, namely the dependent variable of assent. These studies enable researchers to develop conclusions about the effects of research elements on participation decision making. However, these studies are generally *in vitro* by nature, typically relying on "cold cognition," or studying the decisions of participants who are not in reality assenting or consenting to research, only responding as they believe they would were they actually being asked to assent to research. As a result, their decisions lack the full heuristics that go into a "hot cognition" or a decision that has real-life consequences (see Spears, 2010 for discussion of hot and cold cognition in adolescence). Quantitative researchers have tried to augment the ecological validity of their studies by creating vignettes based on actual clinical trials and by sampling populations who actually have the illness being studied in the hypothetical research (e.g., Brody et al. 2003; Geller et al. 2003; Miller, Reynolds, and Nelson 2008; Ondrusek et al., 1998; Reynolds and Nelson 2007; Snethen et al. 2006; Unguru, Sill, and Kamani 2010).

Methodological issues that limit generalizability

Other issues also limit the external validity and generalization of research findings in assent studies. For example, in assent research, participants' assent and parental permission must be acquired before assent can be studied (Sachs et al. 2003). As a result, the sample of assent research participants is unlikely to include participants who decline to participate in research and is typically conducted with a sample of participants who are predisposed toward assent. It is not clear to what extent sampling bias influences the data that assent research participants provide or if responses to stimulus materials are biased or confounded by the study's own assent process. Because assent research findings may be assent-biased, these findings are suspected to lack generalizability to the general population and tell us very little about those who are ambivalent about research participation and those inclined to dissent. Moreover, research assent is often conflated with treatment assent (Kodish 2003; Miller et al. 2004). Upon cursory review, the two processes seem to have similar demand

characteristics and in some circumstances they are confounded (e.g., much pediatric cancer treatment is conducted via a clinical trial). Yet research assent involves a quite different risk-benefit analysis, different motives for participation, and is often more optional than treatment.

A more problematic complication is generalizing across research for different types of pediatric diseases. Some researchers have studied assent in research participants with a specific disease, such as asthma (Scherer, Annett, and Brody 2007) or cancer (Joffe et al. 2006; Unguru et al, 2010), thereby creating a vector for studying the research assent process. Others have conducted studies or analyses of assent that include participation decision-making responses to research for a variety of diseases and with children who manifest different maladies or none at all (Broome et al. 2003; Knopf et al. 2008; Ondrusek et al. 1998; Snethen et al. 2006). It is not clear that the findings regarding assent to research for one type of disease are applicable or generalizable to other types of diseases.

Critical disease-specific factors make many research participation decisions unique. Some diseases, and the research procedures used to study them, have clear external manifestations and implications that readily can be comprehended even without adult cognitive capacities (e.g., children with asthma have concrete experiences with shortness of breath, children being treated for cancer know what it feels like to have nausea and vomiting). Other illnesses and procedures are more abstract and involve internal physiology (e.g., ADHD) that may not easily be apprehended. Different disease processes evoke entirely different emotional reactions that can affect participants' decision-making capacities. For example, coping with a diagnosis of pediatric cancer may evoke a fearful emotional response, loss of life potential, and a sense of vulnerability that overrides rational decision-making or volition and invokes parental control, whereas participation in a minimal risk, minimal intrusion research study about asthma may seem routine.

The interdependence and intercorrelation of important variables

The science of assent, what constitutes assent for children of different ages, and how to acquire a valid assent are further complicated because the capacity to assent to research hinges on a variety of inextricably linked variables (Drotar 2008; Kon 2006; Masty and Fisher 2008; Miller and Nelson 2006; Miller, Reynolds, and Nelson 2009; Rossi, Reynolds, and Nelson 2003; Sterling and Walco 2003; Unguru, Coppes, and Kamani 2008). To begin with, assent is only valid when accompanied by parental permission[1] (Code of Federal Regulations 1994; Miller et al. 2009). Consequently, by definition, adolescents asked to assent to research are making a research participation decision that to some degree is affected by family dynamics (Baines 2011, Kon 2006; Sibley, Sheehan and Pollard 2012). Other social context factors such as physician/researcher influence and the demand characteristics of settings (particularly settings in which adolescents rarely experience choice and are generally expected to comply with adult authorities) also are assumed to affect the quality (e.g., namely how informed and volitional it is) of adolescent assent to biomedical research (Miller et al. 2008; Kon 2006; Scherer 1991; Scherer and Reppucci 1988; Snethen et al. 2006; Waterman and Blades 2011; Weithorn and Scherer 1994).

[1]There are circumstances where parental permission may be waived because it is either an impracticable requirement or represents an unreasonable means of protecting a child. Moreover, many states have legislation that authorizes adolescents to seek health care and make independent medical decisions (English and Keeney 2003), and federal regulations specifically reference these laws as a means of determining circumstances where minors may provide an independent consent for biomedical research participation. In these cases, the standards governing research participation decisions are akin to consent rather than assent, and although parental influence may be diminished, other forms of social influence that can constrain participant volition are still present.

Secondly, the capacity to assent is contingent on developmental maturity (Rossi et al. 2003) since ethical standards require that potential biomedical research participants with uncertain competence be granted a maximal level of decision-making autonomy consistent with their decision-making capacities (Field and Behrman 2004; The National Commission for Protection of Human Subjects of Biomedical and Behavioral Research 1978; Ross 2006; Society for Adolescent Medicine 2003). There is considerable discontinuity and variability in the psychological development of pediatric populations, particularly in cognitive, socio-emotional, and neurological development which makes it implausible to establish a single age-based standard for when to defer to the judgments of pediatric research participants (Kon 2006; Masty and Fisher 2008; see Spears 2010 for excellent review of adolescent neurological capacities). Moreover, the standards for a valid assent may change over the course of longitudinal studies because of changes in an adolescent's development (Helgesson 2005; Swartling et al. 2009).

Lastly, there are idiosyncratic features to pediatric biomedical research that lack parallels in everyday life, making it difficult for pediatric research participants to understand and evaluate a research protocol. For example, there is considerable concern that biomedical research participants often have a "therapeutic misconception" in which they fail to understand that the scientific purpose of research is to seek generalizable knowledge that may or may not result in individual benefit (Henderson et al. 2007), and some contend that because of this biomedical research participants overestimate therapeutic benefits (Brody, Scherer, et al. 2012; Lidz et al. 2004). Unique features of biomedical research, such as placebo treatments or being assigned to a no/delayed treatment control group, also may be difficult for pediatric research participants to comprehend (Blake et al. 2011). Another unique ethical concern is the heuristic value and influence of financial compensation on adolescent participants and their families and the degree to which this may hamper volition and undermine altruism as a research participation motive (Diekema 2005; Scherer et al., 2004).

Despite a variety of shortcomings in research methods and design, research on assent to biomedical research has advanced. Contemporary research on adolescent assent recognizes that the assent process is a highly contextualized process. The steps in making research participation decisions involve a complex algorithm that takes into account a variety of factors and the interactions between them. Unlike research on adult informed consent, which has focused largely on issues of comprehension, studies of assent are driven by questions about autonomy in decision making, the types of research information adolescents and their parents attend to, and how they interact with one another and with medical researchers to arrive at a mutual research participation decision (Miller et al. 2009; Swartling et al. 2011). Consequently, contemporary studies of assent are theoretically grounded in our current scientific understanding of how adults and youth process risk and benefit information, the types of family dynamics that come into play as adolescents and parents make mutual decisions, and the susceptibility of adolescents (and their parents) to persuasive social influences.

The Empirical Evidence Regarding Assent to Pediatric Research

The use of risk and benefit information in research participation decision making

Early informed consent researchers studied child and adolescent cognitive competencies, in particular, factual comprehension of information about the research protocol, their reasoning ability, and their aptitude for mentally manipulating information to infer the implications of research involvement, and the weighing and evaluation of these considerations (see Weithorn and Scherer 1994). Because of its central role in research participation decision making, contemporary assent investigations have also specifically addressed questions

related to the apperception of research risks and benefits. Two key themes dominate this literature: What are adolescents' capacities and how do they compare to similar capacities in adults?

Recent reviews of adolescent decision making in general (Downs and Fishoff 2009; Reyna and Farley 2006) and in health-related situations (Byrnes 2002; Halpern-Felsher and Cauffman 2001; Millstein and Halpern-Felsher 2002) note that as adolescents age, they acquire greater cognitive and metacognitive abilities and gain more experience with making important life-impacting decisions, although significant differences have been detected in the decision-making processes of adolescents and adults. Some researchers have found that adolescents and adults are fairly comparable in their perceptions of personal invulnerability (Quadrell, Fischoff, and Davis 1993) and capacities to evaluate risk (Burke et al. 2005; Weithorn and Campbell 1982). Others assert that adolescents are less risk averse than adults, tend to minimize the potentially harmful consequences of occasional risk-taking behaviors, and are limited in their capacities to identify research/treatment risks and benefits in response to either hypothetical or actual research and treatment protocols (Abramovitch et al. 1995; Abramovitch et al. 1991; Cohn et al. 1995; Kaser-Boyd, Adelman, and Taylor 1985; Susman, Dorn, and Fletcher 1992).

Assessments of adolescent capacities to evaluate research risk are complicated by ambiguous federal regulations that fail to appreciate the complexity of the construct (Glass and Binik 2008). Physical considerations (e.g., medication side effects, pain associated with a particular procedure such as injections or venipuncture) have dominated interpretations of the definition of risk, to the exclusion of psychological, economic, or social sources of risk. For example, some procedures (e.g., using an experimental medication) can be risky but not aversive, while others (e.g., venipuncture) may be aversive and psychologically troubling, although not physically risky (Arnold et al. 1995; Fradet et al. 1990; Ondrusek et al. 1998). Adults, and researchers in particular, may be focused on physical and invasive risks, while adolescents may be more attuned to the immediate psychological discomfort (Ondrusek et al. 1998; Gowda et al. 2012).

Given the complexities of defining constructs such as risk and benefit, it can be difficult to tease apart true assent capacities from differences of opinion or perspective. A recent set of research findings highlights the conundrum through comparisons of parents', adolescents' and physicians' perceptions of risk and benefit for a variety of asthma-related research procedures and protocols (Annett et al. 2004; Brody et al. 2003). In these quantitative studies using asthma research participation vignettes, adolescents with asthma and their parents rated the risk and aversion potential of minimal risk protocols and procedures fairly comparably, with one exception; parents and physicians are less concerned about the risk and aversion of venipuncture than adolescents. By contrast, physicians and adolescents were less concerned about the risks associated with experimental medication than were parents. This latter finding emphasizes that differences in risk perception may not be due to developmental considerations alone, and point toward the need for a greater understanding of the factors underlying evaluations of research protocols by parents as well as by adolescents.

Assessing child and adolescent capacities to evaluate research benefits are even more complicated given the prevalence of the therapeutic misconception among adults (Vitiello 2008). Annett et al. (2004), in a quantitative study using asthma research participation vignettes, highlight this point when they demonstrated that parent and adolescent ratings of research benefits were often similar and that both groups inferred they would derive benefit from research procedures (e.g., placebo) even though physicians rated them as having little beneficial potential. These findings are compatible with qualitative research that has

demonstrated lapses and faults in adult and adolescent comprehension of risks and benefits (Kupst 2001; Kupst et al. 2003; Reynolds and Nelson, 2007; Susman, Dorn, and Fletcher 1992) and significant differences in their evaluation of research risk compared to research investigators (Michaels and Oetting 1979; Sullivan and Deiker 1973).

The social context in which assent occurs

The value of an adolescent's assent to biomedical research depends in large part on how he or she contends with a variety of social influences. In general, early adolescents tend to defer to parental authority, although by the middle adolescent years they begin to assert, and attempt to exercise, greater control over personal choices (Wray-Lake, Crouter, and McHale 2010). Similarly, Miller et al. (2008) suggest that parents are less willing to urge their children to participate in research as their children cognitively mature. However, children and adolescents have a normative subservient role in family settings and experience significant power differentials in their relationships with adults and in most institutional settings, especially medical settings, where they likely perceive less decision-making autonomy. Moreover, parents and healthcare professionals often have ambivalence about child and adolescent rights to make healthcare and medical research decisions and omit them from participation discussions (Cox, Smith and Brown 2007; Swartling et al 2009; Kumpunen et al. 2011; Varma, Jenkins, and Wendler 2008). The voluminous psychological literature on autonomy and social influence indicates that even adults are quite conforming in the face of social pressure and compliant to authority (Cialdini 2001). This social norm for compliance to authority can result in the assent process for research participation being relegated to an act of submission rather than an exercise of independent choice (Grisso 1992).

The empirical literature regarding the influence of social context variables on assent has been indeterminate. Some have concluded that adolescents are deferential to parental preferences in treatment decision making (Scherer 1991; Scherer and Reppucci 1988); others assert that parents do not appear to be unduly influential (Abramovitch et al. 1995; Abramovitch et al. 1991). Similarly, some researchers have raised the concern that physician influence and the routine and ritualized nature of research participation requests may minimize patient autonomy (Lidz et al. 1984), while others have concluded that physician influence is usually exerted in a way that enhances patient autonomy (Ong et al. 1995). The general consensus is that children and young adolescents are likely to perceive less autonomy and exercise less resistance to social influence in medical decision-making situations than older adolescents and young adults (Nucci and Smetana 1996; Pomerantz and Ruble 1998; Smetana and Daddis 2002; Weithorn and Scherer 1994).

A more nuanced perspective emerges from recent studies of parental influence and family dynamics in the assent process. Snethen et al. (2006) discovered four different family involvement strategies (i.e., Exclusionary, Informative, Collaborative, and Delegated) when families were approached about involvement in pediatric research. They determined that family communication and decision-making strategies vary from parent's assuming complete control to family decision-making processes that are open and inclusive. Brody and colleagues (Brody et al. 2003; Brody et al. 2005) have examined the prevalence and nature of differences of opinion between parent and adolescents while making simulated asthma research participation decisions. They have consistently found that parents and adolescents disagree about asthma research participation as much as 30–40% of the time. Moreover, both parents and adolescents claim decision-making responsibility for biomedical research participation decisions, with parents expecting adolescents to acquiesce, and adolescents indicating they would not have to comply with their parents' wishes. These finding are similar to the attitudes expressed by adolescents in a qualitative study on enrollment in a genetic susceptibility study (Geller et al. 2003). Furthermore, adolescents in

Brody et al.'s studies have been more willing to enroll in above minimal risk asthma research than their parents are willing to permit, However, parents are generally more likely to provide permission for minimal risk asthma studies, allowing adolescents the opportunity to participate in the decision-making process, either through assent or dissent. Still, Brody et al. (2009) found that when pressed to make a joint decision, adolescents have tended to defer to parents.

Brody and colleagues (Brody et al. 2006; Brody et al. 2009) also have examined physician influence on the assent process for participation in asthma research. They concluded that both parents and adolescents endorsed an openness to input from physicians, especially when considering participation in above minimal risk asthma studies, particularly when the adolescent was female. Moreover, physician influence appears most significant when parents and adolescents hold initially discordant views about participating in the research. Families with initially discordant views were more likely to enroll in an asthma research when they had a prior relationship with the physician-investigator who also recommended research participation; otherwise, families with initially discordant views were more likely to decline enrollment.

Financial compensation as a factor in the assent process

The effect of financial compensation on participation in pediatric research has received some empirical attention (Bagley, Reynolds, and Nelson 2007; Halpern et al. 2004; Kimberly et al. 2006; Scherer et al. 2005). What is compensated and the quantity of compensation varies widely across pediatric research studies making cross study comparisons difficult (Diekema 2005). Nonetheless, studies on how child and adolescent research participants respond to offers of financial compensation have arrived at several conclusions. Bagley et al. (2007) found that older children and adolescents understood the value of money and that compensation for time and effort in research was appropriate for those older than nine years of age. Scherer et al. (2005) concluded that the financial compensation offered to potential participants in pediatric asthma protocols tended to surpass what prospective participants considered to be "fair" compensation particularly for above minimal risk studies. Scherer et al.'s analysis indicated that the financial compensation deemed appropriate by adults seemed large to adolescents and that, while not necessarily irresistible or coercive, low income families may find financial compensation a more salient factor in their participation deliberations.

Modeling the inter-relationships of contextual variables in the assent process

Understanding the dynamic interaction between the independent variables critical to an assent decision calls for more sophisticated statistical analysis techniques than are currently represented in the research literature on assent. For example, Brody, Turner, et al. (2012) employed a Structural Equation Modeling (SEM) approach which enables an investigation of the inter-relationships between perceptions of the physician investigator, study procedures, financial compensation, discomfort, risk, and benefit in pediatric asthma research. They concluded that parent and adolescent research participation decisions were influenced by these variables in similar ways. In particular, perceptions of risk, benefit, and compensation were direct predictors of research participation decisions in both adolescent and parent models. For both adolescents and parents, a positive perception of the relationship with the physician-investigator was associated with a positive view of the protocol procedures. Furthermore, a positive assessment of the protocol procedures contributed to the perception the study would be beneficial and not uncomfortable. For both parents and adolescents, a positive perception of the physician-investigator also enhanced the extent to which financial compensation was perceived as a motivator to participate.

However, there were important differences in how parents and adolescents weight these variables in the assent process. Only adolescents perceived a significant direct study benefit from the relationship with the physician as measured by their responses to questions about the quality of care they would receive and the competence of the clinician providing that care. Adolescents and parents also varied in the value they placed on perceptions of study discomfort and research risk. For both parent and adolescent models, there was a positive association between discomfort and risk, but the relationship between these variables was much stronger for parents. For parents, a lack of perceived research risk was the strongest direct predictor of decisions to permit adolescent research participation. By contrast, the adolescents' perceptions of research risk contributed about as much to their assent decisions as did their perceptions of study benefit and compensation. It appears that parents interpret asthma research risk more broadly than do adolescents, and parent perceptions of research risk have a greater weight in their research participation decisions than their perceptions of benefit and compensation.

In a similar study (Scherer et al. 2011), SEM provided insight about family factors that may influence adolescent assent to asthma research. Preliminary results from this study indicated that adolescents with positive perceptions of their family were more likely to indicate comfort and agreement with a mutually agreed upon family research participation decision. Conversely, when parents indicated they were somewhat unpredictable or harsh in their parenting, adolescents were less likely to indicate comfort or agreement with the family participation decision. Moreover, adolescents who rated themselves as more socially competent and mature felt less comfort and agreement with the family participation decision.

Like most other assent studies, these studies have methodological weaknesses and may have limited generalizability. Yet, they represent the first attempts to gain insight on the inter-relationships between important contextual variables that affect the assent process. At a minimum, the findings from these studies detail the complex manner in which research protocol features and family dynamics mediate the assent process that adolescents and their parents engage in when approached to participate in pediatric asthma research.

Studies of the Assent Process and Participant Understanding of the Elements of Research

There are few empirical data characterizing current pediatric assent processes used in the field, although a small body of qualitative research has identified ways in which parents and clinical investigators perceive the consent process (de Vries et al. 2011). Although not exclusively about adolescents, the most extensive research has been conducted with pediatric cancer patients. Findings indicate that both parents and clinician-investigators are aware of a variety of contextual considerations that complicate the assent process (Kupst, Patenaude, Walco, and Sterling 2003; Levi et al. 2000; Olechnowicz et al. 2002; Pletsch and Stevens 2001; Simon et al. 2001).

Pediatric cancer is unique among childhood illnesses by virtue of in the high percentage of patients who are enrolled in a clinical trial for their treatment (Field and Berman 2004; Kodish et al. 1998). From both parents' and clinician-investigators' perspectives, the proximity between the initial diagnosis and the request to participate in a clinical trial creates complications for the assent process. Parents report emotional distress, misunderstanding of the relationship between research and treatment, and a perception that their choices are constrained by the need for immediate and aggressive treatment (Levi, et al. 2000, Pletsch and Stevens 2001). Some parents appreciate and seek details about their child's condition, treatment options, and specifics of the research protocol, while others feel

overwhelmed by the complexity of the treatment and research options. Many parents reported the desire to include their children, particularly adolescents, in the treatment/ research discussions.

The data on the informational disclosures by pediatric oncology clinician-investigators is mixed. Simon et al. (2001) reported that clinician-investigators perceive themselves as being relatively detailed and directive when seeking assent and parental permission. They also report taking more time to discuss research as they gain experience in talking with families about their child's condition. However, many indicate that the informed consent process could be improved by separating diagnostic discussions from research consent discussions, allowing patients and families more time to consider their options. Furthermore, these clinician-investigators recommend simplifying the information given during the research consent process, and advocate that children be included in consent discussions and decisions only after they reach adolescence. On the other hand, de Vries et al (2010) reported clinicians see adolescents as inadequately competent for meaningful participation in discussions about research; do not always provide adolescents with complete information; deem parent permission sufficient; and, as found in Brody et al's. (Brody et al.,2003, Annett et al., 2004) quantitative hypothetical asthma studies, generally perceive research protocols as having minimal risk.

Qualitative observational studies of pediatric oncology informed consent encounters have confirmed that clinician-investigators utilize a range of approaches in discussions with families (Olechnowicz et al. 2002). The patient-centered approach is characterized by direct communications with and involvement of pediatric oncology patients in research participation discussions and assent decisions. In the family decision-making model, clinician-investigators seek to establish a decision-making partnership between parents and their children and emphasize parent-child collaboration. In the parent-centered approach, clinician-investigators address themselves exclusively to the parents, minimizing the patients' role in the decision-making process.

Olechnowicz et al. (2002) note that various consent approaches interact with family dynamics and family functioning in ways that have significant ethical implications. While some families find the patient-centered approach empowering of the patient and respectful of the assent process, others feel it diminishes parental authority and control. The family-centered approach, while appealing to the notion of partnership, may be difficult to implement effectively, especially in families that lack experience with this approach and endorse a different family process (e.g., traditional hierarchical family structure). Although more expedient, the parent- focused approach excludes pediatric patients from meaningful roles in the assent process and may be perceived as coercive. In short, clinicians and research investigators have endorsed disparate philosophies and developed a wide variety tactics for attaining the assent of children and adolescents in biomedical research. In doing so, it is unclear whether they are guided by their own personal perspectives, clinical intuitions, moral judgments, or other factors in determining the appropriate role of the patient in the decision-making process.

Future Directions for the Study and Practice of Assent to Research

Empirical research into the capacities of adolescents to assent to biomedical research has deepened our understanding of this process. While adolescents and their parents frequently agree about research participation, a significant proportion of adolescents and their parents disagree in their evaluation of research risk perceptions, the value placed on financial compensation, and who has the final decision-making authority. Moreover, families employ different degrees of child and adolescent involvement in research participation decision

making, and finding an effective balance of parental control and adolescent inclusion in the process can be complicated for families of adolescents (Swartling et al. 2009). Parents tend to expect their adolescents to acquiesce, and younger adolescents often do, but as adolescents mature into the middle adolescent years and begin to assert more decision-making authority over personal choice, the role of parents and adolescents in the decision-making process becomes more complex. Moreover, the degree to which an adolescent willingly agrees to participate may depend on issues that researchers have no control over, such as a positive emotional tone in the family and adolescents' perceptions of their parents' parenting style (e.g., harsh or authoritarian versus supportive or egalitarian) (Baumrind 2005; Wray-Lake et al. 2010).

Still, empirical studies of adolescent assent to research have their flaws, and conscientious consumers of this literature are careful about over-generalizing from the data we have accumulated to date. There are numerous compelling questions that assent research has not yet examined (Drotar 2008; Vitiello 2008). We have very limited empirical data regarding family decision making for families that decide against pediatric research participation.

Another crucial issue is how to assess and assure assent in younger children. The majority of studies on assent have been conducted with adolescents to the exclusion of elementary school-aged and younger children. While we have data on how physician/researchers and parents affect the decisions made by adolescents, and we have made inferences based on existing data, we do not yet know how children of different ages are variably affected by these social influences and research protocol factors. For example, we do not know how idiosyncratic factors such as the influence of financial compensation or the therapeutic misconception varies across the pediatric age range. Nor do we have data on how the assent process can or should be used in longitudinal research in which both contextual and developmental issues change over the course of the study.

There is a need for studies on how the consent process varies across cultural and language contexts (Acevedo et al. 2003). Another need is for studies that examine how assent differs for research on different diseases and how disease-specific factors and research protocol features have a direct impact on child assent. Lastly, there is a vital need to take our existing knowledge, apply it to the assent process, and then study different methods of acquiring assent. Ultimately, this type of empirically-derived data will be most useful to researchers who are designing pediatric biomedical studies and the Institutional Review Boards (IRBs) who are evaluating the assent process.

Answering these questions will require more sophisticated research designs that address some of the weaknesses that exist in assent research and that use analytic methods such as hierarchical linear modeling and structural equation modeling that are designed to more fully capture the nested relationships and the multifaceted interactive nature of the process of assent. Brody and colleagues (unpublished data) recently conducted such a study. They designed an *in-vivo* experimental study of the assent process that operated concurrently with an asthma research study on exercise-induced bronchospasm. Parent/adolescent dyads were randomly assigned to an "assent-as-usual" condition in which adolescents and parents were informed about the asthma study together or an "autonomy-enhanced assent" condition in which adolescents and parents received separate presentations of the asthma trial. Participants were asked to complete questionnaires that provided quantitative data on their perceptions of the asthma protocol, provide free-recall of the information presented to them which was later coded for analysis, and were observed as they reached a family decision about participation. The study design will enable the researchers to simultaneously evaluate the social context of assent, namely the parent/adolescent decision-making process, to

consider how this process compares under two different strategies for providing information and to assess the degree of information acquired by both youth and their parents.

The challenge for assent researchers, ethicists, and pediatric researchers is, in the face of unbounded contextual and developmental variability, to define an assent process that can be adapted for general use in pediatric biomedical research (Gibson, et al 2011, Masty & Fisher, 2008, Kumpunen, et al. 2011). In fact, given the variability in adolescent maturity, the diversity of family decision-making styles, and the logistics of seeking adolescent assent and parent permission, investigators need to use flexibility in designing an assent process. In cases of mature adolescents making minimal risk research participation decisions, it may be entirely reasonable to seek assent from adolescents outside of their parents' presence. With less mature adolescents and research that involves greater risks, family-level adolescent assent/parent permission conferences may be more appropriate. In family conferences, investigators could augment adolescent assent, by assuring parents, especially authoritarian parents, that adolescents' opinions are vital to the research endeavor and encouraging adolescents to voice their questions, concerns, and preferences.

To date, research on assent has identified key factors that researchers can assess in their efforts to develop an assent process appropriate for their individual research areas that provides information to parents and adolescents in a way that meets their respective interests, augments protocol understanding, and enhances ethical enrollment. Studies on comprehension of risks and benefits suggest that adolescents and adults often perceive research benefit where none exists. Because parents and adolescents generally have relatively little experience with this type of decision making, they need support to cognitively process the variety of parameters involved in biomedical research participation decisions. A positive relationship with a physician-investigator can mitigate concerns about research protocol procedures for both adolescents and parents, but physician-investigators must also be conscientious about alerting parents and especially adolescents to the risks of research participation, clarifying distinctions between the discomfort and risk of research procedures, and clearly articulating the prospects for personal benefit (Brody, Scherer, et al. 2012). Taking these steps are particularly important to the integrity of the research endeavor, because pediatric research participants' decisions to remain engaged in the research process may be related to *their* judgments of a study's risks and benefits rather than to the parents' or experimenters' judgments (Cox, Smith, and Brown 2007; Skinner et al. 1991). Consequently, attending to the developmental differences in perspective on risk and benefit and clarifying the purpose and probable benefits of research participation will help to ensure that both parents and adolescents do not over-estimate either the risks or benefits associated with biomedical research participation. In turn, this may improve participant retention, which is vital to the robustness, validity, and generalizability of conclusions that can be drawn from a clinical trial.

Furthermore, given the role of compensation as a variable in adolescent research participation decision making, researchers should use discretion in discussing compensation and how it is disbursed, and perhaps raise the issue of the relative importance of altruism as an alternative and perhaps more gratifying motive for research participation. The degree to which financial compensation influences research participation decisions may be minor in minimal risk studies where the amount of financial compensation is fairly modest and the risks of participation are negligible. However, above minimal risk studies that offer substantial compensation for research participation require careful scrutiny, especially in the presentation of how the compensation will be distributed. Telling a child or adolescent participant that he or she will earn $1000 for participating may result in a different response than telling him or her that he or she will receive $20 per visit for 50 visits over 2 or more years.

Lastly, and perhaps most importantly, we need to convince the pediatric research community that engaging in an assent *process* is more ethical and efficacious than a more cursory assent event that relegates children and adolescents to a passive role (Fisher 2005; Unguru, Coppes, and Kamani 2008). It stands to reason that adolescents actively involved in the research enterprise, who know what they are doing and why, will be more engaged and motivated (Cox, Smith, and Brown 2007) and provide better data and less attrition; and empirical support would further strengthen this claim.

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