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REVIEW ARTICLE

Ethical Issues in Adolescent and Parent Informed Consent for Pediatric Asthma Research Participation

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This article reviews the empirical literature related to knowledge, competence, volition, and financial compensation in the biomedical research decision-making of children, adolescents, and parents. Research findings indicate there are differences in adolescent and parent understanding and appreciation of research risks and procedures, that opinions about decision-making authority and physician influence for research participation are different in adolescents and parents, and that financial compensation can be a salient factor in the research-related decision-making process. Pediatric asthma researchers can consider these psychological factors involved in adolescent and parent research participation decision-making processes to develop effective informed consent procedures.

Keywords biomedical research ethics, informed consent, adolescent assent, research participation decision-making, pediatric asthma research

Complying with the dictates of informed consent for biomedical research and treatment with children, adolescents, and families raises a number of complex and ambiguous issues (1–3). Generally, three criteria must be met for a consent to be valid. The first, *knowledge*, requires that the consenter be given sufficient information to make a decision knowingly. Secondly, the consenter must be *competent* to make the decision and do so fully appreciating the ramifications of his or her choice. Lastly, the consent must be provided *voluntarily* and absent any coercive influence. Adults are ordinarily presumed to have the requisite maturity to provide an informed consent. Children and adolescents, conversely, are a protected population and in most circumstances are not accorded the right to consent but instead are subject to the lesser standards of dissent (the right to refuse treatment or research participation) or assent (agreement to participate which must be accompanied by parental permission) (4).

Translating the moral-ethical and legal imperatives concerning the participation of minors in biomedical research into practice has become increasingly important particularly to researchers studying asthma and asthma treatments in the pediatric population. Asthma is the most common disease of childhood and increasing in prevalence (5), making the need to develop more efficacious treatments and relieve illness burden a critical priority. Asthma research protocols often involve placebo-controlled clinical trials to evaluate promising medications, studies on medication benefits and side effects,

and education for patients and families. Many of the features of these varied studies are complex and tax the decision-making capacities of potential participants. Compared to the choices available to patients with other diseases such as cancer, where research trials dominate treatment options, asthma research participants have more freedom to choose to engage in the research process. This requires asthma researchers to attend to the practical issues of participant recruitment and retention, such as where and how participants are recruited (6, 7), how the consent process can augment or detract from enrolling participants, and how family factors can affect attrition in pediatric asthma clinical trials (8, 9).

The empirical findings regarding consent and assent to participate in biomedical research have been sparse and preliminary, particularly regarding the questions surrounding the extent to which children and adolescents can appreciate the vagaries of agreeing to participate in biomedical research or permitting a medical procedure. Initially, our understanding of the capacities of children and adolescents faced with treatment and research participation decision-making was based on developmental theory and a small number of studies conducted with healthy volunteers responding to hypothetical medical and research vignettes. Following these beginning efforts, theorizing on the capacities of adolescents to participate in research and treatment decision-making focused on the broader issues of adolescent judgment (10, 11) and the degree to which social and environmental context affects volition in research and treatment decision-making (1, 12–18). Recent research efforts, studying children, adolescents, and families are beginning to tackle these and other issues with research methodologies that have improved the ecological validity of the findings by employing participants who have an actual illness (19–28).

Understanding the abilities of children and adolescents to participate in research decisions is a key issue for researchers and health care practitioners because Federal laws establish

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special assent rights for these decisions. In most situations, these rights go well beyond the legal rights of children and adolescents to participate in treatment consent decisions. Furthermore, these enhanced rights confer specific obligations to researchers to involve the adolescent in the research decision-making process. This article reviews the empirical findings regarding knowledge, competence, and volition in biomedical research decision-making for adolescents, with specific attention to the findings related to asthma research by Brody et al., which focuses on the research decision-making of adolescents with asthma and their parents (19–23, 93). Our objective is to provide clinicians and investigators with an analysis of the key issues associated with voluntary research consent and assent for this population, identify gaps in the literature, and provide a framework for enhancing the participation of adolescents in the research decision-making process. In providing this information researchers can better understand the core components of valid informed consent and the ethical and legal factors bearing on the adolescent and parent research decision-making process.

ENSURING THAT A CONSENT OR ASSENT IS GIVEN KNOWINGLY

Researchers and health care professionals seeking consent for research participation are required to provide adequate information about the study. Research participants have the right to a description of the procedures they will undergo, the risks and discomforts they might anticipate from these procedures, the possible benefits they might receive, the alternatives available to them (including not participating in research or receiving no treatment) and a statement affirming their participation is voluntary. In contrast to the other components of an informed consent or assent that depend in large part on the capacities of the consentor, providing adequate information is an obligation incurred by the researcher.

The majority of studies in this arena focus on the larger issue of physician/researcher communications with patients. This is a voluminous literature and there are a few empirical conclusions worth considering. For example, it is widely accepted that written consent forms are tedious and difficult to read and understand, especially for people who lack medical knowledge (29–32). This has come about partly because all too often written consent forms have assumed a risk management function. When this happens, written consent forms no longer serve solely to inform prospective research participants but instead are used as a means of attempting to minimize researchers' or health care providers' liability. This condition has been augmented by recent regulations requiring HIPAA compliance and HIPAA mandated language.

Studies of verbal communications between physicians and patients have revealed several vulnerabilities for the informed consent and assent process. For example, research has suggested that miscommunication may arise between adolescents and physicians when the probability of risk is described (1, 33, 34). Moreover, studies on physician communications with children have revealed that children are minimally involved in pediatric consultations, that physician-child communications are usually social and affective in nature, and that most diagnostic and treatment information is directed at parents (35, 36). Moreover, parents tend to exert "strategic

control" over physician-child communications by filtering and modulating what children are told by their physicians, relegating children and even adolescents to a passive role in medical treatment decision-making (35–37). Similar patterns have been found in the pediatric oncology research consent process, although there is considerable variability among children and adolescent patients across the age range (28).

A variety of strategies and tactics for obtaining informed consent for biomedical research in general and with children and adolescents have been identified and debated (24, 28, 37–43). One major question currently lacking empirical data is whether adolescent participation in research decisions might be enhanced if adolescents were first approached alone rather than the generally standard practice of presenting research participation to the whole family simultaneously. Adolescents might attend more, and they might perceive more decision-making responsibility when the study is presented directly to them. Furthermore, some evidence suggests that parents will ask more questions when their child is not present at informed consent discussions (28), raising the possibility that both parents and adolescents might be better informed with separate discussions.

COMPETENCY AND THE PERCEPTIONS OF ASTHMA RESEARCH RISKS AND BENEFITS

Ethicists and informed consent scholars debate about the appropriate standards for determining whether a potential research participant has the requisite competency for research participation decision-making. From a psychological perspective, there are several variables that can be used to judge an individual's cognitive abilities and decision-making maturity. One simple measure of cognitive appreciation is a person's factual comprehension of the information provided to him or her about the protocol in which they are considering getting involved. However, a more sophisticated measure of a person's competency involves their reasoning ability; in particular their aptitude for mentally manipulating information, for inferring beyond the facts about the implications of research involvement, and for weighing and evaluating these considerations.

The empirical literature on this topic has been ambiguous. Some have concluded that relatively young adolescents have decision-making capacities in informed consent situations that are comparable to that of adults (43–45), whereas others raise doubts (13, 46). In general, as adolescents age they acquire greater cognitive and metacognitive abilities and gain more experience with making important life-impacting decisions, prompting Weithorn and Scherer to conclude that older adolescents have a cognitive potential in informed consent situations that is comparable to the cognitive abilities typically by competent adults (4).

Arguably, the most important aspect of the competence/appreciation criterion involves the apperception of research risks and benefits. Conducting biomedical research with children requires establishing a balance between research risks and benefits. Exposing minors to above minimal risk research without the possibility of a commensurate benefit, is unethical and illegal, so that when research has no direct benefit to a child, risks associated with research participation must be minimal. However, neither the concept

of research risk or benefit is well defined by federal regulations and guidelines. Minimal risk in biomedical research is formally defined as "risks ordinarily encountered in daily life" (47). Local Institutional Review Boards (IRBs) are responsible for interpreting this definition, which has resulted in disagreement, confusion, and inconsistencies in the application of federal guidelines (48). Physical considerations have dominated interpretations of the definition of risk to the exclusion of psychological, economic, or social sources of risk (48). For example, the IRB Guidebook provides several benchmark examples of minimal research procedures including urinalysis, venipuncture, EEG, allergy testing, and the use of standardized psychological tests (49). In contrast to risk, the definition of benefit associated with research participation has lacked benchmarks. Benefit can be framed in terms of benefits to the individual for participation in a research study, as the benefit to society, or both.

Furthermore, there is substantial ambiguity in the psychological literature on the differences between how adolescents and adults evaluate risk (10, 18). Some researchers have found that adolescents and adults are fairly comparable in their perceptions of personal invulnerability (50, 51). Others have concluded that adolescents may be less risk averse than adults and tend to minimize the potentially harmful consequences of occasional risk-taking behavior (13, 50). Similarly, studies of differential risk perceptions in medical and research decision-making have come to varied conclusions. For example, one study found that adolescents and adults were statistically indistinguishable from one another in their comprehension of and ability to identify risks and benefits in hypothetical medical treatment vignettes (45). Conversely, others have concluded that adolescents were limited in their capacities to identify research/treatment risks and benefits in response to either hypothetical or actual research and treatment protocols (1, 12, 52, 53).

One important consideration in the differential perception of risk between adolescents and adults may be the distinction between risk and aversion. Some procedures (e.g., using an experimental medication) may be risky but not aversive, while others (e.g., venipuncture) may be aversive and contain a significant and often unacknowledged psychological threat without being physically risky (54–56). This distinction highlights the differences between the abstract analysis of physical and invasive risk that researchers and IRBs tend to emphasize over the more immediate psychological discomfort to which children and adolescents may be more attuned. Furthermore, it is not known whether these psychologically aversive conditions have a lasting impact on patients and research participants.

These issues are important for ethical and methodological reasons. Research with adults has found differences in research risk evaluation between investigators and their participants (57, 58), and studies of actual medical treatment situations have found adults and parents of ill children having considerable lapses and faults in their comprehension of risks and benefits (52, 59). Given adult frailties in this situation and the fact that adolescents have even less experience with this type of decision-making, adolescents may need adult support when faced with research participation and medical treatment decisions. Moreover, participants' willingness to remain engaged in the research process may be re-

lated to their judgments of a study's risks and benefits rather than to the experimenters' judgments (60). Consequently participant retention, which is vital to the robustness, validity, and generalizability of conclusions that can be drawn from a clinical trial, is contingent, in part on avoiding these misconceptions.

One factor that may contribute to misunderstandings about research and treatment risks and benefits may be a lack of appreciation for differences in risk perceptions among parents, adolescents, and physicians. Our studies of this issue with adolescents who have asthma, their parents, and physicians who treat and study asthma have provided some important insights (19, 21). Adolescents and their parents rate the risk and aversion potential of minimal risk protocols and procedures fairly comparably, with one exception. Our data indicate that parents and physicians are less concerned about the risk and aversion of venipuncture than adolescents. One difference has emerged in our analyses of above minimal risk research. Both physicians and adolescents seem less concerned about the risks associated with experimental medication than parents. Our studies suggest that parent and adolescent ratings of benefit are fairly similar, although parents tend to be more hopeful in their perceptions of benefit. Curiously, adolescents and parents sometimes infer they will derive benefit from research procedures (e.g., placebo) that physicians rate as having little beneficial potential. Awareness of differences in perspective on risk and benefit, especially for the procedures of venipuncture, experimental medication, placebo, and attention to clarifying the purpose and probable risks and benefits of these procedures during the consent process will help ensure that parents and adolescents do not overestimate either the risks or benefits associated with asthma research procedures.

VOLITION AND AUTHORITY IN ASTHMA RESEARCH PARTICIPATION DECISION-MAKING

One essential element of a valid informed consent is that the consentor be acting voluntarily. There is a wide range of opinions about whether adolescents possess the requisite autonomy to exercise volition and should have the authority to make research participation and medical treatment decisions. In most circumstances, federal regulations governing research authorize parents to provide permission, with adolescent assent or dissent generally considered binding. Some maintain that for certain types of minimal risk biomedical research and particularly in the case of mature minors requiring parental permission is unnecessary (61) and may inappropriately constrain adolescent research participation. Similarly, minimal risk research on important yet sensitive issues like HIV or substance use may be impeded by privacy concerns when parental permission is required (3). In fact, there are circumstances where parental consent may be waived because it is either an impracticable requirement or represents an unreasonable means of protecting a child. Many states have legislation that authorizes adolescents to seek health care and make independent medical decisions (62), and federal regulations specifically reference these laws as a means of determining circumstances where minors may provide an independent consent for biomedical research participation. Adolescents may also be authorized to consent independently

for research participation in some situations, such as when they do not meet the regulatory definition of a child (47).

Many IRBs support revising federal regulations to allow adolescents to consent independently to some kinds of research, including anonymous surveys, biomedical studies involving only venipuncture, minimal risk research on mature minors, and FDA approved medication for pediatric patients (63). The Society for Adolescent Medicine (SAM) endorses this position and has authored guidelines articulating detailed analyses and recommendations of the situations under which adolescents may ethically provide informed consent for research participation. The SAM guidelines also take note of situations when parental waivers for both minimal and above minimal risk studies may be appropriate and alternative strategies that might permit ethical participation of adolescents in research when parental permission is unrealistic (64). Moreover, the ethical considerations inherent in allocating greater adolescent decision-making autonomy for non-beneficial medical research have recently received extensive discussion, and highlight the existence of a spectrum of views (65, 66).

Whether it is wise to extend this degree of self-determination in biomedical research and treatment contexts depends in part on the capacities adolescents have for making independent decisions and contending with the variety of social influences that could compromise their volition. The normative subservient role of adolescents in family settings and the significant power differentials that exist in relationships between adults and adolescents in most institutional settings, especially medical settings, is likely to greatly influence perceived freedoms and decision-making autonomy. The degree of autonomy granted to adolescents varies across culture, gender, and as adolescents age. In general, young adolescents tend to defer or submit to parental authority, although by the middle adolescent years they begin to assert, and attempt to exercise, greater control over personal choice. Adolescent boys are typically accorded more autonomy at an earlier age than are girls. Still, the social norm for compliance to authority among adolescents (and adults) can result in the assent process for research participation being relegated to an act of submission rather than an exercise of independent choice (14, 67).

The empirical literature on this topic has been sparse and inconclusive. While some studies have found adolescents to be deferential to parental preferences in adolescent treatment decision-making (15, 68) others concluded that parents did not appear to be *unduly* influential (1, 12). Conversely, concern has been raised that physician influence, along with the routine and ritualized nature of research participation requests, may minimize patient autonomy (69). Studies on the influence of physician communication have found that patients typically heed treatment recommendations provided by physicians although this influence is usually conducted in a way that enhances patient autonomy (69, 70). In sum, and abstracting from a wide variety of studies, the general consensus is that young adolescents, especially girls, are likely to perceive less autonomy and exercise less resistance to social influence in medical decision-making situations than older adolescents and young adults (4, 71–73).

Our research on this issue with adolescents with asthma and their parents responding to a variety of simulated asthma

research protocols has provided an even more nuanced perspective. We have reasoned that it can be difficult to protect and honor the rights and responsibilities of parents and adolescents when they differ in their opinions about biomedical research participation. Consequently, understanding the prevalence of differences of opinion between parent and adolescents and the contexts in which they are likely to emerge is necessary to address situations that may impede the ethical conduct of research with adolescents. Our studies have indicated that parents and adolescents disagree about asthma research participation as much as 40% of the time (20–22). For example, adolescents in our studies have been more willing to enroll in above minimal risk asthma research than their parents would be willing to permit. Our analyses consistently indicate that both parents and adolescents claim decision-making responsibility for research participation decisions with parents expecting adolescents to acquiesce and adolescents indicating they would not have to comply with their parents' wishes. However, for minimal risk research; parents are generally more likely to provide permission, allowing adolescents the opportunity to participate in the decision-making process, either through assent or dissent. Still, when pressed to make a joint decision in our studies, adolescents have tended to defer to parents.

Trust in physicians has been identified as an important factor in some research participation decisions (21, 74) and our research has found that physician guidance seems to be important to families contemplating asthma research participation. Parents and adolescents in our research endorsed an openness to input from physicians, especially when considering participation in above minimal risk asthma studies (22). Both parents and adolescents recognized the increase risk associated with protocols rated as above minimal risk, and they also reported greater interest in physician's views of these studies, although this finding was strongest for both parents and adolescents when the adolescent was female.

VOLITION AND FINANCIAL COMPENSATION FOR PARTICIPATION IN ASTHMA RESEARCH

Research ethicists have raised concerns that financial compensation for biomedical research participation may constrain voluntary decision-making. Financial compensation for research participation poses the potential to exploit people with fewer economic resources, presents the possibility that financial compensation may lead prospective participants to overlook potential risks in favor of financial gain, and raises the prospect that financial compensation may undermine altruistic motives (75–80). Others support providing financial compensation arguing that research participation imposes costs on participants and that monetary payments are offers that expand options, not threats that coerce (81–86).

Offering financial compensation to children and adolescents for research participation raises even more ethical questions (87–89). Children and adolescents may find relatively small amounts of money irresistible or enough to overlook the risks of a study. Moreover, the promise of monetary gain may compromise volition by deterring children and adolescents from withdrawing from participation when they believe they are compelled to continue participation to receive their "pay." Although researchers and ethicists are aware of the need for

additional safeguards, there are few guidelines. In the course of our examination of numerous asthma research protocols we have found research compensation ranging from no compensation or a small gift certificate to financial compensation ranging from \$20 to \$2,400. The varied requirements of these studies make them difficult to compare to one another, but in general, studies requiring more time, effort, and discomfort generally offer greater compensation.

Our research on this issue suggests that the financial compensation offered to potential participants in the pediatric asthma protocols we sampled, particularly in more complex studies that place greater burden (e.g., time commitment, invasive procedures) on participants, tends to surpass what prospective participants anticipate to be "fair" compensation (23). However, we have not ascertained that compensation has an irresistible or coercive affect on research participation decisions. In fact, financial compensation is only one consideration among a complex variety of factors that adolescents use to decide about research participation. Still, our findings do suggest that the amount of financial compensation deemed appropriate by adults seems large to adolescents and that low-income families may find financial compensation a more salient factor in their participation deliberations. The psychological effects and ethical implications of financial compensation may be minor in minimal risk studies where the amount of financial compensation is fairly modest and the risks of participation are negligible. However, greater caution must be exercised in above minimal risk studies that offer substantial compensation for research participation. Providing financial compensation that exceeds expectations may not be unethical, particularly if the compensation does not unduly influence enrollment decisions or compromise pediatric research participants' autonomy. However, paying careful attention to avoid "over-compensation" may help to foster altruistic and intrinsic motivations that enhance enrollment and retention.

THE LIMITATIONS AND APPLICATIONS OF OUR CURRENT KNOWLEDGE OF PEDIATRIC INFORMED CONSENT

There are strengths and limitations to the body of research reviewed above. Only recently have studies been conducted with clinical samples of adolescents with asthma and their parents evaluating a variety of asthma research protocols. This has enhanced the ecological validity and the applicability of these findings. Conversely, this research still uses only small samples that don't adequately represent the range of socioeconomic and ethnic groups involved in asthma research and treatment. Also, these studies continue, for the most part, to use simulated assent processes and not a naturalistic assent/consent procedure. Consequently the conclusions presented here represent participants' beliefs about how they would act in a research setting, not necessarily their actual behaviors.

We do not know to what extent the research examined here on research decision-making applies to medical treatment situations. Medical research decisions are often quite similar to medical treatment decisions, so it is tempting to infer that adolescents and families facing medical treatment decisions bring similar capacities to these decisions as they do to research participation decision-making. However, treatment

decisions and research participation decisions differ in fundamental ways that may have substantial affects on knowledge provision, appreciation and competence to process the relevant information, and the capacity to respond voluntarily to the options available. While treating health care providers have a single goal of providing optimal care for their patient, medical researchers attempt to meet what can be competing goals of relieving suffering, but also advancing knowledge through research, which may require a research participant to receive less than optimal medical care. Hence, the types of communications researchers have with prospective participants are potentially much more complex than the conversations between physician and patient. Moreover, potential research participants are prone to the *therapeutic misconception*, which is the predilection to believe that enrolling in a clinical trial will certainly provide therapeutic benefit and that experimental treatments are certainly better than regular treatment options (90, 91). Coupling this with the consistent findings, across a variety of studies, that research participants frequently misunderstand biomedical research procedures, risks, and benefits, suggests that adolescents and their parents may be inclined to perceive benefit from asthma research participation even when no benefit exists or is intended.

It is important for researchers and clinicians to put concerted thought into how to describe research to their potential participants. Consider that adolescents may be more attuned to the aversive (e.g., venipuncture) and bothersome (e.g., keeping a log) qualities in research protocols than either parents or researchers. As pediatric asthma researchers recruit and enroll adolescents and parents in studies, they should be sensitive to the interpersonal process of establishing trust and credibility with both parents and adolescents. These interpersonal processes are not static and are likely to unfold over the duration of the study. Consequently, rather than a one time conversation and consent signing event, discussions of research procedures, risks, and benefits may need to occur regularly across the duration of longer studies with adolescent participants and their parents.

Balancing parent's rights with adolescent volition also can challenge the asthma researcher. Given the potential for struggles around decision-making autonomy and participation voluntariness, researchers should attempt to establish reliable procedures for physician dialogue with adolescents and parents that enhance participant knowledge and appreciation of research participation, while simultaneously preserving and respecting their autonomy. There may be no single procedure that is best for all circumstances and in the absence of hard empirical data, researchers will need to analyze the demand characteristics of their research protocol. Developing a procedure that works best for approaching adolescents and parents may be driven by research characteristics such as the risks inherent in study participation or the duration of study procedures. These issues may be less problematic in the case of minimal risk research. However, in above minimal risk research, a conscientious researcher must consider how factors such as the type of risk, gender, child/adolescent age and maturity, and the sensitivities of parents may dictate one assent seeking procedure over another. For example, parents are more concerned about research risk than adolescents and will frequently decline if approached first for permission for their

adolescent's participation in above minimal risk research. As a result adolescents would have a limited opportunity to participate in decisions concerning above minimal risk research participation. In some cases this may be wholly appropriate; in others it may be important to address families together so that adolescents can be included in decisions about research participation.

Lastly, researchers should be judicious in their use of financial compensation for research participation with adolescents. Even minimal wage calculations may result in dollar values that, though not necessarily coercive or unethical, exceed participants' expectations. This creates the potential for compromising child and adolescent volition, for conflict between parents who prefer to not engage in the research and adolescents who want to earn the money, and for participants to focus on compensation and neglect research risks. Moreover, care should be taken to describe compensation accurately. Adolescents will likely respond differently to biomedical research offers to compensate them with \$1000 versus offers to compensate them with \$50 a visit for 20 visits over two or more years.

These considerations are important because they enhance the credibility and integrity of researchers and clinicians, but also because attending to these ethical issues may affect retention and compliance of children and adolescents in biomedical research. Asthma research and treatment are already plagued with high drop-out rates and treatment non-compliance (9, 92). Dissatisfaction with informed consent disclosures may heighten poor research retention and compliance (93). Carefully attending to the rights of adolescents and their parents is apt to improve the research endeavor for both participants and researchers.

In summary, obtaining valid informed consent for research participation with adolescents and parents requires unique considerations by the research team. The empirical knowledge to date suggests that differences exist in adolescent and parent understanding and appreciation of research risks and procedures, that authority and influence for research participation are different in adolescent and parents, and that compensation can be a salient factor in the research-related decision-making process. Investigators must develop a sense of the knowledge base that adolescent and parent participants inherently bring to the consent procedure, sense how adolescents and parents apprise the activities associated with research participation, and be sensitive to the voluntariness of adolescents' and parents' decisions. This requires the investigator to temporarily put aside pressures they may feel to recruit and enroll participants to ensure that these ethical imperatives are maintained.

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