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Parental Permission and Child Assent in Research on Children

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Grounded on the ethical principle of respect for persons, parental permission and child assent function together to protect the child and to foster the development of the child's self-determination. Although both parental permission and child assent involve the same components of information sharing, comprehension, and voluntariness, how these three components are understood and operationalized should differ depending on the developmental level of the child. For example, the amount of information that a child must comprehend to provide meaningful and developmentally appropriate child assent (or dissent) should be allowed to vary with the age and maturity of the child. By understanding child assent together with the important protections of parental permission, child assent does not need to be burdened with the same informational and process requirements. As a result, the age (as a proxy for developmental stage) at which a child is deemed capable of assent would be lower (i.e., 5 to 7 years old). By assuming a lack of capacity, the potential arises to dishonor and disregard a child's wishes by failing to solicit meaningful assent or dissent. Further research needs to be done on how best to obtain truly informed and voluntary parental permission and child assent for research participation.

INTRODUCTION

The ethical justification for the enrollment of human subjects in research requires, at a minimum, two procedural safeguards: prior scientific and ethical review by an independent committee followed by the informed and voluntary consent of the prospective research participant.

For research involving children, both of these safeguards are modified given the vulnerability of children to undue influence

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†Abbreviations: DMCI, Decision-Making Control Instrument; FDA, Food and Drug Administration; HHS, Health and Human Services; MacCAT-CR, MacArthur Competence Assessment Tool for Clinical Research.

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or coercion.[1] There are limits set to the risks that a child may be exposed to in research that does not offer a prospect of direct benefit and limits set to the justification of risks that a child may be exposed to in research that offers a prospect of direct benefit.[2] As discussed below, these additional requirements for research involving children arise from the difficulty in applying a model of self-determination to parental permission and child assent.

The requirement for parental permission and child assent is an application of the more general principle of respect for persons as articulated by the National Commission in The Belmont Report [1]. The principle of respect for persons affirms the primary importance of allowing individuals to exercise their moral right of self-determination. However, this principle also implies that persons who are not capable of self-determination should be protected, if necessary, by requiring permission from an individual authorized to consent on their behalf. Parents or legal guardians serve this important function for children who are younger than the age of majority. In other words, the doctrine of "informed consent" has only limited direct application in pediatrics.

Only persons who have the appropriate capacity and are legally empowered can provide effective informed consent for themselves. In all other situations, parents or other surrogates provide permission for diagnosis and treatment of children with the assent of the child whenever appropriate [2]. Thus, parental permission[3] serves to protect a child while the child's capacity for self-determination matures.

The principle of respect for persons requires that both the child, if capable, and the parent exercise voluntary choice concerning research participation. However, the nature of the choice and the information necessary to exercise that choice differ. Because of the protective function of parental permission, parents must be provided with detailed information concerning the nature and purpose of the research, the risks and benefits that may reasonably be expected, and any alternatives to research participation. In other words, the purpose of parental permission is to protect a child from assuming unreasonable and unjustified risks given his or her immaturity. To accomplish this task, a parent must receive all of the necessary information and be afforded the same opportunity to make a voluntary choice as would be provided to an adult making a personal decision to enroll in a research study.

Child assent must be linked to a protective mechanism such as parental permission, even if the requirement for parental permission has been waived.[4] As such, the meaning and function of child assent should be understood in the context of the protection afforded by parental permission [3]. The linked requirement for parental permission means that we do not need to burden child assent with the same informational and decision-making standards as adult informed consent. Thus, child assent is limited to a simple preference in favor of research participation.[5] A child's inability to understand otherwise important informational elements of informed consent, such as any reasonably foreseeable risks, does not establish that a

[1]See FDA regulations at 21 CFR 56.111b. For all FDA references regarding IRB approval, parental permission, and child assent, comparable regulations (45 CFR 46) exist for research that is not FDA regulated but falls under the purview of other agencies within the Department of Health and Human Services.

[2]See FDA regulations at 21 CFR 50.51 and 21 CFR 50.53 for research without a direct benefit, and 21 CFR 50.52 for research that holds out the prospect of direct benefit.

[3]Parental permission will be used in this article to refer to permission from either a parent or legal guardian.

[4]FDA regulations do not allow a waiver of parental permission except for research that is conducted under the emergency exception from informed consent found in FDA regulations at 21 CFR 50.24. HHS regulations allow for a waiver of parental permission if the research is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects, as noted at 45 CFR 46.408(c).

[5]See 21 CFR 50.3(n) "Assent means a child's affirmative agreement to participate in a clinical investigation."

child is incapable of agreeing or disagreeing to research participation. If children are required to fully understand research in order to provide adequate assent, the capacity required will approach that of an adolescent and thus limit younger, less cognitively developed children from participating in the assent process [4]. Once we accept the premise that the assent of younger children should not be held to the same informational standard as parental permission (or even adolescent assent), the challenge is to identify those elements that are important for adequate and voluntary child assent. In addition, the related question as to when a child develops the capacity to provide meaningful and developmentally appropriate child assent (or dissent) must be addressed. For example, when does a child develop the capacity to understand that a proposed intervention does not offer him or her any prospect of direct benefit? In other words, when would a young child be sufficiently mature to realize that failing to require assent (or to respect dissent) in the absence of any prospect of direct benefit shows disrespect for the child's wishes?

In this article, we will review the empiric evidence regarding parental permission and child assent, including both comprehension of information and assessments of whether research participation is voluntary. Differences between child and adolescent assent will be highlighted, and the effects of compensation on assent and permission will be reviewed. Finally, we will consider circumstances in which parental permission or child assent may be waived.

PARENTAL PERMISSION

Permission means the agreement of a child's parent(s) or guardian to the participation of their child or ward in a clinical investigation.[6] Parental permission is held to the same standards as informed consent and is required (absent a waiver) for research involving children. The disclosure of information required for voluntary and informed parental permission is the same as that required for informed consent and includes a discussion of the potential risks, benefits, and alternatives to research participation. The permission of one parent is sufficient for research involving minimal risk and greater than minimal risk but presenting the prospect of direct benefit to the child participant. For research involving greater than minimal risk without the prospect of direct benefit to the child and research that is not otherwise approvable absent review by a federal panel, the permission of both parents is generally required.[7]

The limitations of the informed consent process for research participation have been well-described in the literature [5,6] and are beyond the scope of this article. Parental permission for the participation of children in clinical research is considered valid if it is informed and voluntary. As with informed consent, threats to the validity of parental permission include a failure to recognize that the research protocol is designed to answer a scientific question rather than to offer individualized clinical benefit (therapeutic misconception). Evidence of the therapeutic misconception in the setting of parental permission includes lack of clarity about research versus clinically indicated procedures [7] and conflicts of interest that arise when the treating physician is also an investigator [8]. Therapeutic misestimation may also occur if subjects overestimate the benefits or underestimate the potential risks associated with a particular study.

Studies that purportedly evaluated the ability of parents to provide valid informed permission have generally assessed parents' memory of the study from months to years after the time the child participated. The results of studies in which parental permission was assessed based on recall have generally reported a therapeutic misconception, a therapeutic misestimation, or both. But it is un-

[6]21 CFR 50.3(r). As required under § 50.55(f), permission by parents or guardians must be documented in accordance with, and to the extent required by, § 50.27, and thus must include the elements of informed consent required by § 50.25."
[7]See the conditions under 21 CFR 50.55(e)(1) and (e)(2).

clear whether these problems indicate that an informed decision was not made at the time permission was given or merely indicate a limited ability to recall past events. For example, parents of infants who were enrolled in a study designed to evaluate the effect of continuous infusion morphine or placebo on the neurologic outcome of premature infants were asked a series of open-ended questions designed to assess the purpose, benefits, risks, and voluntary nature of the study. Only 3 percent of parents were able to answer these questions accurately, but the time interval from signing the parental permission document to completion of the questionnaire ranged from 3 to 28 months [9]. The model of parental permission used in a European study held that valid permission was obtained when four criteria were met: parents were able to think clearly (e.g., were not overwhelmed with emotion), sufficient information was received to make an informed choice, parents understood the information presented, and parents understood that they were free to withdraw [10]. The authors reported impairment in at least one of these domains in 70 percent of cases, but the relationship between these criteria and valid permission may not be empirically established, and again parents were interviewed months to years after the initial research. A smaller study in which parents were interviewed within 10 days of the initial intervention and were allowed to refer to the parental permission document during the interview if they desired demonstrated good understanding, appreciation, and reasoning about research participation, suggesting that poor recall may have been partly responsible for the results of previous studies [11].

Tait et al. interviewed parents who had been approached for permission to allow their children to participate in an anesthesia or surgery study within approximately 1 day of being approached for permission to determine whether they understood 11 elements of consent [12]. Although parents perceived their overall understanding of the elements of consent as high, the assessors' measures of understanding were significantly lower. This finding may be explained by the possibility that a parent's perception of understanding at the time of the decision may be high, even though the parent may be unable to recall the facts on which that decision was based. Parents who agreed to allow their children to participate had greater understanding than parents who did not consent. Other predictors of understanding included education level, clarity of disclosure, having a child in previous study, the age of the parent, whether the parent listened to the disclosure, and the degree to which the parent read the consent document. A small study also suggested that parental perception of adequate time to decide about research participation was associated with willingness to enroll the child in research [13].

Most studies of parental permission to date have focused on whether parents understood informational elements of informed consent, such as risks, benefits, and alternatives. Less is known about the voluntariness of such decisions, despite its potential importance from both an ethical and legal perspective. Previous research has indicated factors that may influence parental decision-making about research participation. These include demographic characteristics, previous experience with a similar decision, concern about upsetting medical personnel, time pressure, and the amount of information provided [14-16]. However, research related to parental voluntariness has generally either been qualitative or focused on whether parents understood (from an informational perspective) that participation is voluntary and they can choose to withdraw. In qualitative studies, parents of children with cancer reported high levels of distress that they perceived made discussions about research participation more difficult, and many parents perceived an inadequate discussion of the research aspects of treatment [17,18]. They also perceived few alternatives with respect to treatment or clinical trial enrollment [18,19]. Particularly in the setting of serious illness, the available options may be limited, leading some authors to conclude that voluntariness may also be compromised [20,21], though the ability to make a voluntary choice is not per se related to the number of treatment options.

Most studies of voluntariness have lacked a careful operational definition of the concept of voluntariness. The only validated empiric instrument to measure voluntariness is the Decision-Making Control Instrument (DMCI†) [22]. The DMCI contains nine parent-reported items that assess perceived voluntariness. The instrument defined voluntariness as control over the decision about whether to agree to a research or treatment protocol. Data collected with this instrument indicate that less formal education, male gender, minority status, and not having previous experience with a similar decision was associated with lower perceived voluntariness. In a multivariate regression analysis, education, minority status, gender, external influence, and too little information remained significantly associated with voluntariness. Parents who reported lower voluntariness also perceived more external influence and time pressure, had more concern about the child's care being negatively affected if they declined, and perceived that they had either too much or not enough information about the decision [23].

More empiric work is needed to address multiple issues relating to parental permission and voluntary decision-making. Previous research suggests that there is variability in what role parents prefer to assume in treatment decision-making, but most parents preferred shared decision-making with medical personnel instead of perceiving that they were either solely responsible or not responsible for the decision [24,25]. Little is understood about the relationship between decision-making autonomy and measures of understanding or voluntariness. Additionally, less is known about predictors of voluntariness in potentially vulnerable groups or whether family members or medical staff have a greater influence over perceived choices.

Limited options exist to improve the quality of permission. When the general timing of a particular event is known, it may be feasible and advisable to obtain permission in advance [9,10]. However, if permission is obtained during times of stress, concerns about the validity of permission are often raised [10]. In such situations, a technique such as continuous permission in which information is given to research participants at different stages in a trial may improve the quality of permission [26]. For example, investigators were able to obtain parental permission within 6 hours of delivery for the use of induced hypothermia in term infants at risk for perinatal hypoxic-ischemic brain injury [27]. A multimedia presentation has also been shown to improve parents' perception of informed permission [28] and comprehension of information disclosed [29]. However, the initial information provided to a parent must satisfy all of the required elements for informed consent.

CHILD ASSENT

As noted earlier, assent is defined simply as a child's affirmative agreement to participate in a clinical investigation. The definition goes on to stipulate that mere failure to object may not, absent affirmative agreement, be construed as assent. The regulations specify factors that should be taken into account when assessing capacity, including age, maturity, and psychological state. Assent may be waived if the child is judged incapable of providing it or if the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the child's health or well-being and is only available in the context of the research.[8] This waiver of assent reflects appropriate parental authority to guide a child's health care when a research intervention holds a prospect of direct benefit that is not otherwise available.

The regulations do not specify the informational elements required for assent. In 1978, the National Commission noted four essential elements for obtaining informed and voluntary assent in individuals with limited capacity [30]. According to their recommendations, the assenting individual

[8]See 21 CFR 50.55 (b) regarding factors that should be assessed, and 21 CFR 50.55(c)(1) and (c)(2) for conditions under which assent may be waived.

must 1) know what procedures will be performed; 2) choose freely to undergo the procedures; 3) communicate this choice unambiguously; and 4) be aware of the option to withdraw. Discussing assent in the pediatric population, William Bartholome outlined four essential elements: 1) a developmentally appropriate understanding of the nature of the condition; 2) disclosure of the nature of the proposed intervention and what it will involve; 3) an assessment of the child's understanding of the information provided and the influences that impact the child's evaluation of the situation; and 4) a solicitation of the child's expression of willingness to accept the intervention [31]. These elements of assent reflect the basic provisions for informed consent stated in the Belmont Report, modified to reflect the child's developing capacity. In essence, a child should understand why he or she is being asked to participate and what will be his or her experience if he or she decides to participate. During this conversation, the investigator should assess a child's understanding of these facts and the context in which the child is evaluating these facts. Finally, the child must agree to participate. It should be noted that these elements do not include much of the information required for parental permission, such as the reasonably foreseeable risks and benefits, and appropriate alternate procedures or courses of treatment, reinforcing the importance of parental permission for understanding the role of child assent.

Considerable disagreement remains about many fundamental components of assent, including: the age at which investigators should solicit assent from children; how to resolve disputes between children and their parents; who should be involved in the assent process; the relationship between assent and consent; the quantity and quality of information to disclose to children and their families; how much and what information children desire and need; the necessity and methods for assessing both children's understanding of disclosed information and of the assent process itself; and what constitutes an effective, practical, and realistically applicable decision-making model.

Several studies have examined comprehension of research studies by children and adolescents, using the typical elements of informed consent to assess understanding. Overall, the research demonstrated that children as young as 7 to 8 years old generally understand concrete concepts such as the freedom to withdraw, the freedom to ask questions, and the potential benefits of the research [32,33]. One study disagreed, however, citing poor understanding of most aspects of the studies in children younger than 9 years [34]. Comprehension of research goals and procedures, risks, and alternatives are generally not as well understood [32-35]. While one study reported that older children understood more of these concepts than younger children [32], another reported that chronologic age (between 7 and 20 years) was not related to knowledge of the elements of informed consent [33].

Each of these studies, however, has important methodological limitations that make the results difficult to interpret. For example, the study by Hurley et al. [32] enrolled 178 children between the ages of 8 and 12 years and was conducted in conjunction with an observational study of how children respond to peer provocation. After debriefing, the children's perceptions of voluntary assent, their understanding of what they would be doing and why, their belief in voluntary participation and freedom to withdraw, and their comprehension of confidentiality were assessed. However, the authors note that children who had difficulty understanding the simple assent instructions were excluded from the study, and the study did not use any validated instruments to assess comprehension.

The studies by Susman [33] and Ondrusek [34] were small and enrolled children in a wider age range. Basic questions that were explored in both studies covered the purpose of the study, procedures, potential harms and benefits, and the right to withdraw. Assessments were performed using either a structured or semi-structured interview. Susman et al. primarily utilized a binary coding system, whereby the elements were coded based on whether the participant had "cor-

rect" knowledge of that element. Procedures or risks were coded yes if the participant knew 50 percent or more of the stated information. The article by Ondrusek did not specify how the responses were coded or the demographic or socioeconomic backgrounds from which the children originated. Neither study explained how the "correctness" of the participant responses were assessed or utilized validated instruments for assessing understanding.

The study by John et al. [35] utilized younger children, with a mean age of 7 years. Children were enrolled in a study examining the persistence of antibodies after receiving two different booster vaccinations for diphtheria. The follow-up study involved a single venipuncture and an assessment of their understanding of the study. The study used either closed-ended questions or open-ended questions with responses categorized. Following venipuncture, 59 percent of the children had grasped some aspect of the reasons for the venipuncture, with nearly 1/3 mentioning that the blood sample had been obtained to assess protection against various diseases.

In recent years, there have been attempts to use a more standard measurement to determine children's understanding of research. For example, Koelch et al. [36] reported on a pilot study to adapt the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) for use in children. Initial studies with the instrument demonstrated that its use was practicable, that the time required was acceptable, and that interrater reliability was excellent in children. However, there is no threshold for a competence score in the MacCAT-CR, and its use has not been validated in a larger pediatric population. For the complex judgment about a person's decision-making capacity, the threshold could be set based on its relevance to the research project and its risks. Children performed less well than parents on this test, but clinicians performing a global assessment rated all children as competent. The differences between assessment by clinicians and the low scores obtained in the MacCAT-CR suggest that investigators believe that children may be capable of assent even if they do not understand the research completely.

Among pre-adolescent children, limited data indicate that the majority of parents and a substantial number of children believe that the parent should make the decision about study participation [35], although many parents believe the child should be involved in the process. Families appear to vary in the stage at which, and degree to which, children should be involved. Factors that contribute to a greater likelihood of joint decision-making include increased age or maturity of the child, more open communication between parents and children, and decreased perceived risk of the research [37]. These data are consistent with the view that parental permission and child assent should be understood in relation to each other. Broadly, assent can be understood to evolve from a choice by young children that is largely dependent on the parent's decision, to joint decision-making as children mature, to a largely independent decision made by an older adolescent with parental affirmation [4].

There appears to be little data in the literature that specifically measures the voluntariness of child assent or the factors that may contribute to whether children perceive their choice as voluntary. Some commentators report that voluntariness may be compromised in children due to their belief that failure to complete the study would displease others [34], but it is unclear that parental influence over a young child's decision is inappropriate. In addition, seeking the approval of authority figures is a developmental stage that is necessary and appropriate for pre-adolescent children [38].

Adolescent Assent and Consent

Many states grant certain classes of mature adolescents the right to consent to treatments or procedures involved in a clinical investigation for some disorders or conditions. These mature minors would not meet the definition of children under § 50.3(o) and thus would not be subject to the requirements of 21 CFR 50 subpart D. Simi-

larly, minors deemed "emancipated" by state law would be subject to the same exception. Mature or emancipated minors would be allowed to consent to participation in FDA-regulated research without the need for parental or guardian permission. Most, but not all, states allow adolescents who are minors to consent to medical care for their child, even if the adolescent is not considered mature or emancipated by state law.

A different model of assent is necessary for adolescents, because many adolescents have the capacity to understand important informational elements in a research study in a manner similar to adults. Available evidence suggests that the ability to understand medical decisions among adolescents greater than the age of 13 is similar to that of adults [12,39,40]. Adolescents as young as 12 years old may be less likely to disclose personal information if they know that their disclosure may result in a break in confidentiality [41]. However, executive function among adolescents is not fully developed, and as a result, adolescents' judgment may be more prone to distortion than their adult counterparts [42]. Another study suggests that adolescents may have an initial tendency to underestimate the risks of genetic susceptibility research, unless asked to personalize the implications of uncertain test results, or whether and how to share results with others [43]. Adolescents questioned about a hypothetical study were more likely to provide lower risk ratings for procedures than their parents [44]. These data suggest that there remains an important role for parental permission even though adolescents may be able to assume responsibility for deciding whether to participate in research.

Estimates for the rate of concordance between adolescents and their parents on whether adolescents should participate in research range from 26 to 40 percent across a variety of protocols [44,45]. Adolescents appear significantly more willing than parents to enroll in above-minimal risk research [45]. Interestingly, despite this discordance, both adolescents and their parents claimed ultimate responsibility for the participation decision [44].

Compensation for Research on Children and Adolescents

Compensation for participation in research is a common practice for research studies that involve both younger children and adolescents. However, there is little research on the effects of this compensation on permission or assent. Incentive payments are often seen, however, as essential to the recruitment and retention of pediatric study subjects [46]. A number of different types of compensation for parents are used in clinical studies, including material or monetary compensation such as reimbursement for travel, parking, or inconvenience. However, there is concern that payments to parents for their child's research participation could potentially influence parents to decide in favor of participation without regard for the child's wishes, because there is no personal risk to the parent. However, there are no data that support this concern. The European Union prohibits inducements in pediatric trials, either for the parents, legal representatives, or children, but allows parents or legal representatives to be compensated for their time and expenses [47]. With respect to children and adolescents, the American Academy of Pediatrics recommends the giving of gifts, instead of money, as a token of appreciation after the child has completed (or withdrawn from) the trial [2], but many institutions do not appear to follow this practice [48]. While this model may be appropriate for younger children, remuneration using a wage model based on time or effort (e.g., a percentage of trial visits or procedures that have been completed) may be more appropriate for older adolescents [46].

WAIVING PERMISSION AND ASSENT

Both parental permission and child assent may be waived under the emergency research provisions found at 21 CFR 50.24. Research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent can proceed when certain criteria are met and additional protections are in place. These protections in-

clude public disclosure, consultation with representatives of the communities in which the investigation will be conducted, and the use of a data monitoring committee. This exception has been used successfully for a pediatric resuscitation trial open to any child younger than the age of 18 [49]. A previous study of parents of children in the pediatric intensive care unit demonstrated that inpatient pediatric resuscitation research is feasible using handouts to inform parents of a study and by providing a prospective opportunity to opt out [50,51]. Every effort must be made to respect the parents' involvement in such studies even if a decision must be made to initiate experimental treatment prior to obtaining fully informed permission.

HHS regulations at 45 CFR 46.408(c) allow for a waiver of parental permission if the research is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children). FDA regulations do not allow for such a waiver for FDA-regulated clinical investigations [52]. Absent an open and transparent process of establishing an appropriate surrogate decision maker, parental permission should not be waived for FDA-regulated clinical investigations. There are limited empirical data on the application of the HHS waiver [53] or on protections that are substituted for parental permission. Both FDA and HHS regulations allow assent to be waived if the research offers a therapeutic benefit to the child that would otherwise be unavailable to them. Although the intent of this waiver is to reflect the authority of parents to direct the health care of their children independent of their wishes, we know of no data on the extent and appropriateness of the use of this assent waiver.

CONCLUSIONS AND OUTLOOK

The principle of respect for persons requires that both the child, if capable, and the parent exercise voluntary choice concerning research participation. However, the doctrine of "informed consent" has only limited direct application in pediatrics. Only persons who have the appropriate capacity and are legally empowered can provide informed consent for themselves. In all other situations, parents or other surrogates provide permission for diagnosis and treatment of children with the assent of the child whenever appropriate.

Unless criteria are met for waivers of parental permission and/or child assent, both are necessary conditions for the enrollment of children in research. Parents must be provided with detailed information concerning the nature and purpose of the research, the risks and benefits that may reasonably be expected, and any alternatives to research participation. Parents may place greater weight on the preferences of children when the risks of participation are lower and when children are older or more mature. Children who are capable must affirmatively agree to participate. The amount of information that a child must comprehend to provide meaningful and developmentally appropriate child assent (or dissent) should be allowed to vary with the age and maturity of the child. Many adolescents have the capacity to understand important informational elements in a research study in a manner similar to adults. However, the age (as a proxy for developmental stage) at which a child is deemed capable of assent may be lower (i.e., 5 to 7 years old) if assent is understood as the ability to express a simple preference regarding research participation. By assuming a lack of capacity among young children, the potential arises to dishonor and disregard a child's wishes by failing to solicit meaningful assent or dissent.

More empiric research is needed particularly with respect to the voluntariness of permission and assent. Little is understood about the relationship between decision-making autonomy and measures of understanding or voluntariness among adults, adolescents, or children. There appear to be no data on the factors that may contribute to whether children perceive their choice as voluntary. Finally, little is known about predictors of voluntariness in potentially vulnerable groups or whether family members

or medical staff have a greater influence over perceived choices.

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