

Original Articles

A Retrospective Study of Children's Perceptions of Participation as Clinical Research Subjects in a Minimal Risk Study

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ABSTRACT. The purpose of the study was to evaluate children's perceptions of their participation as research subjects in a minimal risk research study (a methylphenidate population pharmacokinetic study conducted 8 months earlier). We identified 115 children of an original 189, aged 6 to 19 years, who were responding well to regular methylphenidate for attention-deficit hyperactivity disorder. By using a structured format, telephone interviewers unconnected to the original study questioned the children about what it had been like to be a subject in terms of voluntariness, accuracy of informed consent, reasons for participating, and satisfaction with their experience. Children overwhelmingly perceived their involvement as voluntary (89%) and the information about the study as accurately presented (80%), and they reported a high level of satisfaction with their participation (97%). Self-interest was the most frequently reported reason for participation (47%). In a subsample of 25 children, the percentage of agreement of a 1-week test-retest equaled or exceeded 72% for all answers. *J Dev Behav Pediatr* 22:211-216, 2001. Index terms: children, research subjects, ADHD, informed assent, satisfaction.

Recent regulatory changes by the National Institutes of Health and the United States Food and Drug Administration mandate that children be included in clinical research.^{1,2} Involvement of children in clinical studies will provide needed information of the effects of medication in the pediatric population.³

To provide humane and ethical experiences, researchers must understand how both parents or guardians and children feel about their involvement in studies. Several authors have explored parent's reactions to their children's participation in research studies.⁴⁻⁸ Few studies have evaluated children's perceptions of their experiences as research subjects.⁹ No studies have investigated the important questions of whether specific elements of research participation place children at greater psychological risk than adults or whether children of specific developmental stages are more sensitive to specific aspects of research participation.

Children's perceptions may actually be quite different from what adults think they are. For example, children with attention-deficit hyperactivity disorder or conduct

disorder were asked to rate hospital experiences in an inpatient study. In that setting, children ranked going to the hospital, school, and having an electroencephalogram (EEG) as worse than undergoing a lumbar puncture or a venipuncture.¹⁰

Federal regulations require that parents or legal guardians give consent and that children assent to be research subjects in clinical studies that involve "minimal risks." Minimal risks have been defined as "risks (that) are not greater, considering probability of routine physical or psychological examinations or tests"¹¹ (generally interpreted by institutional review boards to include physical examinations, venipunctures, electrocardiograms, or EEGs).¹² Assent is defined as "a child's affirmative agreement to participate in research."¹² If assent is to be truly informed, it should mirror parental consent characteristics. The child must understand the purpose and procedures of the research protocol, understand the risks, benefits, and alternatives to the research, and realize that their participation is voluntary.¹³

We could identify only four previous studies that evaluated children's understanding of their assent to become research subjects. In the earliest study, no child under the age of 11 years and only 6 of 19 children (31.5%) over 11 years who underwent a research hospitalization understood that they were involved in "research."¹⁴ The

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view that children who are more developmentally mature can understand the assent process more accurately was widely held.¹⁵ Yet, in 1992, it was shown that children's understanding of the research process is influenced by anxiety and lack of global control rather than by their age or cognitive development.^{16,17} Susman et al¹⁶ carefully investigated 12 elements of assent. They found that although most children reported that their participation was voluntary (66%), only one third of them felt as if they could withdraw from the project. Two percent of children knew the purpose of the research.

In the only investigation of parental consent and child assent in the evaluation phase of a psychiatric double-blind placebo controlled study, 74% of children believed that they could leave the study at any time, and 37% believed that their participation would definitely help their symptoms.¹⁸

One study evaluated children's satisfaction with participation in a clinical study. Although the authors concluded that children's reactions to being research subjects were positive and without significant distress, only 43% of patients with depression and 80% of controls without depression were willing to "repeat the experience."¹⁹

This study expands knowledge of children's research experience by retrospectively assessing their perceptions of (1) their participation as voluntary at enrollment and at venipuncture, (2) their sense of how accurately the researchers described the procedures of the study, (3) their reasons for agreeing to be in the study, (4) their perceived distress with venipuncture, and (5) their satisfaction with the entire research experience. The variable of age was particularly scrutinized because the theoretical importance of cognitive development in children in understanding "the research process" was not supported by the single study that evaluated this subject.¹⁷

METHOD

Subjects were drawn from 189 children aged 6 to 19 years who had only a single venipuncture as part of a methylphenidate population pharmacokinetic study (MPPS) of children with attention-deficit hyperactivity disorder (ADHD) who were good responders to regular methylphenidate at standard dosing.²⁰ MPPS results were intended to provide information to a drug company for the future formulation of a long-acting medication. These children were treated for ADHD at a university medical school outpatient clinic by developmental pediatricians, child psychiatrists, or a nurse practitioner. One of the clinicians, a child psychiatrist, was the investigator of the MPPS and of this study. Before study admission, at the only visit, the investigator or study nurse of MPPS read an assent/consent form to the child and parent outlining the study's procedures and purpose: "to take a blood sample" and "to help develop a long-acting form of Ritalin." Children were asked if they understood what had been read to them. They were told that participation in MPPS was their decision and that they could change their mind about being in the study at any time. All children were asked if they wanted their parents to stay with them during venipuncture. Two experienced phlebotomists performed all venipunc-

tures in the antecubital vein. All children were distracted during venipuncture by research personnel speaking to them about favorite hobbies. Subject's parents were provided a small stipend (\$25) for meals and travel. Four children became distressed before venipuncture and were excused, and their parents were provided a stipend. Sixteen children who evidenced no distress during venipuncture were invited to have a second venipuncture later, and their parents were given a similar stipend.

Eight months later, the Human Subjects Committee of the University of South Dakota approved this study. A single letter was sent to all 189 MPPS subjects (including the four children who refused venipuncture), and 168 (89%) were located. Written assent from children and written informed consent from one parent or legal guardian was obtained from 115 of 168 children (68%), who agreed to be interviewed by telephone by an interviewer not associated with MPPS and not known to any of the subjects. One-week test-retest reliability was assessed on a random subsample of 25 children. Children received a small stipend for each interview (\$5).

This sample had a mean age of 11.34 years ($SD = 2.20$) and a median age of 11.48 years, 76 children were younger than 12 years (66.1%), and 27.8% had at least one psychiatric diagnosis in addition to ADHD. Boys comprised 75.2% of the sample, 93% were white, 3.5% were Native American, and 3.5% reported other ethnic backgrounds. Twenty percent of the sample had not had a venipuncture previously. Children remembered being asked to participate in MPPS at the request of the doctor (42.6%), parent (41.7%), both (5.2%), or another person (5.2%), and 5.3% did not remember.

We assessed possible differences between those we located and who chose to participate in the current study versus those who chose not to participate on four variables. This information was available from the MPPS dataset. We assessed possible differences in age, gender, race, and the existence of a comorbid diagnosis of any type. A *t* test was conducted to assess age, and all other variables were assessed with χ^2 . No differences were significant (for age, $t = -1.27$, $df = 166$, $p = .21$; for gender, $\chi^2 = .82$, $df = 1$, $p = .37$; for race (white vs nonwhite), $\chi^2 = .66$, $df = 1$, $p = .42$; for comorbidity, $\chi^2 = .50$, $df = 1$, $p = .48$).

A 14-question structured interview was developed to assess children's perceptions and understanding of having been a research subject. The first six questions were as follows:

1. Who asked you to be in the study? (Doctor, parent, other, do not remember)
2. Was this the first time someone tried to take some blood from your arm? (Yes/No response)
3. If this wasn't the first time, how many times before was blood taken from your arm? (Open-ended response)
4. How did you feel before blood was drawn? (Sick, dizzy, and a four-point Likert scale for "scared")
5. How did you feel during blood-drawing? (Sick, dizzy, and a four-point Likert scale for "scared")
6. How did you feel after blood was drawn? (Sick, dizzy, and a four-point Likert scale for "scared")

Table 1. Comparison of Younger and Older Children's Responses to Questions About Voluntariness

	Yes ^a	No ^a	Don't Know ^a
Could you have said no when first asked to be in the study? ^b			
Younger children—below age 12 yr (n = 76)	86 (85)	13 (10)	1 (1)
Older children—age 12 yr and above (n = 39)	97 (38)	0 (0)	3 (1)
Total (n = 115)	90 (103)	9 (10)	2 (2)
Could you have said no when it was time for your blood to be drawn? ^c			
Younger children—below age 12 yr (n = 76)	70 (53)	28 (21)	3 (2)
Older children—age 12 yr and above (n = 39)	80 (31)	18 (17)	3 (1)
Total (n = 115)	73 (84)	24 (28)	3 (3)

^aData presented as % (n).

^bChi-square = 1.33, *df* = 2, *p* = .515.

^cChi-square = 5.77, *df* = 2, *p* = .056.

Eight questions involved evaluation of the children's attitudes toward research participation: voluntariness, accuracy of informed assent, description of the study, reasons for participation, perceived distress, and satisfaction.

1. Voluntariness: Could you have said "no" when first asked to be in the study? (Yes/No response) Could you have said "no" when it was time for your blood to be drawn? (Yes/No response)
2. Accuracy of informed assent: Was MPPS like you had been told? (Four-point Likert scale response)
3. Reasons for participation: Why did you want to be in MPPS? (Open-ended response) Would you have been in MPPS even if you hadn't gotten any money? (Yes/No response)
4. Perceived distress: How much did it hurt to have your blood drawn? (Four-point Likert scale response)
5. Satisfaction: How did you feel about being in the study? (Six-point Likert scale response) Would you be in another study? (Yes/No response)

RESULTS

In test-retest reliability of 25 children, percentage of agreement exceeded 80% for these eight attitudinal questions except for the question of whether the MPPS experience was similar to the assent explanation given to the child (72%).

To assess the potential influence of age and gender on subject response, χ^2 analyses were completed on assessment items. Only one achieved significance: children younger than 12 years were more likely to be "pretty sure" they would agree to be in a future study ($\chi^2 = 17.16$, *df* = 5, *p* = .004).

Voluntariness

An overwhelming majority of both male (89.5%) and female (89.7%) subjects believed they could have said "no" when initially asked, whereas 6.9% of females and no males reported that they were unsure. Most children (73%) believed they could have refused venipuncture, and 2.6% were not sure. Table 1 shows the percentage of younger and older children's responses to questions about voluntariness.

Accuracy of Informed Assent

Responses in this category were as follows: 31.3% reported that the methylphenidate population pharmacokinetic study (MPPS) procedures were "exactly" as explained; for 30.4%, it was "a lot like it was explained"; 23.5% did not remember; and 14.8% reported that it was "a little" or "a lot" different. Of those who remembered, 80.7% reported that it was at least "a lot like" it had been explained. Table 2 shows the percentage of younger and older children's responses to questions about the accuracy of informed assent.

Reasons for Participation

Reasons for participation in the study were aggregated into four categories: (1) altruism (to help science, to help other kids), (2) self-interest (for the money, to get once-a-day pills), (3) perceived coercion (doctor or parent wanted me to be in the study), and (4) excitement (sounded like fun). The reason reported by 39.1% was altruism, whereas 47% reported self-interest. Perceived coercion was primary for 6.1%, 4.3% endorsed excitement, and 3.5% did not respond. Additionally, 87.8% of children reported that

Table 2. Comparison of Younger and Older Children's Responses to Question About Accuracy of Informed Consent

	Exactly like we said ^a	A lot like we said ^a	A little different than we said ^a	A lot different than we said ^a	I don't know/remember ^a
Was MPPS like you had been told? ^b					
Younger children—below age 12 yr (n = 76)	26 (20)	29 (22)	15 (11)	3 (2)	28 (21)
Older children—age 12 yr and above (n = 39)	41 (16)	33 (13)	8 (3)	3 (1)	15 (6)
Total (n = 115)	31 (36)	30 (35)	12 (14)	3 (3)	24 (27)

MPPS, methylphenidate population pharmacokinetic study.

^aData are presented as % (n).

^bChi-square = 4.50, *df* = 4, *p* = .335.

Table 3. Comparison of Younger and Older Children's Responses to Questions About Reasons for Participation

Why did you want to be in MPPS? ^b	Altruism ^a	Self-Interest ^a	Perceived Coercion ^a	Excitement ^a
Younger children—below age 12 yr (n = 73) ^c	45 (33)	45 (33)	6 (4)	4 (3)
Older children—age 12 yr and above (n = 38) ^c	32 (12)	55 (21)	8 (3)	5 (2)
Total (n = 111) ^c	41 (45)	49 (54)	6 (7)	5 (5)

Would you have been in MPPS if you hadn't gotten any money? ^d	Yes	No	Don't know
Younger children—below age 12 yr (n = 76)	92 (70)	5 (4)	3 (2)
Older children—age 12 yr and above (n = 39)	80 (31)	15 (6)	5 (2)
Total (n = 115)	88 (101)	9 (10)	4 (4)

MPPS, methylphenidate population pharmacokinetic study.

^aData are presented as % (n).^bChi-square = 3.97, *df* = 2, *p* = .138.^cNumber change is due to missing data.^dChi-square = 1.97, *df* = 3, *p* = .579.**Table 4. Comparison of Younger and Older Children's Responses to Question About Perceived Distress**

	Didn't hurt ^a	Hurt a little ^a	Hurt a medium amount ^a	Hurt a lot ^a
How much did it hurt to have your blood drawn? ^b				
Younger children—below age 12 yr (n = 76)	33 (25)	49 (37)	15 (11)	4 (3)
Older children—age 12 yr and above (n = 39)	33 (13)	51 (20)	10 (4)	5 (2)
Total (n = 115)	33 (38)	50 (57)	13 (15)	4 (5)

^aData presented as % (n).^bChi-square = .47, *df* = 3, *p* = .925.

they would have participated in MPPS without payment. Table 3 shows the percentage of younger and older children's responses to questions about reasons for participation.

Perceived Distress

Thirty-three percent of children reported that it did not hurt to have their blood drawn, 49.6% responded that it hurt "a little," 13% stated that it hurt a moderate amount, and 4.3% stated that it hurt "a lot." Table 4 shows the percentage of younger and older children's responses to questions about perceived distress.

Satisfaction

Almost unanimously (97.4%), children reported that they were "happy" about being in MPPS. Only 2.6% reported that they were "unhappy." Both older (94.9%) and younger (89.4%) children reported that they would be in another study if asked. Table 5 shows the percentage of younger and older children's responses to questions about satisfaction.

Pain or First Venipuncture and Outcomes

We conducted a further data analysis because it is possible that children who are experiencing a first

Table 5. Comparison of Younger and Older Children's Responses to Questions About Satisfaction

	Very happy ^a	Pretty happy ^a	A little happy ^a	A little unhappy ^a	Pretty unhappy ^a	Very unhappy ^a
How did you feel about being in MPPS? ^b						
Younger children—below age 12 yr (n = 76)	53 (40)	36 (27)	9 (7)	1 (1)	0 (1)	0 (0)
Older children—age 12 yr and above (n = 39)	31 (12)	54 (21)	13 (5)	3 (1)	0 (0)	0 (0)
Total (n = 115)	45 (52)	42 (48)	10 (12)	2 (2)	1 (1)	0 (0)

	Very sure yes ^a	Pretty sure yes ^a	A little sure yes ^a	A little sure no ^a	Pretty sure no ^a	Very sure no ^a
Would you be in another study if asked? ^c						
Younger children—below age 12 yr (n = 76)	45 (34)	18 (14)	26 (20)	1 (1)	3 (2)	7 (5)
Older children—age 12 yr and above (n = 39)	36 (14)	51 (20)	8 (3)	3 (2)	3 (2)	0 (0)
Total (n = 115)	42 (48)	30 (34)	20 (23)	2 (2)	3 (3)	4 (5)

MPPS, methylphenidate population pharmacokinetic study.

^aData presented as % (n).^bChi-square = 5.86, *df* = 4, *p* = .210.^cChi-square = 17.16, *df* = 5, *p* = .004.

venipuncture or who have a lot of pain during venipuncture might report differences in satisfaction or in accuracy of informed assent when compared with children who have had previous venipunctures or little pain. In this study, there were nonsignificant differences of memory of venipuncture pain between children who never had venipuncture and those who had ($t = .66, p = .51$). There were also nonsignificant differences between these two groups in their perception of accuracy of informed assent ($t = .97, p = .33$) or of their satisfaction with participation in MPPS ($t = -.07, p = .95$).

DISCUSSION

Federal guidelines have been changed so that children will increasingly be mandated to participate in clinical research, and drug companies may provide increasing financial incentives to parents to include their children in research. This study of children's perception of being research subjects provides data that suggest that children were generally satisfied with their experience and would agree to be in another study. The authors of the only previous study that evaluated this question drew the same conclusion from less compelling data.¹⁹ Both studies also conclude that children view their experience as research subjects as voluntary and that self-interest, rather than altruism, was the primary motivation for participation.

Although the findings of this study are compelling, the reliability of children's recollection of events 8 months earlier is of concern. One cannot assume that children's memory of their perceptions is identical to their perceptions during the study. However, a study of children's recall of the intensity of the pain and the affective distress of venipuncture 2 months earlier revealed that children aged 5 to 17 years have good recall of both aspects of the pain.²¹ However, they may not remember other aspects of a past clinical study.

Differences in inpatient status, clinical diagnosis, and type of study in the five studies of children's perceptions of

being research subjects make it difficult to compare and to generalize conclusions. Although children with attention-deficit hyperactivity disorder are among the most extensively researched in pediatrics, results from such a sample may not generalize to all children. Future research is needed to validate the findings. The methylphenidate population pharmacokinetic study did not involve an alternative treatment or a placebo arm. Children may have little difficulty in understanding the assent of a single blood draw pharmacokinetic study, but they may have substantial difficulties understanding that they may or may not receive active or alternative drug. For example, 37% of children in such a study believed that their participation would definitely help them.¹⁸ Finally, the experience of one venipuncture may not be comparable to participation in a more complex or longer clinical trial.

In this study, only a single question yielded a statistically significant difference of age: younger children were more likely to be "pretty sure" they would agree to be in another research project. It is not clear if this difference is caused by an actual difference in perception related to a developmental issue or by another unknown reason.

Future longitudinal research including diverse groups of children of different ages and different developmental stages in different designs is needed. Particularly valuable would be studies in which children were interviewed about their participation in research before, during, immediately after, and long after the experience to determine whether time or maturation changes their perceptions.

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