Published in final edited form as:

Pediatr Blood Cancer. 2013 May ; 60(5): 873–878. doi:10.1002/pbc.24326.

Adolescent Perspectives on Phase I Cancer Research

Victoria A. Miller, PhD¹, Justin N. Baker, MD², Angela C. Leek, BA³, Sabahat Hizlan, BA, BS³, Susan R. Rheingold, MD⁴, Amy D. Yamokoski, MA⁵, Dennis Drotar, PhD⁶, and Eric Kodish, MD⁷

¹Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA

²Division of Quality of Life and Palliative Care, St. Jude Children's Research Hospital, Memphis, TN

³Department of Bioethics, Cleveland Clinic, Cleveland, OH

⁴Division of Oncology, The Children's Hospital of Philadelphia, Philadelphia, PA

⁵Center for Clinical Research, Cleveland Clinic, Cleveland, OH

⁶Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁷Center for Ethics, Humanities and Spiritual Care, Cleveland Clinic, Cleveland, OH

Abstract

Background—The aim of this study was to examine adolescent patients' perspectives on their understanding and decision making about a pediatric Phase I cancer study.

Procedure—Participants included adolescents ages 14-21 years with cancer ($N=20$), all of whom attended a Phase I study consent conference. Participants responded to closed- and open-ended questions on a verbally administered structured interview, which assessed aspects of understanding and decision making about the Phase I study.

Results—All participants decided to enroll in the Phase I study. The majority of participants understood that participation was voluntary, entailed risks, and that they could withdraw. Most also believed that participation in the Phase I study would increase the length of their lives. The most frequent reasons for enrolling were positive clinical benefit, needing an option, impact on quality of life, and few side effects or fewer than those of current or past treatments. Eighty-five percent of participants reported that they themselves made the final decision about enrollment in the Phase I study.

Conclusions—Most participants hoped or expected that the Phase I study would provide a direct benefit (increased survival time or cure) and reported that they themselves were the final decision-maker about enrollment. Clinicians may underestimate the role of adolescents, especially if they believe that parents typically make such decisions. Future research should assess the actual participation of children and adolescents during the informed consent process and explore the role of hope in their decision making about Phase I studies.

Keywords

informed consent; decision making; pediatrics; oncology; ethics; Phase I

Corresponding Author: Eric Kodish, MD, Center for Ethics, Humanities and Spiritual Care, Cleveland Clinic, 9500 Euclid Avenue JJ60, Cleveland, Ohio 44195. Phone: (216) 444-3850. Fax: (216) 636-0712. kodishe@ccf.org.

Conflict of Interest Statement The authors have no conflicts of interest to disclose in relation to this research.

Introduction

Approximately 70% of children with cancer participate in a clinical trial during the course of the illness [1], and as many as 33% of children who die of cancer participate in Phase I trials (see Supplemental Appendix)[2]. Phase I trials are designed to establish the safety profile of novel agents. Therapeutic effect is not the primary scientific endpoint, and only patients who have no remaining curative options are candidates for these studies [3]. The offer of a Phase I trial often follows a significant and distressing transition in the illness trajectory (i.e., disease relapse). Ethical concerns have been raised about informed consent for Phase I trials, including the emotional state of patients and families and whether they understand that the likelihood of medical benefit is low [4, 5].

Several studies have examined adults' understanding and motivation for enrolling in Phase I oncology trials. Adults estimate their chance of medical benefit as high [6-8] and as higher than participants in general [9, 10], a phenomenon referred to as therapeutic optimism. One study examined participants' reasons for how they rated the likelihood of benefit. Most participants indicated that they were expressing their hope and positive attitude rather than stating a fact [8]. Prior research also suggests that most adult patients are motivated to participate in Phase I trials in hope of medical benefit and/or because they have no other options [7] [8] [10]. Other reasons include maintaining hope and helping others [8, 10]. Data on child and adolescent decision making are more limited.

We are aware of two prior studies that examined the perspectives of children and adolescents about Phase I trials [11, 12]. One study interviewed 20 patients within one week of a decision about a Phase I study, do not resuscitate order, or initiation of palliative care [11]. Four of the seven patients involved in a decision about a Phase I study reported that a chance of cure was one of the things they considered when making the decision. Two of the seven patients reported that they were uncomfortable with the decision to enroll in the trial. These patients reported that they did not want any more disease-directed interventions, but they agreed because loved ones wanted them to. One of the authors' conclusions was that decision making about end-of-life care is primarily relationship-based. Another study interviewed parents and three children regarding the quality of life of children offered participation in a Phase I trial [12]. The hope for cure was a consistent theme amongst both parents and children.

These studies reflect a step forward in our understanding of how pediatric patients perceive the decision about Phase I study enrollment. However, neither was focused exclusively on Phase I decisions, and they did not examine multiple dimensions of patients' perspectives. More data is needed to assess what children and adolescents understand about Phase I research, how they perceive the benefits, and how they experience the decision making process. The voices of child and adolescent patients are important, especially because they are often experienced with respect to their illness and decision making when they are offered a Phase I study. Data about their perspectives may shed light on ways to improve the assent/consent process, enhance their involvement in decisions, and facilitate coping.

We examined the perspectives of adolescents with cancer who were offered participation in a Phase I trial. We utilized a comprehensive interview that focused on four areas related to decision making about Phase I research: 1) understanding, 2) the decision-making process, including the adolescent's role, impact of faith on the decision, and perceived pressure, 3) expectations regarding the effect of trial participation on quality and length of life, and 4) reasons for agreeing to or declining the Phase I study.

Methods

Recruitment

The study on which this analysis is based was designed to assess communication and physician, parent, and patient perspectives, understanding, and decision making in pediatric Phase I cancer research. We approached parents who were considering enrolling a child in a Phase I study at six children's hospitals in the US. Data were collected between June 2008 and June 2011. The study was approved by the Institutional Review Board at each site.

After parents consented to participate, their informed consent conferences (ICCs) for the Phase I trial were observed and audio-taped. Parents were interviewed about factors related to the ICC and the decision making process, as soon as possible after making a decision about the Phase I study, and they completed several questionnaires. Patients age 14 through 17 years were also interviewed if permission was obtained from the parent and the adolescent assented. Patients age 18 through 21 years were approached directly for consent to participate.

Patient Interview

Study personnel verbally administered the interview, which was audio-taped and transcribed. The interview contained closed- and open-ended items addressing key unanswered questions related to Phase I trial participation (see Supplemental Table).

Data Analysis

We calculated the frequency of responses to closed-ended questions and generated descriptive statistics (mean, standard deviation, range). One member of the study team initially coded responses to open-ended questions. All coding was verified by the first author. We then calculated the frequency of responses for each coded category.

Results

Participants

Of the 85 ICCs observed as part of the larger study, 60 parents were subsequently interviewed, and 26 of these parents had children ages 14-21 years. Of these 26 patients, 19 completed interviews. Seven patients were not interviewed: two patients were not present for the ICC, two declined the interview (one due to feeling too ill; one gave no reason), one lacked cognitive capacity, one was too ill to approach, and one did not respond to our attempts to schedule the interview. An additional patient who was interviewed was 21 years-old and made decisions without parental involvement. Therefore, there were 20 patient participants included in this analysis; 7 participants were 14-17 years of age, while the remaining 13 were 18-21 years. All 20 had agreed to enroll in the Phase I trial, as did 95% of patients overall [13]. Additional sample characteristics are in Table I.

What do Adolescents Understand about Phase I Research?

All participants indicated that a Phase I trial was discussed during the ICC. Eighteen (90%) understood that they did not have to participate in the trial to receive care at the hospital; one participant answered "don't know" and one indicated that he was at the institution specifically to enroll in the trial. Most participants understood that they could withdraw from the trial and that the trial involved risks (both questions, $n = 18$, 90%). Eighteen (90%) indicated that the trial would provide medical benefits. When asked specifically whether most patients who participate in Phase I trials receive medical benefit, 30% ($n = 6$) said "yes," 20% ($n = 4$) said "no," and 50% ($n = 10$) said "don't know." In response to the

question about the percentage of patients who will get medical benefit from participation in this Phase I trial, eight (40%) participants answered “don’t know” or did not provide a percentage; among the 12 who provided a percentage, answers ranged from 1% to 90% (mean, 35.17%; $SD = 28.86$). When asked about their own chances of getting medical benefit, 13 (65%) participants answered “don’t know” or did not provide a percentage, while seven provided percentages ranging from 5% to 100% ($M = 55.71\%$; $SD = 37.13$). Participants rated the information that was given to them as easy to understand ($M = 1.95$, $SD = 1.22$; range = 0-4, on a scale of 0 (very easy)-10 (very confusing)).

How do Adolescents Experience the Decision Making Process about Phase I Research?

Variables related to the decision making process are in Table II. Most ($n = 17$, 85%) participants reported being the final decision maker. When asked who was most important in influencing the decision, 50% ($n = 10$) indicated the patient him/herself and 35% ($n = 7$) indicated the parent. Participants also rated their opportunity to ask the doctor questions as high ($M = 8.95$, $SD = 1.22$; range = 6-10, on a scale of 0 (not much)-10 (much)). Half ($n = 10$) of participants indicated that faith was important to the decision, primarily because it gave them strength to make decisions. The majority ($n = 13$, 65%) of participants perceived the decision as “easy.” Those who reported that the decision was “somewhat” or “very” difficult gave reasons related to uncertainty and the magnitude of the decision (see Table III).

The majority of participants ($n = 13$, 65%) indicated that the clinician recommended enrollment on the Phase I trial. Participants rated the strength of this recommendation as moderate ($M = 4.84$, $SD = 2.75$; range = 1-10, on a scale of 0 (very strongly)-10 (not very strongly)). Perceived pressure to participate was rated at a mean of 2.00 ($SD = 2.77$, range = 0-10, on a scale of 0 (no pressure)-10 (much pressure)), indicating low perceived pressure.

What do Adolescents Expect Regarding Impact of Phase I Research on Quality and Length of Life?

Participants responded to two open-ended questions about the expected effect of the Phase I trial on quality and length of life. Responses are categorized in Table II, and illustrative quotes are provided in Table III. Many ($n = 10$, 50%) expected or hoped that the Phase I trial would positively affect quality of life. Other participants noted that the Phase I drug could reduce quality of life as a result of side effects ($n = 5$, 25%) or more time in the hospital ($n = 3$, 15%), although these effects were sometimes seen as less negative than other past or current treatment options. The majority ($n = 16$, 80%) expected or hoped for positive effects on length of life. Overall, the qualitative data suggest that there was also uncertainty with respect to the impact of Phase I trial participation on quality and length of life (see Table III).

Why do Adolescents Participate in Phase I Research?

Participants responded to two open-ended questions about reasons for deciding to participate in the Phase I trial (Supplemental Table). Responses were collapsed into a single variable (Table IV). Illustrative quotes are provided in Table III. The mean number of different reasons given was 3.15 ($SD = 0.88$, range = 1-5). The majority ($n = 15$, 75%) of participants indicated the potential for a positive clinical effect, including cure or longer survival, as a reason for participating. Almost half ($n = 9$, 45%) reported that they decided to participate because there was no other treatment option. Some ($n = 8$, 40%) participants reported that they decided to participate because of the possibility of improved quality of life. A minority ($n = 4$, 20%) of participants noted that they enrolled to contribute to science or to help other people. Some ($n = 5$, 25%) participants reported that they decided to participate because the

new drug had been tested previously, it was the first option to become available, or because they had seen positive results in others.

Discussion

This study examined the perspectives of adolescents with cancer who were offered participation in a Phase I study. Patients were interviewed at a mean of 6 days after the ICC for a Phase I study, so perceptions were not likely to be biased by trial participation experience or change in health status. We utilized a comprehensive interview to address unanswered questions, such as what adolescents understand about Phase I research, how they experience the decision making process, and what they expect with respect to quality and length of life. Our analysis included both quantitative and qualitative components, allowing us not only to describe the perspectives of our sample as a whole, but also to capture the rich and heterogeneous voices of the patients themselves.

The perceptions of adolescents were similar to those of adults [6-10]. The majority of adolescents expected or hoped that participation in the Phase I trial would increase length of life, and the most frequent motivations for enrolling were clinical benefit, no other option, impact on quality of life, and few or fewer side effects compared to current or past treatments. The finding that participants were motivated to enroll because of direct medical benefit is important, because previous research indicates that only 8-10% of children experience a response to Phase I cancer therapy [14, 15]. Like adults [9, 10], adolescents rated their own likelihood of benefit as higher than others, although we were not able to test this difference statistically because of the sample size. The quantitative and qualitative findings also suggest that there is uncertainty regarding the potential for medical benefit. While some have raised the concern that hope for direct benefit reflects a therapeutic misperception [16, 17], prior research has attempted to differentiate between patients' expression of hope versus their understanding of the facts regarding Phase I trial participation. In one study adult participants reported that expressing optimism would enhance their likelihood of benefitting from Phase I research [8]. Some participants' responses in that study also suggested that they were conforming to social expectations in expressing a high level of hope, and some reported a sense of duty to express optimism to reassure loved ones [8]. This finding is consistent with Bluebond-Langner's concept of "mutual pretense," in which parents and children convey optimism rather than openly acknowledge the gravity of the child's prognosis, to avoid causing distress [18]. The same phenomenon may be reflected in adolescents' responses to our interview questions.

It is informative to consider our findings in light of clinicians' reports about informed consent for Phase I research. In a previous report 73% of clinicians reported that for children older than 14 years, the parent usually makes the decision about Phase I trial participation [19]. In contrast, 85% of adolescents in our sample reported being the final decision maker. Therefore, clinicians may misperceive who makes such decisions. This finding is important because the belief that parents will make the decision is likely to shape communication during the ICC. Another study found that the majority of pediatric oncologists thought that adolescents were not capable of meaningful participation in research decisions and reported that they withheld information due to their heightened vulnerability [20].

Our findings have several clinical implications. Oncologists may be underestimating the adolescent's role in decision making; this underestimation may lead to less effective communication about the Phase I study and other medical decisions. It would be helpful to discuss with families their previous approach to medical decisions and how they expect to make the current decision. This information will allow clinicians to target their communication effectively. Some adolescents may prefer that their parents make the

decision or provide substantial guidance and advice. Such preferences should be respected, as outcomes such as satisfaction and adjustment may be optimal when the discussion is congruent with expectations for control (see [21, 22]). This approach is consistent with recommendations from the Children's Oncology Group, which included promotion of a continuum of patient involvement and encouragement of family decision making [23]. Another clinical consideration is that most adolescents expressed hope that the trial would benefit them in terms of cure or increased length of life. This hope is not necessarily incompatible with a factual understanding of the likelihood of benefit [24]. Indeed, the qualitative responses reflected more uncertainty, and a number of participants answered "don't know" or did not provide a response to questions about the likelihood of benefit. Adolescents' hopes about the outcome of participation may be an important coping mechanism at a time of uncertainty and distress [3, 25]. Their expression of hope is also likely to reflect the family's coping and communication strategies related to the prognosis. Clinicians should explore parent and child responses to changes in prognosis and health status and understand that such responses will shape decision making about end-of-life options [18, 26, 27]. Investigators conducting informed consent should provide accurate information about Phase I research, including disclosure of the low likelihood of benefit and the availability of other options such as palliative care, while recognizing that the hope for cure or increased length of life may serve an important function.

The limitations of this study include the small sample size and predominance of white male patients. The sample may not have included adolescents who were more distressed, struggled with the decision, or were less involved in the decision. Another limitation is that the breadth of our assessment limited our ability to explore specific areas in more depth. For example, we did not undertake a comprehensive assessment of understanding or explore what adolescents meant by their use of the word "hope." Finally, we did not report findings related to adolescent-clinician or -parent communication during the ICC. In the broader study, the patient was present for 83 out of the 85 ICCs that were observed [13]. It is important to elucidate how children and adolescents are participating in the ICC and how parents and clinicians attempt to engage them. This information will allow us to identify targets for intervention to enhance the communication and decision making process. This objective will be the focus of our next analysis.

More empirical work is needed to understand the benefits of hope for children and adolescents in the context of end-of-life decision making and whether there is a point at which such hope becomes detrimental [24, 28]. Additional research is needed to determine the optimal level of involvement of children and adolescents in decisions about research participation, and whether such involvement is beneficial and under what circumstances. For example, children who are more distressed may actually be harmed by efforts to involve them. Future research should also examine parent-adolescent communication about Phase I studies and how disagreements are managed. Families may engage in extensive discussions about Phase I trial participation *prior* to meeting with the physician. The extent to which such discussions shape communication during the ICC is unknown.

Conclusions

This study contributes data that gives voice to those most affected by Phase I trial participation for pediatric cancer. Adolescent perspectives have not been previously examined and provide insights into the decision-making process of this patient population at an extremely difficult time in their lives – having to make life altering decisions while facing an incurable illness. These insights will help guide clinicians and researchers to improve the Phase I consent process and may apply more broadly to other areas of research on potentially vulnerable subjects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank all of the families who participated in the study on which this paper is based. We are especially grateful to the 20 adolescents who shared their experiences and whose voices are reflected in this paper.

This research was supported by the National Institutes of Health (NIH) via the National Cancer Institute (NCI) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) (1R01CA122217). The funding agreements ensured the authors' independence in designing and conducting the study; collecting, managing, analyzing, and interpreting the data; and preparing, reviewing, and approving the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, NCI, or NICHD.

Abbreviations

ICC informed consent conference

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Table I**Participant Characteristics**

Characteristic	
Years of age (<i>M</i> [<i>SD</i> , range])	17.8 (2.35, 14-21)
Male sex (<i>N</i> (%))	15 (75%)
Race, self-report (<i>N</i> (%))	
White	16 (80%)
Black or African-American	2 (10%)
American Indian/Alaskan Native	1 (5%)
Asian	1 (5%)
Parent index of social position ^a (<i>N</i> (%))	
1-2	6 (32%)
3	8 (42%)
4-5	5 (26%)
Cancer type (<i>N</i> (%))	
Bone or soft tissue	11 (55%)
Brain/CNS	7 (35%)
Leukemia	1 (5%)
Sertoli-Leydig cell tumor	1 (5%)
Years from diagnosis to Phase I consent conference (<i>M</i> [<i>SD</i> , range])	2.93 (2.68, 0.27- 12.29)
Days from Phase I consent conference to interview (<i>M</i> [<i>SD</i> , range])	6.05 (6.57, 0-24)

^aLower scores are representative of higher SES[29]. Data missing for one participant.

Table II

Perceptions of the Decision Making Process and Expected Impact of Phase I Trial on Quality and Length of Life

Variable	
Clinician's recommendation (<i>N</i> (%))	
Phase I enrollment	13 (65%)
No recommendation	6 (30%)
Standard/Off study	1 (5%)
Strength of clinician's recommendation to participate in Phase I study, from 0 (very strongly) to 10 (not very strongly) (<i>M</i> [SD, range])	
	4.84 (2.75, 1-10)
Perceived pressure to participate in Phase I study, from 0 (no pressure) to 10 (much pressure) (<i>M</i> [SD, range])	
	2.00 (2.77, 0-10)
Perceived role ^a (<i>N</i> (%))	
Final decision maker	17 (85%)
Partial decision maker	2 (10%)
Person most important in influencing this decision ^b	
Patient	10 (50%)
Parent	7 (35%)
Physician	4 (20%)
Clinician at another institution	1 (5%)
Opportunity to ask questions, from 0 (not much) to 10 (much) (<i>M</i> [SD, range])	
	8.95 (1.22, 6-10)
Difficulty of decision (<i>N</i> (%))	
Easy	13 (65%)
Somewhat difficult	6 (30%)
Very difficult	1 (5%)
Was faith important to your decision? (<i>N</i> (%))	
Yes	10 (50%)
How was faith important? (<i>N</i> (%))	
Strength to make decisions	8 (80%)
Prayer	1 (10%)
Left decision up to God	1 (10%)
Impact on Quality of Life ^b (<i>N</i> (%))	
Improve quality of life	10 (50%)
More side effects	5 (25%)
More time in hospital	3 (15%)
No effect	3 (15%)
Uncertain	3 (15%)

Variable	
Fewer side effects	2 (10%)
Less time in hospital	1 (5%)
Act more cautiously (i.e., avoid getting cuts while shaving)	1 (5%)
Impact on Length of Life (<i>N</i> (%))	
Increase length of life	16 (80%)
Uncertain	3 (15%)
No effect	1 (5%)

^aData missing for one participant.

^bSome adolescents provided more than one response.

Table III

Illustrative Quotes

Theme	Selected Quotes
Reasons for difficulty making decision	<p>"I just kind of felt like we were shootin' in the dark." – 18-year-old male #1</p> <p>"Um, just the weightiness of the decision... more than anything. I wanted to make sure I didn't make any like major mistake, something that was blatant and irrefractable." – 21-year-old male #1</p>
Expectation or hope for positive impact of Phase I study on quality of life	<p>"... if it does its job and um... it will boost it a lot." – 14-year-old male #3</p> <p>"I think it's doing a lot for me. I'm pretty sure the temozolomide wasn't working and that was pretty much the last oral medicine I could take. Um, this is like a second shot at it. Hopefully it will work until they find something else." – 21-year-old male #2</p> <p>"I hope it's positive, um, always hope it's positive. Yeah, I mean I'm really in unknown waters here." – 19-year-old male #1</p>
Expectation of negative impact of Phase I study on quality of life	<p>"Well, I mean I'll be sicker for the time being but afterwards I'll be much better. I can go on with my normal life." – 21-year-old female</p> <p>"Well...it'll just make me tired and I won't be able to get up and around as often but other than that it's not much different." – 14-year-old male #1</p> <p>"Uh, while I'm on the study I don't think it will drastically affect the quality of life. It might cause some discomfort but um, I think that's manageable compared to the other options, and then, it compares to the other treatment options. It's much better quality of life than um, chemo and continued surgeries." – 21-year-old male #1</p>
Expectation or hope for positive impact of Phase I study on length of life	<p>"Hopefully, I'll live forever. Well, you can't live forever, but you get what I mean – live for a long time." – 18-year-old female</p> <p>"I think it should make me live longer than past ... longer than 15 years old. <laughter> I hope so." – 14-year-old male #2</p> <p>"Hopefully, it will uh, make it longer. Before this I was only like given 6 months to live. And then now I think this will help." – 17-year-old male #2</p> <p>"If it's successful, I hope it, it elongates it, does not make it shorter. And I honestly have no idea how long that would be. And I asked the doctors about that too just how, uh, like how much time I have without it, how much time it might increase it. They had no idea because it is very variable, 6 months to 5 years to beyond." – 21-year-old male #1</p>
Uncertainty regarding impact of Phase I study on length of life	<p>"No one knows, ... because it's, again, undetermined how much benefit it will have." – 18-year-old male #2</p> <p>"I am undecided on that one." – 19-year-old female</p>
Reason for participating: Positive clinical effect	<p>"OK, because I didn't want to die at 14 if I went with the other trial, um, let's see. They said that this was one of the best hospitals in the United States for this and, um, let's see... don't think it's my time to leave." – 14-year-old male #2</p> <p>"Living. Living and living." – 21-year-old female</p>
Reason for participating: Need for an option	<p>"Because it's a different opportunity – it's a different treatment and I've pretty much exhausted most other treatments..." – 18-year-old male #2</p> <p>"Because I was out of options to – I've done chemo and the chemo hadn't worked twice and uh, done radiation for 6 weeks and the tumors were inoperable so...I thought this might be the best decision. " – 17-year-old male #2</p> <p>"Well, the other drug I was using stopped working and they felt this would be the best option and because it was the first one that became available. " – 15-year-old female</p>
Reason for participating: Quality of life	<p>"It'll help me and hopefully I'll get back to being my normal self." – 14-year-old male #1</p> <p>"Just to get rid of the tumor so I can get on with my life and I don't know what else to say." – 19-year-old female</p>
Reason for participating: To help science and	<p>"To cure it, not get surgery, and um, help out, you know, their numbers. So if it doesn't work on me then maybe they can start working on other kids that have it, too." – 17-year-old male #1</p>

Theme	Selected Quotes
other children	“Mainly because it furthers medicine. For all we know it might help something or something that we get from this medicine might help somebody in the future.” – 19-year-old male #2
Reason for participating: Previous testing/availability	<p>“Well, because it has been tested in my type of tumor in adults and animals...” – 18-year-old male #4</p> <p>“Well, the other drug I was using stopped working and they felt this would be the best option and because it was the first one that became available.” – 15-year-old female</p> <p>“Cause it had good results in everyone else I’ve seen it in- since I had done research before the doctor actually offered it... and I wanted it.” – 14-yearold male #3</p> <p>of trial drug</p>

Table IV**Reasons for Participating in Phase I Trial**

Category^a (N (%))	
Positive clinical effect	15 (75%)
No other options	9 (45%)
Positive impact on quality of life	8 (40%)
Few or fewer side effects	8 (40%)
Logistics related to participation (e.g., "It's easy to do.")	6 (30%)
Previous testing/availability of trial drug	5 (25%)
Other ^b	5 (25%)
To help science and other children	4 (20%)
Doctor's recommendation	3 (15%)

^a Adolescents could provide more than one response.

^b Other reasons included: Won't harm the patient; parents' recommendation; reputation of hospital/physician; "not my time to leave"; easy to understand.