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Parental Experiences of Child Participation in a Phase I Pediatric Oncology Clinical Trial: “We Don’t Have Time to Waste”

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Abstract

Children with cancer are only eligible for phase I clinical trials (PITs) when no known curative therapy remains. However, the primary aims of PITs are not focused on directly benefiting participants. This raises ethical concerns that can be best evaluated by exploring the experiences of participants. An empirical phenomenology study, using an adapted Colaizzi method, was conducted of 11 parents’ lived experiences of their child’s participation in a pediatric oncology PIT.

Study findings were that parents’ experiences reflected what it meant to have a child fighting to survive high-risk cancer. Although elements specific to PIT participation were identified, more pervasive was parents’ sense of running out of time to find an effective treatment and needing to use time they had with their child well. Even though some problems were identified, overall parents did not regret their child’s PIT participation and would recommend PITs to other parents of children with cancer.

Introduction

Cancer persists as the second most common cause of death (after accidents) for children aged 1 to 14 years, and the incidence of cancer in children and adolescents is continuing to increase (Siegel, Miller, & Jemal, 2016; Ward, Desantis, Robbins, Kohler, & Jemal, 2014). However, survival rates for childhood cancers are improving; between 1975 and 2011 overall five-year survival rates for childhood cancer improved by over 43% (to 83%) (Siegel et al., 2016; Ward et al., 2014). These improvements in childhood cancer outcomes are attributed to better therapies and high levels of participation in clinical trials (Hudson, Meyer, & Pui, 2015; Weber et al., 2014).

Phase I clinical trials (PITs) are the critical first stage of clinical trials, and determine the recommend dosage and test the safety of new therapies (Craft et al., 2009; Kim et al., 2008; Lee, Skolnik, & Adamson, 2005; Weber et al., 2014). In pediatrics, PITs involve testing an investigational therapy (either as a single agent or a novel combination of agents) not approved for use in children. Enrollment in PITs is typically limited to cohorts of three to six children at a time. To minimize the risk of untoward adverse events, the dose of the

investigational therapy administered is incrementally increased in consecutive cohorts based on how the therapy is tolerated, until a maximum tolerated or recommended dose is established. Additional monitoring and research-only procedures are required of P1T participants, to ensure their safety and to understand the pharmacology of the therapy in children. Despite the challenges involved, P1Ts are necessary for developing new therapies that will improve outcomes for children with cancer.

The Declaration of Helsinki requires that “while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects” (World Medical Association, 2013). The ethical challenge inherent in pediatric oncology P1Ts is that the primary aims of these trials are focused on developing new therapies and are not intended to provide direct benefit to participants. Due to the investigational nature of the new therapies being tested, children are only eligible to participate in P1Ts when their cancer is considered incurable (Bautista et al., 2015; Crites & Kodish, 2013; Deatrck, Angst, & Moore, 2002). The median life expectancy of children with relapsed cancer enrolled in a P1T is less than seven months (Bautista et al., 2015; Kim et al., 2008; Morgenstern et al., 2014). Despite this, clinicians and parents pursue P1Ts for children with cancer based on hope that the investigational therapy being tested will improve the child’s disease prognosis (Barrera, D’Agostino, Gammon, Spencer, & Baruchel, 2005; Crites & Kodish, 2013; Deatrck et al., 2002; Oppenheim, Geoerger, & Hartmann, 2005; Weber et al., 2014).

To address the ethical challenges of pediatric oncology P1Ts, it is important to understand the experiences of participants in these trials. Experiences with P1Ts may vary widely given the toxicities of the P1T therapy, distance travelled to the P1T center, previous relationship with the P1T medical team, response of the child’s cancer to the P1T therapy, and previous clinical trial experiences. Although there are numerous studies on the P1T consenting process (Barrera et al., 2005; Cousino et al., 2012; Deatrck et al., 2002; Hinds et al., 2005; Hinds et al., 1997; Hinds et al., 2009; Levine et al., 2015; Marshall et al., 2012; Maurer et al., 2010; Miller et al., 2013; Oppenheim et al., 2005), no studies have been done with children with cancer or their parents on the experience of actually participating in a P1T.

The purpose of this study was to describe the meaning of the experience of P1T participation from the perspective of parents of children with cancer. A descriptive, cross-sectional, empirical phenomenological study was conducted using an adapted version of Colaizzi’s method, based on Husserl’s philosophy of phenomenology (Colaizzi, 1978; Haase, 1987). The goal of Colaizzi’s method of empirical phenomenology is to generate an exhaustive description of the phenomenon, and from the exhaustive description to describe the essential structure of the experience (Colaizzi, 1978). Identification of the essential structure is crucial to meaningfully understand the experience of a phenomenon, and how the experience of a phenomenon impacts behavior and perceptions (Colaizzi, 1978).

Methods

Setting

Parent recruitment occurred at two time points. First, a pilot interview was conducted with one parent recruited by the first author, based on prior knowledge of the parent's advocacy efforts. The main study then recruited participants from two pediatric academic medical centers in the Midwest United States that conduct pediatric oncology PITs. Parents were also recruited for the main study from national childhood cancer support and advocacy groups that were not affiliated with either medical center.

Sample

The purposive sample consisted of parents of children with cancer who participated in a PIT. Sample size in phenomenological studies is not determined in advance. Rather, sampling continues until data analysis yields thematic redundancy, and generally ranges between 3 and 15 participants (Creswell, 2013; Englander, 2012; Lincoln & Guba, 1985; Morse, 1995; Palys, 2008; Speziale, Streubert, & Carpenter, 2011; Starks & Trinidad, 2007). No effort was made to control for demographic variables or clinical history since empirical phenomenology is used to describe the commonalities of experiences, even within a diverse sample (Colaizzi, 1978). Efforts were made to ensure the sample included parents of children with cancer who had a diverse range of positive and negative outcomes following the PIT.

Parent was defined as anyone who served in the role of primary caregiver (e.g. biological parent, guardian, grandparent). To capture a complete picture of all parents' experiences, up to two parents were interviewed for each eligible child. Parent inclusion criteria were: (1) age ≥ 18; (2) self-identification as primary caregiver of child; (3) fluency in English; and (4) having provided consent for child's PIT participation. In addition, the parent's child must have been: (1) enrolled in at least one pediatric oncology PIT in the United States; (2) aged < 18 during the PIT; and (3) removed from the PIT at least 60 days prior (to ensure that the off-study transition was fully experienced). Parents were ineligible if the child had died within the previous 60 days.

Recruitment

Institutional Research Board approval was obtained prior to screening or enrolling participants. Recruitment occurred between March and December 2016.

Parents were recruited at one medical center by the first author and at the second medical center by experienced pediatric oncology clinical research professionals. Parents were pre-screened for eligibility by reviewing all participants enrolled in a PIT within the past four years. Potentially eligible participants were recruited using the method developed for research involving parents of deceased children (Hinds, Burghen, & Pritchard, 2007). Specifically, a recruitment-letter was sent from the phase I center with instructions for enrolling as well as opting out of further contact attempts. After a two-week waiting period, potential participants were contacted via telephone.

Parents were also recruited from cancer support and advocacy groups by the first author. The first author contacted key leaders of the groups who, if they approved, released information about the study to members (i.e. recruitment materials including a link to a Facebook page). Potentially eligible parents then responded if interested in participating.

Parents who responded to a recruitment attempt completed the screening process and were given additional information about the study by the study team member who recruited them. After confirming participants' interest and eligibility, a link was sent to an online Research Electronic Data Capture (REDCap™) survey via electronic mail that allowed participants to formally agree to participate and begin study procedures (Harris et al., 2009). If desired, participants could complete the agreement to participate and other REDCap™ surveys in writing.

Procedures

Parents who agreed to participate completed the demographic form and provided their interview availability through REDCap™. The interview date and time was agreed upon between the participant and the first author. The first author sent the interview question via email at least one day in advance of the interview (Hinds et al., 2007). Interviews were audio-recorded and done over the telephone by the first author at a time convenient to the parent. Seven to fourteen days after the interview, a follow-up call was made by another study team member to clarify any ambiguous details from the interview and to ensure no undue distress resulted from participation in this study. Lastly, the team member who recruited each participant manually extracted data from the child's clinical trial record into the REDCap™ database. Completion of study-related procedures was monitored on a weekly basis by the first author and when needed follow-up reminder emails were sent to participants. Participants received a \$50 gift card at the end of the study in recognition of their time and effort.

Demographic form—Participants electronically completed a demographic form via a REDCap™ survey. Questions included: child's age at P1T enrollment, gender, race, ethnicity, type of cancer, education level, and school attendance at time of enrollment in the P1T; family configuration; household income; parent education level; living arrangements; distance to the P1T center; and details surrounding transitions on and off the P1T.

Phenomenological interview—The goal of empirical phenomenological interviews is to obtain clear, rich descriptions of participants' experiences (Englander, 2012; Wimpenny & Gass, 2000). Of particular importance is ensuring that the participant describes their experiences without analysis or interpretation, using a small number of broad, open-ended questions (Colaizzi, 1978; Englander, 2012; Wimpenny & Gass, 2000). For this study, one broad data-generating question was asked:

I am interested in hearing what it was like when [child's name] was enrolled in [that study/those studies]. I would like to hear as much about the experience as you can remember, including all the circumstances, perceptions, and conversations during [child's name]'s time in the phase I [study/studies]. It is sometimes helpful to begin telling what it was like as a story, starting when you first learned about the

phase I [study/studies] through to the time [child's name] was taken off the [study/studies].

To ensure that the parent guided the discussion, there was no set agenda of topics to cover (Palys, 2008; Wimpenny & Gass, 2000). Probes such as: "Please tell me more about that" and "What did that mean to you?" were used to enhance depth of the discussion (Palys, 2008; Wimpenny & Gass, 2000). After parents finished fully describing their experiences, if any of the following were not mentioned, the interviewer asked the parent for elaboration: learning about and enrolling their child on each PIT, receiving the first dose of each PIT therapy, and transitioning off each PIT. Lastly, the parent was asked if they had any advice for parents considering enrolling their child in a PIT, and if there were any other important events or people who impacted their PIT experience.

Clinical trial data extraction—After the phenomenological interview and follow-up call were completed, selected information was retrieved from the child's clinical trial record and entered into the REDCap™ database by the team member who recruited each participant. This information included: type of trial, investigational therapy and its method of administration, concomitant medications, eating or drinking restrictions, required and optional observations included in the trial, toxicities and serious adverse events the child experienced, length of time on the trial, reason for removal from the trial, and results of disease evaluations.

Data Analysis

Interviews were audio-recorded and professionally transcribed by a contracted, Health Information Portability and Accountability Act (HIPAA)-approved provider. Data were managed using NVivo™ software.

Steps of analysis, per the adapted Colaizzi method, included the following (Colaizzi, 1978; Haase, 1987). The first author began analysis by listening to the audio-recordings to: verify and correct any inaccuracies of the transcriptions, add comments to ensure the tone of the participant was captured (e.g. laughs, pauses, emphasis, sadness, etc.), and gain a sense of the experience as a whole. Steps two to four involved identification of substantive phrases, restatement of substantive phrases in general terms, and formulation of derived meanings (see Table 1 for examples). Step five involved development of themes and organization of themes into theme clusters and categories. Step six was to generate an exhaustive description of the experience. Step seven was to describe the essential structure of parents' experiences of having a child participate in a PIT. Colaizzi's method includes a final step of participant validation of research results which was not performed in this study (Colaizzi, 1978). Concerns existed surrounding participant validation because results of a phenomenological study cannot be appreciated without parents having a phenomenological attitude or a disciplinary perspective (Giorgi, 2006; Morse, Barrett, Mayan, Olson, & Spiers, 2008; Porter, 2007).

Data analysis occurred simultaneously with participant recruitment. Thematic redundancy was established when new themes no longer emerged from interview transcripts. The demographic form and clinical trial record were used to describe the sample, understand

details specific to the PIT in which the child was enrolled, inform parents' descriptions of their experiences, and provide context for interpreting experiences.

Crucial elements of the empirical phenomenology method that were used included a phenomenological attitude adopted through bracketing and avoiding premature closure to the phenomenon, and imaginative variation to determine the essential structure of the phenomenon (Beck, Keddy, & Cohen, 1994; Colaizzi, 1978; Dowling, 2007; Gearing, 2004; Giorgi, 1997, 2006). Prior to beginning this study, the first author reflected in writing on personal and theoretical knowledge of the PIT experience. These reflections were used to recognize when the phenomenological attitude was compromised. In addition, a reflexive diary of decision-making, theme emergence, and personal responses was kept by the first author throughout interviewing and data analysis (Koch & Harrington, 1998; Kumar & Cavallaro, 2017). Lastly, the dissertation chair reviewed the first nine interview transcripts and weekly or bi-weekly assisted with data analysis to ensure that the phenomenological attitude was maintained, each step of the process was performed through discussion and consensus, and authors cared for themselves (Kumar & Cavallaro, 2017).

After data analysis was complete, two clinicians were contacted to enhance the clinical transferability of the findings (Guba, 1981; Lincoln & Guba, 1985). The first author sent the exhaustive description and essential structure to an experienced phase I physician and nurse who were asked to answer the following. (1) What ways do these findings ring true? (2) What ways do they not ring true? (3) How could these findings be useful in the design or conduct of pediatric oncology PITs? Primarily the clinicians' feedback helped to frame aspects of the discussion section, although one idea in the exhaustive description was clarified through their feedback (i.e. the team parents "formed" was changed to the team parents "assembled").

Findings

Description of Sample

The accrued sample consisted of 12 parents. Nine parents (75.0%) were recruited from pediatric medical centers, two parents (16.7%) from childhood cancer groups, and one parent (8.3%) who completed the pilot interview. The response rate at Medical Center 1 was 35.3% (6 of 17 parents of children with cancer approached to participate enrolled in this study); the response rate at Medical Center 2 was 33.3% (3 of 9 approached). All eligible parents (100%, n=2) recruited through childhood cancer groups chose to enroll. Of the parents enrolled, one parent from Medical Center 1 completed the consent and demographic forms but did not follow through and complete the interview, resulting in an evaluable sample of 11 parents (91.7% retention rate). Mean interview length was 59.1 minutes (SD=15.1, range 29.9–85.3 minutes).

Parents were mostly female (81.8%, n=2 males) and white (100%) with non-Hispanic ethnicity (90.9%; one parent did not specify ethnicity). The mean age of the children with cancer was 11.2 years (SD=5.2, range 3–17 years) at enrollment to the first PIT. Only two parents enrolled were a couple; all other participants were parents of different children. Most of the children with cancer were deceased (60%, n=6), although two children were surviving

and still receiving treatment (20%) and two children were long-term survivors and off treatment (20%). The children participated in a total of 15 P1Ts, with a mean of 1.6 P1Ts per child (range 1 – 3; median 1). The number of grade 2 or greater toxicities that the children experienced during a P1T varied from 2 to 15 (median 7, mean 7.9, SD 4.7). The maximum toxicity grade experienced by the children during a P1T ranged from grade 2 to grade 5 (median grade 3). Although racial, ethnic, and social diversity was lacking in the sample, a strong diversity in P1T experiences was captured. P1T experiences included: being removed early in the first course of a P1T, participating in multiple P1Ts, dying unexpectedly during a P1T, achieving a full remission from P1T therapy, and actively participating / considering participating in another P1T. See Table 2 for further characteristics of the sample and their P1T experiences.

Theme Categories

Data analysis identified five main theme categories. Theme categories abstracted were: (1) Being the parent of a child with high-risk cancer; (2) Contending with high-risk cancer; (3) Perceptions of their child's experiences; (4) The nature of P1T participation; and (5) Remembering and forgetting. As an exemplar, Table 3 provides a list of theme clusters and themes associated with the theme category 'Being the parent of a child with high risk cancer'. In the text below, quotes from parents are linked to the original interview transcripts via a designation which reflects participant number followed by transcript line number.

Theme Category 1 - Being the parent of a child with high-risk cancer: “This is my child here”—The overall experience of being the parent of a child with high-risk cancer embodied the weight of being fully responsible for the child's well-being and knowing that “it's all on our shoulders”. This responsibility included the child's inherent full reliance on the parent for all their needs. In addition, this responsibility necessitated that parents become an expert in their child's cancer, find a way to help their child get better, protect their child from undue harm and distress, be vigilant, prioritize their child's needs and desires over everything else, advocate for their child when needed, and encourage their child to keep trying. As one parent stated:

“I look at it kind of like ... the movie ... where he [the father] and his son are in the concentration camps and he's trying to shield his son from the horrors and trying to show him the beautiful aspects of life.”

This sense of total responsibility meant that parents felt like they knew their child and their child's medical condition better than anyone, and they felt they did not have anyone to blame when treatments they agreed to did not work. “If something does happen, and knowing that you don't know, you just kind of got to accept it.”

Parents sought and primarily achieved alignment with their child regarding the treatment plan. They looked to the child for direction and strove for open parent / child communication, e.g. “That's the decision we have to let [her] make. If she wants to try another one [P1T], if she don't want to try another one, whatever it be.” Due to the parent's underlying need for their child to agree and cooperate with the treatment plan, whenever

parent and child were misaligned, the parent sought ways to realign. “I didn’t want to be forceful I was just very hopeful that she would say, ‘yeah Mom, let’s do this’.”

Finally, being the parent of a child with high-risk cancer involved parental suffering. The emotional burdens parents faced resulted in intense angst – “that pit in my stomach” (see Table 3 for full list of emotional burdens). Underlying the burdens was the need to make good decisions on their child’s behalf and to ensure the time they had with their child was used well. “I just wish I’d had a little bit more power, a little bit more strength, a little bit more knowledge.”

Theme Category 2 - Contending with high-risk cancer: Fighting “this beast”—

Woven throughout parents’ PIT experiences was a pervasive struggle to contend with their child’s high-risk cancer. One parent described this as:

“You almost have a feeling of ... hopelessness ... you just kind of wonder from day to day, well is this the day that we’re going to have something that is going to work? ...even though you feel defeated, you still have that glimmer of hope that there’s something that’s going to work. There’s got to be something that’s going to start shrinking it.”

The full continuum of the cancer journey, which extended from diagnosis to the child’s survival or death, was focused on overcoming the cancer, underscoring the importance of not wasting time with ineffective, intolerable, or unavailable treatments. Contending with the cancer was complicated by a perception of the child’s wellness that was separate from the child’s cancer status, and made it difficult to accept the cancer worsening. “[The doctor] said, ‘Um, the cancer is back.’ And I was like, ‘What?’ I mean she never, ever showed signs.”

The team parents assembled to help fight the child’s cancer consisted primarily of the medical team and close family members, although some parents fortified their team with support from other parents of children with similar cancer diagnoses. The processes involved with having a team to help in the struggle against the child’s cancer included aligning or connecting, becoming misaligned or disconnected, and managing misalignment or disconnectedness with team members. Parents who felt disconnected from medical team members were reluctant to share those concerns with the team. “It was kind of hard to bring up our anxieties... We were just prayerful that we were being pushed in this direction [to the PIT] for good reasons.”

Parents left no stone unturned in the search for treatments, but had specific requirements for acceptable treatment options based on anticipated impact on quality of life. Parents were aware that “you necessarily have to start looking at quality of life instead of quantity at some point.” Although parents clung to hope that the next treatment would help, they also felt challenged to begin thinking about stopping their search for treatment. Parents bore the burden of decision-making at potential stopping points as they had no choice but to make a choice. They conscientiously approached decision-making by “weighing everything out”, balancing potential risks and benefits with expected impact on quality of life. Parents were

generally able to be decisive in their decision-making, and not look back after decisions were made.

Being locked in this struggle against the child's cancer necessitated finding ways to manage constant challenges and uncertainty day to day. "You're just on this moving treadmill and you're trying to keep up with the speed as it increases." Parents managed by finding a new norm for their child and family, i.e. by getting "to where we could all breathe". This resulted in a redefinition of what was considered truly difficult or problematic.

Parents transcended the day to day challenges and uncertainty of their child's struggle with cancer by finding meaning, being grateful, having hope, and relying on faith and spirituality. Parents expressed gratitude for how things went for their child, no matter the outcome. The sense that "we've been very fortunate" pervaded their experiences as they compared aspects of their journey with what they observed other families enduring. Parents' hope focused on slowing or stopping their child's cancer. At some point though, parents lost hope that their child's cancer could be stopped, regardless of their child's outcome. They were aware that their child's life was at stake. "We were okay with it [the child's unexpected death during the PIT]. I mean I was not okay with it at the time, but we knew it could happen." Parents found meaning when the time with their child was well spent and had a sense of achievement in the cancer journey – on behalf of their child and for themselves as a parent.

Theme Category 3 - Perceptions of child's experiences: "There is something about them that is very, very different"—Parents' widely perceived their child as special in two ways. They perceived their child as medically complex, e.g. "he always got the 1% side effect.". And, they described their child in a very positive light (e.g. brave, optimistic, resilient), from which parents conveyed deep pride and derived strength. Underlying parents' perceptions was a cherishing of their child and the time they spent together on meaningful activities. One parent shared a story of her daughter's interaction with another cancer patient:

"She went over [to a man just diagnosed with cancer] and she said, 'I just want you to know, you got this! You can beat this! ... It's not as bad as what people say it is.' He had said, 'It's not?' She goes, 'No, you'll have your good days and you'll have your bad days, but you'll get through it, I promise.' 'Another thing, you look good bald, so when you're done you might just stay bald.' He started dying laughing and he said, 'Well, you look good bald too.' She said, 'Yeah, it's just taken me awhile to get my baldness.'"

From the parent perspective, children's understanding of the cancer, its treatments, and decision-making was influenced by the child's age and cognitive ability. The child's age impacted their PIT experience as younger children were "too young to really have any conversations about what it [the cancer] meant" and to ask tough questions, and did not remember any other way of living. That said, almost all parents reported their children being very cooperative with cancer treatments and procedures, e.g. "they didn't really balk at it" and "he never complained". This reflected a maturity beyond their years that the children developed through their cancer journey. Regardless of age, parents described how their child

“knew how to get what [they] ... wanted” and used their cancer diagnosis to achieve their goals.

The child’s age and cognitive ability influenced parents’ decisions regarding their child’s level of involvement in treatment decision-making. All children ages 10 years and older without cognitive challenges were described by parents as making their own treatment decisions with parental support. Older children and adolescents had this decision-making role despite some parents being less certain of their child’s understanding of their own cancer, e.g. “I don’t think he realized the extent of how things had gotten at that point.” The lack of parent clarity regarding their child’s understanding of their condition occurred despite the child’s presence at and involvement in treatment discussions. “The doctors were very good at choosing words that would kind of let us know what was going on, but not so much a 12-year-old.” Parents recognized adolescents’ inherent tendency to take risks, and still let them make decisions, e.g. “he was a 17-year-old boy, so he was a risk-taker, too. So, that [PIT participation] fit right in for him.”

Theme Category 4 - The nature of PIT participation: “The further you get into a poor prognosis, the easier a phase I trial becomes”—This theme category reflects the elements of parents’ experiences specific to the PIT, and it encompasses a broad range of theme clusters, including underlying characteristics of PITs, choosing to participate in a PIT, ebb and flow of PITs, emotional stances towards PITs, and the impact of PIT participation.

The underlying PIT characteristic impacting parents the most was the uncertainty of PITs; the sense that “nothing’s ever a given” This uncertainty encompassed having to meet criteria to initially start the trial and to continue to the next course of the trial, as well as not knowing what the PIT therapy would do to or for their child. One parent stated:

“Nothing's ever a given. Even in medicine that's been proven..... we knew that... everything was a ticking time bomb. ... we just knew that certain things would not work. ... it just seemed like [the PIT] was the one that offered the most hope. And, I don't know if that was a tangible hope or not.”

Parents understood there weren’t any guarantees that the PIT would help against their child’s cancer. Some clearly expressed that “I knew it wouldn’t help [my child]”, yet were still willing to participate given their child’s poor prognosis. The hope that the PIT would help slow or stop the child’s cancer was reported by all parents. Parents were realistic in this hope, e.g. “with these studies ... we aren't even looking for the cancer to shrink; we're just looking for it to stay at bay.” Altruism and leaving a legacy were only identified by parents of deceased children ages 12 and older as reasons for participation. The appeal of PITs was a sense of trying something completely novel and of pursuing everything possible to help their child, as well as being part of research that potentially could lead to a cure.

There was evidence that PIT participation impacted how a parent managed their child’s symptoms. “Him being sick right now ... we're trying not to give him any Tylenol or anything that could whack his body out.” This resulted from an overriding fear that additional medications could exacerbate toxicities (e.g. liver or renal laboratory

abnormalities) and cause the child's premature removal from the PIT. In addition, some parents were not educated about palliative care and hospice services until after the PIT enrollment, late in the child's illness. "Nobody ever really counseled us on that. I also had this stigma about hospice services because I thought that was giving up, but it turns out [hospice services] was a very good decision."

Overall, parents approached the PIT as "just another medicine" for their child's cancer. Specific advantages parents experienced while participating in a PIT included feeling better informed and cared for during the PIT, and having access to more resources and opportunities by being at a larger PIT center. Disadvantages included having to wait to start PIT therapy, burdens of extra and longer medical appointments as well as additional procedures and venipunctures, and a sense of their lives revolving around the PIT. Parents strove to minimize the burdens of PIT participation by incorporating enjoyable activities around required PIT appointments (i.e. by making visits to the PIT center feel like "a family trip... a little get-away"). Despite feeling negative emotions at times, almost without exception parents did not regret their child participating in a PIT and recommended PITs to other parents of children with cancer.

Theme Category 5 - Remembering and forgetting: "Sometimes your brain kind of blocks things out"—All parents described a fogginess in their memories of their child's participation in a PIT and cancer treatments in general, e.g. "a lot of it is a blur." This fogginess meant that many specific details were not remembered. One parent shared:

"I'd like to forget it completely... Again, the Ronald McDonald House, ... the activities we did, the love of the city are all positives. The treatment itself, yeah, I'm really not interested in remembering a lot about it."

Parents whose child was surviving and continuing to pursue PITs remembered the specific challenges of PIT participation the clearest. Regardless of how much time had lapsed, parents remembered seminal events very clearly, including when they received particularly devastating news or were deeply offended by clinicians. Parents reported that younger children who were long-term survivors did not "remember anything about ... cancer treatments" in the long run, although they "remember some of the happy things" associated with the cancer treatment (i.e. playing with child life specialists). Most parents were not concerned with their challenges remembering PIT details, and even took comfort in not remembering.

The Essential Structure of Having a Child with Cancer Participate in a PIT

Pervasive throughout parents' descriptions of their lived experiences during PIT participation was a sense of running out of time to find an effective treatment for their child, and their need to use well the time they had with their child. Despite unique aspects of PIT participation, parents' experiences were not focused on the PITs themselves. Instead, parents were focused on their role and responsibilities as a parent, the specialness of their child, and their child's contending with aggressive high-risk cancer to survive. Parents' perceptions of their child's experiences reflected a sense of pride in their child and how their child dealt with the cancer and its treatments. What parents remembered following

participation in a PIT reflected what stood out in the experience, and how parents managed the PIT experience. Particularly important aspects of the PIT experience included the connection with the clinicians who managed the child's care during the PIT, making the choice to continue trying to slow or stop the child's cancer by participating in a PIT, and being burdened by additional requirements when participating in a PIT.

Discussion

The purpose of this study was to address the gap in our understanding of PIT participation for children with cancer or their parents, by providing a rich description of parents' experiences during their child's participation in a PIT. The overarching thread throughout parents' descriptions of their experiences was "we don't have time to waste". All participants recognized that, due to the advanced nature of their child's cancer, "the commodity is time, and you run out of it, and you don't get it back." The meaning of using time well differed between families and varied within each families' cancer journey. In some situations, it was a reason for participating in a PIT, in other situations it was a reason to stop. Further research is needed to better understand parents' decision-making related to stopping cancer-focused treatment efforts for their child, as well as to understand the role children should have in this decision.

Ethicists and clinicians have proposed that the potential benefits of pediatric oncology PIT participation may include improved QOL and hope (Barnes, Pressey, Adams, Hensler, & Madan-Swain, 2014; Beardsmore & Fitzmaurice, 2002; Carlson, Reilly, & Hitchens, 2005; Chang, 2008; Estlin, Cotterill, Pratt, Pearson, & Bernstein, 2000; Gilliam, Madan-Swain, Adams, & Pressey, 2013; Oberman & Frader, 2003; Ulrich, Grady, & Wendler, 2004). Although this study did not attempt to assess QOL benefits associated with PIT participation, study findings confirmed that PIT participation fosters hope to slow or stop the child's cancer. A potential risk of PIT participation posited in the literature was the fostering of unrealistic hope (Barnes et al., 2014; Beardsmore & Fitzmaurice, 2002; Chang, 2008; Gilliam et al., 2013; Oberman & Frader, 2003; Ulrich et al., 2004). Findings did not indicate parents had unrealistic hope. Parents were able to be realistic in their expectations of direct benefit for their child from the PIT therapy. Parents were fully aware that their child's life was at stake, and that the advanced status of their child's cancer made it unlikely their child would be cured. Parents also seemed to derive benefit from their child's PIT participation through the sense of having tried everything possible, including a novel investigational therapy, to help their child. A prospective research study is needed with parents to confirm that these benefits, which were reflected on retrospectively by parents, are also experienced by parents during PIT participation.

Another risk of PIT participation identified in the literature was the burdening of children with additional medical procedures and toxicities (Barnes et al., 2014; Beardsmore & Fitzmaurice, 2002; Carlson et al., 2005; Chang, 2008; Estlin et al., 2000; Gilliam et al., 2013; Oberman & Frader, 2003; Ulrich et al., 2004). This study found the burdens of PIT participation for children and parents included additional medical procedures, toxicities, and medical appointments, as well as having to wait to start PIT therapy and a sense of their lives revolving around meeting the PIT requirements. However, parents took the

requirements of the PIT protocol and its requirements seriously and strove to comply, even when compliance was burdensome. To make the experience less burdensome, parents incorporated enjoyable activities around the PIT requirements (e.g. special activities with the child life specialist, or visits to a favorite park). To support the efforts of parents to use time with their child well, the medical team can facilitate parents' efforts to minimize the burdens of PIT participation by incorporating enjoyable and meaningful activities around required PIT appointments.

A final risk of pediatric oncology PIT participation identified in the literature was limitations on opportunities for palliation (Beardsmore & Fitzmaurice, 2002; Oberman & Frader, 2003; Ulrich et al., 2004). The study findings provided evidence that PIT participation did impact how some parents managed their child's symptoms. The need to ensure the child stayed in the PIT and did not miss doses of the investigational therapy, sometimes was prioritized over the child's symptom management. In addition, some parents were not educated about palliative care and / or hospice services until late in the child's illness, after they had enrolled in a PIT. The latter does not seem to reflect the impact of PIT participation, but instead appears to reflect the reluctance of clinicians and parents to discuss palliative care and / or hospice when there is a focus on continuing cancer treatment. Indeed, late palliative care and / or hospice referral has previously been described in the literature as a significant problem in general for children with advanced cancer (Levine et al., 2016; Moody, Siegel, Scharbach, Cunningham, & Cantor, 2011; Waldman & Wolfe, 2013). These study findings highlight the need to simultaneously provide effective palliative care throughout the child's PIT participation (Baker et al., 2008; Meyers et al., 2004). One way to achieve this is to ensure palliative care consultations are conducted as part of the PIT consenting process, for children that were not already introduced to palliative care services (Meyers et al., 2004; Ulrich et al., 2004).

PIT decision-making and consent processes were demonstrated in this study to be impacted by the quality of communication between the child, parent, and clinicians. Parents in this study specifically highlighted how double-protection (i.e. the phenomenon of both parent and child attempting to protect each other) negatively impacted open communication and consent processes (Last, 1992). This warrants clinicians and PIT researchers paying particular attention during PIT consent conversations to the transparency of communication. The best methods for including children in cancer treatment decision-making is now better understood through Kelly et al.'s (2016) "Having a Say" construct. This construct demonstrates that children trust that their parents and clinicians act in their best interests, and depending on the specific circumstances may or may not want to have a say in treatment decisions (Kelly et al., 2016). Further research is needed on the role of the "Having a Say" construct to facilitate children's involvement in PIT decision-making. To enhance the quality of communication when cancer treatment decisions are made, clinicians should consider whether a separate conversation alone with the parent(s) is warranted, in addition to a conversation with the parent(s) and child together.

Study findings indicated that parents did not remember many details of their child's cancer treatment experiences in the long term. However, further research is needed to understand

whether not remembering is a potentially problematic repression of traumatic memories or a less worrisome natural adaptation following a period of significant stress.

Overall, parents did not regret their child participating in a PIT and would recommend PITs to other parents of children with cancer. There was a notable exception as one parents' experience with the PIT was substantively more negative, despite their child having prolonged stable disease with tumor shrinkage from the PIT therapy. This parents' PIT experience was fraught with a sense of disconnectedness from the medical team, with the child fighting taking the oral investigational medication, as well as with doubts as to whether they were doing the right thing for their child. The reasons behind this were difficult to fully appreciate without having captured the medical team's perspective. However, this parent was also the only one who really struggled with the initial decision to participate in the PIT. It is important to not dismiss this one parent's experience as an outlier, as it may reflect other unreported problematic PIT experiences. The authors recommend that in future research, an in-depth multiple case study be conducted when profoundly negative participant experiences are identified, in order to capture the perspectives of the parent, medical team, and child and to elucidate the causes of negative PIT experiences. In addition, PIT researchers and clinicians should explore with parents the reasons behind hesitations to participate or continue in a PIT. It is particularly important that PIT researchers and clinicians are aware of the significance of an offer of a PIT for parents of children with high-risk cancer, and the impact that a pre-existing parent / clinician relationship has on parents' ability to decline a PIT offer or to share concerns with clinicians during a PIT.

Limitations

The primary limitations of this study were the lack of racial, ethnic, social, and gender diversity in the accrued sample, and the lower-than-anticipated response rates from medical centers creating concerns for self-selection bias by those who chose to participate. In addition, a fuller description of pediatric oncology PIT experiences would include the child's perspective. Due to the shortened life expectancy of children enrolled in PITs, and the relatively small number of children enrolled per trial, obtaining the child's perspective was not feasible outside of a prospective, multi-center study. Lastly, this study captured parents' experiences retrospectively and parents' perceptions of their experiences may have altered with the passing of time.

Conclusions

Study findings are generally reassuring to PIT researchers and pediatric oncologists who consider recommending PITs for children with cancer. For parents of a child with high-risk cancer, a PIT represents a novel treatment option with potentially more acceptable toxicities. Although some concerns were raised by study findings regarding the experiences of parents and children in PITs, these reflect opportunities for improving the support provided to PIT participants. Parents who describe burdens in PITs would not dissuade other parents of children with high-risk cancer from participating, and indeed would continue to pursue other PITs for their own child with cancer.

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Table 1

Examples of Significant Statements, Restatements, and Formulated Meanings Developed During Data Analysis

Significant Statements (From Original Interview Transcript)	Restatements (Developed by the Authors)	Formulated Meanings (Developed by the Authors)
We just kept telling ourselves that even if we have these hesitations and we think that may be... pushing big pharma or whatever, maybe it's also because they want the best for [child's name].	Family kept telling themselves that even if they have these hesitations and family thinks that the doctors may be pushing big pharmaceutical companies or whatever, maybe it's also because the doctors want the best for their child.	Aware of competing interests. Wary of clinical trials and interests of big pharmaceutical companies. Hoping the doctors were involved in clinical trials because it was best for children with cancer, and for their child; for altruistic and not ambitious reasons.
He was all excited about doing that as well, sending samples out to wherever it needed to go. Knowing that it wouldn't help him, but it would hopefully help other people in the future.	Adolescent was excited about sending blood for research. Adolescent knew that sending the blood would not help him. Adolescent wanted to help others in the future.	It was important to the adolescent to contribute to future scientific advances. Adolescent understood that the research samples would not provide direct benefit to himself. Proud of adolescent's selflessness and for who adolescent was – someone for whom altruism was an important part of the reason for being involved with research.
I think she would have rather - and I don't really blame her since she had a port, or whatever - she would rather go have medicine put in her than have to take a pill.	Parent thinks child would have rather go have medicine put in [port] than have to take a pill.	Would have been easier to do IV medications than to have to take medications at home.

Table 2

Characteristics of the Sample and their PIT Experiences *

Item	n (%)
Parent's Annual Income (N=11 parents)	
<\$40,000	0 (0)
\$40–\$59,999	3 (27.3)
\$60–99,999	2 (18.2)
>\$100,000	4 (36.4)
Don't Know	2 (18.2)
Parent's Education (N=11 parents)	
Less Than 12 th Grade	0 (0)
High School Graduate	2 (18.2)
Some College or Professional Training	2 (18.2)
College Graduate	2 (18.2)
Graduate or Professional Degree	5 (45.4)
Distance from PIT Center (reported for N=10 children)	
Less Than 10 Miles	0 (0)
10 to 29 Miles	3 (30)
30 to 89 Miles	2 (20)
90 to 239 Miles	3 (30)
More Than 240 Miles	2 (20)
Child's Diagnosis (N=10 children)	
Sarcoma	6 (60)
Brain Stem Glioma	1 (10)
Other Brain Tumor	2 (20)
Neuroblastoma	1 (10)
Leukemia	1 (10)
Timing of Removal from PITs (N=15 trials)	
Middle of Course	13 (20)
End of Course 1	3 (20)
During Course 2	2 (13.3)
End of Course 3	1 (6.7)
After Course 3	5 (33.3)
Completed Trial	1 (6.7)
Reasons Removed from PITs (N=15 trials)	
Adverse Events / Toxicities	5 (33.3)
Disease Progression	8 (53.3)

Item	n (%)
Death	1 (6.7)
Completed Trial	1 (6.7)
Best Overall Response to PITs (N=15 trials)	
Progressive Disease	5 (33.3)
Stable Disease	5 (33.3)
Partial Response	2 (13.3)
Complete Response	1 (6.7)
Inevaluable / Unknown Response	2 (13.3)

* N=11 parents of N=10 children, enrolled in a total of N=15 phase I clinical trials.

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Table 3

Theme Clusters and Themes Associated with the Theme Category ‘Being the Parent of a Child with High-Risk Cancer’

Theme Clusters	Themes
Being fully responsible for child's well-being: “It's all on our shoulders”	<ul style="list-style-type: none"> • Child fully relying on parent • Advocating for child when needed: “If you don't, then your child's going to get pushed around” • Protecting child • Being vigilant • Prioritizing child's needs and desires over everything else • Encouraging child to keep trying: “He wasn't going to be at home ... in bed giving up” • Needing to find a way to help child get better • Needing to be an expert • Not having anyone to blame if treatments don't work • Knowing child and child's medical condition better than anyone: “They thought they knew better than I did” • Doing everything possibly can for child
Aligning with child: “We would quit whenever she wanted to”	<ul style="list-style-type: none"> • Looking to child for direction: “If that's what she wants to do ... she knows how she feels” • Striving for open communication with child: “We don't surprise her with anything. We talk about things.” • Needing child to agree with plan: “I was just very hopeful that she would say, yeah mom, let's do this” • Being on the same page: “She was willing to do it and we were willing to do it, so we tried whatever” • Becoming misaligned: “When she started resisting it was very weird for us because she's always been so accepting”
Parental suffering	<ul style="list-style-type: none"> • Indescribable angst • Watching child suffer • Fearful of harming child • Losing oneself in child's journey • Feeling isolated and alone • Doubting OR questioning own abilities • Living with regrets: “I just wish I'd had a little bit more power, a little bit more strength, a little bit more knowledge” • Feeling overwhelmed with what have to handle: Trying to keep up with moving treadmill as speed is being increased