PARTICIPANT EXPERIENCES IN PHASE I PEDIATRIC ONCOLOGY CLINICAL TRIALS

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Participant Experiences in Phase I Pediatric Oncology Clinical Trials

Phase I clinical trials (P1Ts) are the first step in testing new medical therapies in humans, and are essential for developing new and innovative therapies for children with cancer. P1Ts are ethically controversial as they are not intended to directly benefit participants, but are particularly controversial for children with cancer who are only able to participate when there is no known curative therapy for their cancer. Benefits of pediatric oncology P1T participation may include improved quality of life (QOL) and hope. Risks may include fostering unrealistic hope, burdening children with additional medical procedures and toxicities, and limiting the opportunity for palliation.

The goal of this dissertation was to investigate the P1T participation experience for children with cancer and their parents by: (1) assessing what is currently known about the participation experience, (2) exploring ways to understand and assess treatment burden and QOL during participation, and (3) interviewing parents about the experience of having a child participate in a P1T. Following a review of the literature, two studies were conducted: a longitudinal pilot study of 13 parent and child dyads who enrolled in a pediatric oncology early phase clinical trial at the recruiting institution, and a phenomenological study of 11 parents of children with cancer who participated in pediatric oncology P1Ts.

Key findings included a dearth of research on the experiences of children and parents in pediatric oncology P1Ts. Instead, existing research has focused on consent processes. The longitudinal pilot study provided some insight into experiences of children and parents during trial participation, including that there may be time points when parents' and children's perceptions of the child's quality of life substantively differ. Interviews with parents confirmed some of the anticipated benefits and risks of participation in P1Ts, and highlighted parents' sense of running out of time to find an effective treatment and needing to use time they have with their child well. Specific challenges in conducting this research were participant attrition due to disease progression and the need for multi-site research to obtain an adequate sample.

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Abbreviations	Terms
COG	Children's Oncology Group
EPT	Early phase clinical trial
HIPAA	Health Information Portability and Accountability Act
P1T	Phase I clinical trial
QOL	Quality of life
REDCap™	Research Electronic Database Capture™

CHAPTER 1

1.1 INTRODUCTION

This chapter introduces the dissertation topic of participant experiences in pediatric oncology phase I clinical trials (P1Ts). The chapter includes: a discussion of the significance of the topic, a review of the aims of this dissertation and its content, and an outline of the dissertation research study methods.

1.2 SIGNIFICANCE

P1Ts are the first step in testing new medical therapies in humans, and are essential for developing new and innovative therapies for children with cancer.[1,2] The goals of these trials are not to determine if the drugs are effective, but rather to: (1) determine the maximum-tolerated dose of the drug; (2) identify any drug-related toxicities, and (3) describe the absorption, metabolism, and excretion of the drug in humans.[1,2]

Although research related to experiences of communication and decision-making during pediatric oncology P1T consent processes has been conducted, missing is knowledge of parent and child experiences during trial participation. Research on the experiences of adult patients in P1Ts demonstrates that while P1T participation provides hope and a sense of purpose, there are significant physical, emotional, and practical burdens.[3-12] Although some insight may be obtained from adult experiences, due to children's reliance on their parents as providers, caregivers, teachers, moral compasses, disciplinarians, and proxy decision-makers, adult experiences are not directly generalizable to the pediatric population.[3-12]

Ethicists and clinicians suggest that pediatric oncology P1Ts burden children with additional medical procedures and toxicities, and may influence subsequent grief, and bereavement processes in parents and children.[13-16] However, research has not been performed on the benefits, burdens, or impact of P1T participation for children or their families. The first step of the dissertation was to conduct a background integrative review using the guiding question: What is known about how P1T participation can impact the well-being (either positively or negatively) of children with cancer and their

families? Studies identified explored experiences almost solely during the P1T consent process (see Chapter 2 for a full report of the findings).[17-27] Although the consent process is essential to the P1T experience, it is only one small piece of the experience which extends from the first discussion of the P1T, through obtaining consent, administration of therapy, and ending with the off-study transition.[4,5,7,11,28] This dissertation is the first step towards understanding the experience of pediatric oncology P1T participation.

1.2.a Importance of the Pediatric Oncology P1T Experience

P1Ts are necessary for identifying new treatments that will continue to improve outcomes for children with cancer. Cancer remains the leading cause of death due to disease in children under 14 years of age.[29,30] The five-year survival rates for several pediatric cancers have improved to more than 90%.[29-32] However, children with acute myeloid leukemia (67%), medulloblastoma (70%), hepatic (74%) and bone (73%) tumors, and rhabdomyosarcoma (64%) still have low overall five-year survival rates.[29-32]

Ethically, P1Ts are challenging to conduct due to competing interests. Pediatric oncology P1Ts are focused on improving clinical outcomes for future patients rather than directly benefiting the children participating in the trials.[33-35] The costs of running P1Ts are high, and the mean enrollment is 28 to 37 patients per pediatric oncology P1T.[1,34,36] Each child participating in a P1T can impact whether or not the investigational therapy will continue to be developed for the population. From a participants' perspective, there are burdens associated with P1T participation, including that children participating in P1Ts undergo research-only procedures that would not otherwise be performed.[33] By providing insights into participant experiences in P1Ts, this dissertation provides a foundation for balancing the well-being of children with cancer and their parents who participate in a P1T, with the high stakes of the P1Ts.

As the children enrolled in a P1T have a shortened life expectancy, the decision of children and their parents to participate in a P1T can be conceptualized as an end-of-life choice. The cancers of the large majority of children participating in P1Ts will not improve. The percentage of cancers that responded partially or completely to pediatric

oncology P1T therapies is between 3.8% and 9.6%.[1,2,37-40] The median survival time of pediatric patients with relapsed cancer after enrollment in a P1T was between 3.6 and 6.4 months.[2,39,40] The overall death rate of children participating in P1Ts ranged from 7% to 21% during the trial; however, progressive disease accounted for most of these deaths.[37,38] Patient outcomes in P1Ts are evaluated by length of survival, immediate tumor response to therapy, and toxicities. Although the quality of life and/or well-being of children and their parents are assessed in some phase III pediatric oncology clinical trials, these are not currently assessed in P1Ts. This dissertation will provide an initial understanding of how participating in a P1T can impact the end-of-life experience and well-being of children with cancer and their parents.

1.2.b Potential Future Implications

This dissertation will inform current practice and future intervention research targeted to enhance parent and child P1T experiences during their participation in a P1T. Intervention research with adult P1T participants is underway to improve palliative and supportive care provided during trial participation and when being transitioned off the trial.[41-43] Similarly, potential pediatric P1T interventions could include addressing the unique needs of parents and children that arise from trial participation; integrating supportive and palliative care within the trials; enhancing the on-trial procedure; and facilitating the transition off the P1T at trial conclusion. More specifically, this could involve an educational intervention for clinical trial nurses regarding families' experiences, a care coordination intervention which would enable nurses who work with families directly to address burdens, or a decision-making intervention to ensure that families who elect to pursue a P1T are well-informed as to what to expect during their experience in the trial.

The ethical challenge of P1Ts is to balance the need for this research with the well-being of participants. The Declaration of Helsinki requires that "the interests of the [research] subject must prevail over the interests of science and society."[44] In order to uphold ethical principles of autonomy in relation to informed consent, and non-maleficence and beneficence in relation to benefits and burden, it is important to

describe, understand, and optimize the experience and effects of the P1T on pediatric participants and their families.[33,45] Such knowledge can inform the design and management of P1Ts by providing an appreciation of the P1T experience from the perspective of parent participants. By identifying issues in the P1T experience directly from parents using their own words, the findings of this study will provide compelling evidence for securing additional funding and developing future interventions.

1.3 AIMS OF THE DISSERTATION

The central goal of this dissertation was to develop an understanding of participant experiences in pediatric oncology P1Ts. To achieve this goal, the following three chapters describe the P1T experience of participating children with cancer and their parents through an integrative review and two research studies.

Chapter 2 is a comprehensive state of the science integrative review. The primary purpose was to synthesize and appraise the evidence of how P1T participation can impact the well-being (either positively or negatively) of children with cancer and their families. The secondary purposes were to identify gaps in our understanding of the impact of pediatric oncology P1T participation, and to determine how those gaps can empirically be addressed.

Chapter 3 presents the results of the descriptive quantitative pilot study. The purposes were to assess the feasibility of having children with cancer and their parents complete measures of treatment burden and quality of life concurrent with participation in an early phase clinical trial, and to generate preliminary results from those measures.

Chapter 4 reports the results of the phenomenological study. The purpose was to identify the fundamental commonalities and meaning of the experience of P1T participation from the perspective of parents of children with cancer who participated in a P1T.

Chapter 5 synthesizes the findings from the three previous chapters, discusses strengths and limitations of the dissertation, and provides recommendations for future research and pediatric oncology P1T design and management.

1.4 DISSERTATION RESEARCH STUDIES

This section presents summary information about the methods of the two dissertation research studies.

1.4.a Descriptive Quantitative Pilot Study

The purposes of the descriptive, longitudinal pilot study were to assess the feasibility and preliminary results of having children with cancer and their parents complete measures of treatment burden and quality of life concurrent with participation in an early phase clinical trial. A prospective, longitudinal design was used to ensure participant experiences were captured throughout trial participation. Treatment burden was assessed using an adapted version of the Collection of Indirect and Non-medical direct costs (COIN) form found in the literature.[46] Quality of life was assessed with PedsQL™ modules, as these modules are extensively used in children with cancer and are validated.[47-53]

1.4.a.1 Rigor of Research.

Rigor was assured by setting measurable standards for evaluating feasibility prior to commencing data analysis. These standards were set based on an ad hoc literature review of standards used in pilot studies and on study team members' expertise with the population.

1.4.a.2 Participant Safety Plan.

This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board. Potential risks associated with study participation were minimal and included only psychological distress when completing study measures and potential loss of confidentiality. Significant efforts were taken to maintain participants' anonymity. Since participants were closely monitored in the associated early phase clinical trial, additional participant safety monitoring was not instituted for this study.

1.4.b Phenomenological Study

The purpose of the phenomenological study was to identify the fundamental commonalities and meaning of the experience of P1T participation from the perspective of parents of children with cancer. The specific aim was to develop a rich, in-depth,

phenomenological description of parents' lived experiences of having a child with cancer participate in a P1T. Empirical phenomenology with an adapted version of Colaizzi's method was used to answer the specific aim and research question.[54] Phenomenological research is used to describe the essence (i.e. the fundamental commonalities and meaning without which a phenomenon would not be what it is) of the lived experiences of people in similar life situations.[55-58] In addition, child and family demographics and the clinical trial record were used to describe the sample, understand details specific to the P1T in which the child was enrolled, inform the parents' description of their experiences, and provide context for interpreting experiences.

Empirical phenomenology was chosen because: (1) Parents of children who participated in P1Ts are likely to have experiences that are rich in meaning and not previously elucidated. (2) Narratives of personal experiences are an important first data source for capturing the experience, perceived meaning of the experience, and the experience's resultant impact. (3) Empirical phenomenology has been an important first step in programs of research that ultimately focused on developing interventions to improve patient quality of life outcomes. (4) The systematically derived products of empirical phenomenology, both the exhaustive description and the essential structure of the experience, will be rich sources of information for further research.

1.4.b.1 Trustworthiness of Research.

Although there is no consensus on how to achieve rigor in qualitative research, it is generally accepted that qualitative studies must be conducted in ways that enhance the trustworthiness of the findings.[59-63] In this study, trustworthiness was enhanced by strategies reflecting Lincoln and Guba's four components of rigor in qualitative research: credibility, transferability, dependability and confirmability.[59,64]

Credibility, the truth value of the findings,[55,68] was achieved by: (1) adopting a phenomenological attitude when interviewing participants and analyzing data, (2) conducting bi-weekly meetings for discussion, consensus, guidance, and debriefings, and (3) using data from the Demographic Form and the Form for Extraction of Data from

Clinical Trial Record to inform the parents' description of their experiences and provide context for interpreting experiences.[59,60]

Transferability, the generalizability of the findings,[55,68] is inherently achieved by well-conducted empirical phenomenological studies, with adequate sampling.[59,65] The essence of the lived experience of a phenomenon, which is the finding of a well-conducted empirical phenomenological study, is intrinsically generalizable when it captures the fundamental commonalities and meaning - regardless of context - without which the phenomenon would not be what it is.[65] The clinical applicability of the findings is an important consideration in the generalizability of health research. In this study, clinical applicability was evaluated via clinician validation of findings. After data analysis was complete, feedback was obtained on the study findings from two experienced phase I clinicians (one physician and one nurse) from different participating phase I centers.

Dependability, the consistency and repeatability of findings,[55,68] was achieved by: (1) manually verifying the transcribed interview with the audio recording prior to starting data analysis, (2) ensuring adherence to empirical phenomenology and in particular to Colaizzi's method of data analysis, (3) reviewing the transcribed interviews and analysis to ensure that formulated meanings reflect the participants' interview data, (4) using NVivo™ functionality as an audit trail, and (5) maintaining a reflexive research diary of decision-making and theme emergence.[59,60,66]

Confirmability, the consideration of whether the findings can be corroborated,[55,68] was achieved through: (1) adopting a phenomenological attitude when interviewing participants and analyzing data, (2) using written reflections on prior personal and theoretical knowledge to identify lapses in bracketing, (3) using NVivo™ functionality as an audit trail, (4) maintaining a reflexive research diary of decision-making and theme emergence, and (5) using data from the Demographic Form and the Form for Extraction of Data from Clinical Trial Record to inform the parents' description of their experiences and provide context for interpreting experiences.[59,60,66]

Colaizzi's method includes a final step of participant validation of research results.[54] Participant validation is contentious, however, because the results cannot be appreciated without a phenomenological attitude and a disciplinary perspective.[60,61,65] Based on these concerns, participant validation was not done on this study's results. In lieu of this step, clinician validation of results was conducted.

1.4.b.2 Participant Safety Plan.

This study was approved by the Indiana University Institutional Review Board. Potential risks associated with study participation were minimal. Risks included psychological distress due to the sensitive nature of the topic and potential loss of confidentiality. Participants were notified of these risks during the informed consent process. All possible efforts were undertaken to de-identify and secure the data collected. If any concerns related to participant distress arose during study procedures, participants were reminded that participation was voluntary and they could refuse to answer any questions, end the interview, or withdraw from the study without fear of repercussions. Psychological distress was assessed during the interview and the follow-up call through participant comments and by the assessment of study burdens and benefits (i.e. completion of the Modified Pessin et al. Instrument).[67] In particular, participants who responded that they were burdened to any extent by participation in the phenomenological study were asked if it would be helpful to speak to a psychosocial professional.[67] If emotional or psychological distress that could require professional support was identified, there was a clear procedure for intervention and follow-up.

In addition, records of recruitment refusals and feedback from participants were maintained throughout the study. On a bi-weekly basis the following were reviewed: participant responses to recruitment attempts in terms of number of refusals, methods of contact, and reasons for refusal; and any negative feedback from participants. If any concerning trends were found, the Institutional Review Board was to be notified and adjustments made to recruitment strategies and / or study procedures.

Based on prior work with bereaved parents, it was anticipated that negative psychological reactions by participants would be uncommon and generally very mild in

severity.[68] There are no documented instances of research with bereaved parents, in general, that resulted in distress requiring professional help or resulting in lasting harm.[68,69] In contrast, bereaved parents frequently describe research participation as positive and personally beneficial, and afterwards do not regret participating.[68,70,71] Bereaved parents have provided the following recommendations for researchers.[68,70,71] (1) The first recruitment approach be in written form. (2) The parent decides where, when, and how long to meet. (3) Opportunities are provided for the parent to share memories of their child. (4) The researcher uses empathic statements and takes care of the parent throughout the research. (5) The parent controls the pace and direction of interviews. (6) The parent has an opportunity to speak with researchers following the research. (7) The parent is offered an opportunity to learn study results. This study followed all of these recommendations.

1.5 CONCLUSION

The cancers of the large majority of children participating in P1Ts will not improve. To uphold ethical principles of autonomy in relation to informed consent, and non-maleficence and beneficence in relation to benefits and burden, the experience and effects of P1T participation needs to be understood. This dissertation investigated the P1T experience for participating children with cancer and their parents by: (1) evaluating the evidence of how P1T participation can impact the well-being (either positively or negatively) of participating children and their families, (2) considering how treatment burden and quality of life impact of P1T participation might be assessed, and (3) asking parents whose child with cancer participated in a P1T to reflect on and share their experiences from throughout the P1T. This dissertation was the first step towards understanding the experience of pediatric oncology P1T participation. It can inform current practice and the design and management of P1Ts, as well as future intervention research targeted to enhance parent and child P1T experiences during their participation in a P1T.

CHAPTER 2

This chapter presents the results of an integrative review of the literature related to experiences and well-being of participants in pediatric oncology phase I clinical trials.

2.1 INTRODUCTION

Cancer remains the leading cause of death due to disease in children under 14 years of age.[31] Although five year survival rates for pediatric cancers have improved overall to 81%, for some pediatric cancers the five year survival rate is only 60%.[31] New therapies are needed to continue to improve outcomes for children with cancer. Phase I clinical trials (P1Ts) are the first step in testing new medical therapies in humans, and are essential to the development of new and innovative therapies for children with cancer.[1,2]

Although the need for P1Ts is generally accepted, these trials are ethically controversial.[14,72-81] The goals of P1Ts are to: determine the maximum-tolerated dose of the therapy, describe the action of the therapy in humans, and reveal side effects.[1,2] P1Ts are not intended to provide direct benefit to participants. Instead researchers conduct P1Ts to determine how innovative therapies may safely be given. The Declaration of Helsinki requires that "the interests of the [research] subject must prevail over the interests of science and society".[44] The ethical challenge of P1Ts is to assure the well-being of participants within the context of P1Ts.

Ethical concerns regarding P1Ts are greater in children with cancer as they are only eligible to participate in P1Ts when there is no known curative therapy for their cancer. Furthermore, children must rely on their parents as proxy decision-makers.[14,76,77,80] Enrolling a child in a P1T provides the child access to a novel investigational cancer therapy.[82-84] Parents enroll their children in P1Ts primarily based on hope of a cure for their child from the novel therapy.[17,18,25,74] However, the median life expectancy of children after enrollment in pediatric oncology P1Ts is 3.6 - 6.4 months.[2,39,40] Consequently, children enrolled in P1Ts are spending part of their remaining lives being treated in a trial that is not intended to provide direct benefit. Ethicists and clinicians propose that the potential benefits of pediatric oncology P1T

participation may include improved QOL and hope, although the risks include fostering unrealistic hope, burdening children with additional medical procedures and toxicities, and limiting the opportunity for palliation.[13-16,77,85-87] To avoid inadvertent suffering in children with cancer near end-of-life and ensure potential P1T participants are well-informed, a full understanding of how participating in a P1T impacts participants' well-being is needed.

The primary purpose of this integrative review was to synthesize and appraise the evidence of how P1T participation positively or negatively impacts the well-being of children with cancer and their families. The secondary purposes were to identify gaps in our understanding of the impact of pediatric oncology P1T participation, and to determine ways existing gaps can be empirically addressed.

2.2 THE RESILIENCE FRAMEWORK

Review findings were synthesized using the Resilience in Individuals and Families Affected by Cancer Framework (Resilience Framework), the organizing framework for nursing research conducted through the Children's Oncology Group (COG).[88,89] This framework is used to facilitate an understanding of how children and families sustain or regain well-being after a pediatric cancer diagnosis, and guide interventions that can promote child and family well-being (see Figure 2.1).[88-91] For children and their families participating in P1Ts, the Resilience Framework can provide an organizing structure for understanding how experiences during the P1T impact the overall well-being of children and their families.

The Resilience Framework includes two risk factors (illness-related distress and defensive coping); four protective factors (family environment, social integration, courageous coping, and derived meaning), and one outcome factor (well-being).[88,89] See Table 2.1 for definitions of factors. The risk factors are negatively associated with well-being, and the protective factors are positively associated with well-being. The well-being outcome factor includes positive health outcomes such as global QOL, resilience, a sense of confidence and mastery, and self-transcendence.[88] Per the Resilience

Framework, courageous and defensive coping are not mutually exclusive; some coping strategies encompass elements of both factors.[88]

To ensure that burdens associated with P1T participation were captured, for this review treatment burden was an additional indicator of the illness-related distress risk factor. Treatment burden refers to the workload associated with a treatment for a patient and their family, including the physical, financial, time, psychosocial, and procedural demands that a treatment places on a patient and their family.[92-95]

2.3 LITERATURE SEARCH

This integrative review was conducted using the Whittemore and Knafl method.[96] Two literature searches were performed in December 2016 in PubMed and CINAHL Complete (EBSCO) databases, as summarized in Figure 2.2. The first search used the key words (1) 'cancer' or 'oncology'; (2) 'child' or 'pediatric'; and, (3) 'phase 1', 'phase I', 'clinical trials, phase 1 (as topic)', therapies, investigational', 'early phase' or 'early trials'. In total, 2,386 articles were identified. For the purposes of this review, children included individuals less than 18 years of age. Articles that were expert opinions and/or theoretical discussions, non-English, published prior to 1985, lacking an abstract, or not relevant to the purposes of the review were excluded. An extensive date range was included due to the anticipated paucity of articles and the desire to capture historical trends in the P1T experience. Articles concentrating solely on clinical trial procedures (e.g. the quality of the P1T consent process) were excluded. The reference lists of the included articles were examined using the criteria above, resulting in a total of 20 remaining articles.

The second search focused on adults, given the paucity of articles identified for pediatric P1T participant experiences or well-being. Key words were as above, excluding the key words 'child' or 'pediatric'. Since a total of 17,197 mainly irrelevant articles were identified, the following key words were used to refine the adult literature search: 'participation', 'qualitative research', 'psychosocial factors', 'burden' or 'supportive'. In total, 3,237 articles were identified and screened per above. In addition, because informed consent procedures are fundamentally different with adult and pediatric

participants, articles that solely considered participant experiences during P1T consent processes were excluded. After screening and reviewing the reference lists of included articles, 31 additional empirical articles were identified that described the experience or well-being of adults during their participation in oncology P1Ts.

2.4 DATA EVALUATION

Per the Whittemore and Knafl method, all articles were evaluated based on relevance to the review purposes and on theoretical or empirical rigor.[96] Scores were assigned as either 'High', 'Medium', or 'Low' separately for both relevance and rigor (see Table 2.2 and Table 2.3).[96] The primary researcher completed assessments of all articles in the sample. The dissertation chairthen independently performed a confirmatory assessment of 10 randomly selected articles (five pediatric and five adult). Articles were not excluded based on their data evaluation ratings, however, the ratings were considered during analysis when determining the level of available supporting evidence.[96] Table 2.4 summarizes article evaluation results.

2.5 FINDINGS

Of the 20 pediatric articles (listed in Table 2.2), 11 were empirical research studies, one was a case report, and eight were meta-analyses of results from multiple P1Ts. Considering just the 11 empirical studies, one analyzed end-of-life care provided to P1T participants, one considered nurses' perceptions of P1Ts, and the remaining nine examined experiences during P1T decision-making. Minimal empirical evidence was found regarding the experiences or well-being of children with cancer or their families during their P1T participation, beyond the process of consenting to a P1T. All 31 adult-focused articles (listed in Table 2.3) were empirical articles exploring adult patient and family experiences in a P1T.

2.5.a Risk Factor: Illness-Related Distress

For children with cancer and their parents considering participation in a P1T, there was some evidence that overall well-being was associated with being able to perform usual physical activities, and not experiencing side effects from cancer or its treatments.[17] Performance scores are a measure of general well-being and ability to

complete activities of daily living.[97,98] At enrollment, children participating in a P1T had high performance scores overall, despite being heavily pretreated for their cancer.[2] This was similar to adult participants and anticipated as P1Ts have performance status eligibility requirements.[12,99-101] No significant changes in performance or overall QOL scores were found in adult participants who completed one course of P1T therapy, although Rouanne et al. found that physical health of adult participants significantly decreased during one course of P1T therapy.[6,12,101,102]

In terms of distress due to symptoms of disease, adult P1T participants had similar or higher levels of symptom burden than non-participants.[100,103] In particular, George et al.[104] found that adult P1T participants experienced poor sleep quality, which was connected to increased symptom burden and disturbances in temperament. However, there was some limited evidence that being in a P1T may have positively influenced adults' experience of their symptoms by providing hope for therapeutic benefit.[6,9] Interestingly, in one study by Rouanne et al.[12] the level of severe depression in adult P1T participants (2%) was strikingly lower than in both the general cancer population (10 to 25%) and the general healthy population (5%). There was good evidence for incorporating palliative care and / or hospice simultaneously with P1T participation for adults and children, to enhance supportive care and symptom management and to decrease psychological distress.[41,83,103,105-108] No other symptom distress data was available for pediatric P1T participants.

In terms of outcomes of P1T participation, the pediatric meta-analyses established that for most children with cancer participating in a P1T, their cancer did not improve. The combined partial and complete response rate for children enrolled in P1Ts was between 3.8 –9.6%, with reports of 17-24.5% prolonged stabilization of disease (i.e. more than three or four months).[1,2,37-40] Although the median overall survival time of children with relapsed cancer after enrollment in a P1T was between 3.6 and 6.4 months, Morgenstern et al.[40] reported 16% of children survived longer than 12 months and Kim[3] reported 5% survived longer than 36 months.[2,39,40] The median time in a P1T was 1.3 – 1.8 months or 1 cycle.[2,39,40] Overall, 13-24% of children with cancer

experienced a dose-limiting toxicity, 46.7% experienced a grade 3 or 4 toxicity, 7.6% were hospitalized due to toxicities, and 0-2.4% of children died due to toxicities experienced during a P1T.[1,2,37-40] Death rates of children participating in P1Ts ranged overall from 7-21%, however progressive disease accounted for most of the deaths occurring during P1Ts.[37,38] Despite being more heavily pretreated, pediatric patients had a similar or greater medication tolerance than adult patients enrolled on matched P1Ts.[36,109]

Although empirical research had not yet been conducted on pediatric participants' experiences during P1Ts, there was some evidence that logistics and potential impact on QOL contributed to parents' and children's decisions whether to participate in a P1T.[18,22-24] For adults, P1T treatment burdens had a significant impact on their overall QOL.[3,110] These burdens included frequent hospital visits, additional medical procedures and tests, toxicities related to the novel therapy, logistical problems such as transportation and parking, and financial cost.[3,4,110,111] These burdens were manageable and became routine for some participants, yet others continuously struggled with them and feared they would become more than they could handle.[4] There was a strong level of evidence that before entering the P1T, adult participants were either unaware of or underestimated the practical burdens of being in the trial.[3,4] After enrolling in the P1T, these burdens became more significant. Taking part in a P1T was compared to having a job in that there was a strict schedule to follow and specific tasks to be performed.[3,4,11,110,111] Overall, adults participating in a P1T experienced a sense of life being on hold during the P1T, wherein it was difficult to plan for activities as their lives revolved around the trial and its requirements.[4,11,28,111]

The role of illness-related uncertainty (which includes both complexity and ambiguity) was not well explored in the P1T experience of children or adults.[88,90] For adults, there may be more uncertainty experienced during P1T participation than during standard treatments, due to the investigational nature of the novel therapy.[4,11] Parents considering having their child participate in a P1T spoke of a high degree of uncertainty related to unknowns of the P1T and the extra testing needed to verify P1T eligibility.[17]

However, there was some evidence that for adult participants, the specific requirements involved with the P1T may have reduced uncertainty by providing a set plan to follow.[10,43,110,111] In addition, although there are many unknowns regarding the P1T therapy and its potential impact on humans, the information that was available from pre-clinical and early testing helped P1T participants cope with the uncertainty.[43,110,111]

2.5.b Risk Factor: Defensive Coping

There was good support that adult P1T participants and their families employed evasive coping strategies. Adult P1T participants who avoided transitioning to end-of-life care demonstrated the strongest evidence of evasive coping.[7,41,111] Experts similarly hypothesized that participation in a pediatric oncology P1T exacerbates the reluctance of families and healthcare providers to address end-of-life issues in children with cancer, yet there was no difference in end-of-life care provided to children in P1Ts at a large medical center with an active palliative care program.[13,15,26] There was also some evidence that adult P1T participants were at risk for using evasive coping strategies by over-relying on healthcare providers and becoming passive recipients of care.[5] This over-reliance was demonstrated by 80% of adult P1T participants who wanted the healthcare provider to tell them what they should do during trial recruitment.[5]

2.5.c Protective Factor: Courageous Coping

Overall, there was a high level of evidence that participating in a P1T was generally a positive experience that supported courageous coping and optimism in adults. This was due to participants' perception of receiving further treatment, trying something new, having the support of expert medical care, engaging with the healthcare team, contributing to cancer research, and / or having a purpose in their lives.[4,8,10,11,111-114] The stories of adults participating in a P1T consistently reflected courageous coping in attempting the unknown as well as in managing any resulting consequences.[10,28,111] For many adult patients, P1T participation fulfilled their need to have tried everything to fight their cancer.[7,10,28,111] Some courageous coping strategies, including maintaining normalcy and control over daily life, spending time with family, and focusing on QOL, were important to children with cancer and their parents

considering participation in a P1T.[17,19] No other data was available for children participating in P1Ts.

2.5.d Interactions of Defensive and Courageous Coping Factors

Haase's Resilience in Illness Model that defensive coping strategies are most prevalently used when individuals are highly threatened, until courageous coping strategies can be developed to address the threat.[91] As such, defensive coping strategies only become problematic when used exclusively and for prolonged periods of time, without development of courageous coping strategies.[91]

Although the optimism associated with clinical trial participation was potentially beneficial for both adult and pediatric P1T participants (a courageous coping strategy), potential harm could be created by unrealistic optimism (a defensive coping strategy).[15,18,41,80,115] Unrealistic optimism is a belief, regardless of the quality and clarity of information communicated regarding a P1T, that one has a greater chance of personal benefit from P1T participation than any other patient.[74,116] All P1T participants (or their parents / guardians) sign an informed consent document acknowledging their understanding of the nature of the P1T. Despite this, there was a high level of evidence that adult and pediatric P1T participants and their families thought and acted like the P1T therapy would improve, or even cure, their cancer.[18,19,23,24,27,41,114,116] Unfortunately, for adult participants, expectations for tumor response and symptom improvement generally were not met during P1Ts.[11,110,112,117] However, it is unclear how significant a problem unrealistic optimism was for P1T participants.[115,116,118] There was evidence that adult P1T participants were able to be realistic about their prognosis and yet still hopeful about the P1T, which supports Weisman's assertion that patients may be simultaneously accepting and denying the dying experience.[10,28,114,119-121]

There was some evidence of both defensive and courageous coping strategies being used by adult P1T participants at trial conclusion. Trial conclusion was a particularly difficult time for most adult P1T participants because it signaled cancer progression and was accompanied by a loss of optimism.[4,7,10,11,43,111] Despite this, there was evidence that at trial conclusion adult P1T participants maintained hope that others

would be helped by their participation in the P1T.[7,11,43] At trial conclusion, adult P1T participants also coped with disappointment that the P1T did not work for them, relief that they no longer had to manage the P1T burdens, a loss of control when the decision to leave the P1T was made for them by healthcare providers / researchers, and fear of abandonment by the medical experts who had been caring for them.[4,10,11,43,111] No data were available regarding children's experiences at trial conclusion.

The articles describing adults' P1T experiences included discussion regarding whether P1T participation represented 'survival work' and hence detracted from 'death work'.[7,10,41] Survival work refers to the cognitive and behavioral tasks involved with choosing to seek further treatment to improve and / or cure one's disease, versus letting it take its natural course.[28] Death work consists of the tasks involved with preparing for one's death practically, emotionally, socially and spiritually.[122] Unfortunately, most P1T participants died during or shortly after trial conclusion; adult P1T participants engaged in significant survival work and therefore lost opportunities to complete death work.[7,28,112] This trade-off in survival and death work was another example of the interaction between courageous and defensive coping strategies, as P1T participants' survival work reflected courageous coping, while the simultaneous avoidance of death work reflected defensive coping.

The idea that death work may be altered by P1T participation was founded in Glaser and Strauss' recognition that dying involves a psychological process of adjustment, and the most crucial phase in the dying process occurs with recognition that a cure is not possible, and that death will occur in the foreseeable future.[123,124] However, instead of viewing P1T participation as lost time where death work wasn't completed, P1T participation may better be viewed as one of the different trajectories that can be taken in the dying process.[7,10] There was no evidence that adult P1T participants would have engaged in death work absent P1T enrollment.[7,10] Indeed, there was some limited evidence that adult patients who participated in a P1T more frequently enrolled in hospice and were more likely to die at home or in hospice, and that the end-of-life care provided to children with cancer who participated in a P1T did

not differ from non-P1T participants at a large medical center with an active palliative care program.[26,125]

In the pediatric literature, the impact of P1T participation on death work had only been minimally studied. There was some evidence that parents of children with cancer were only able to consider non-curative options, such as hospice, after accepting that their child could not get better.[20,23] Ethicists and clinicians hypothesized that the participation of children with cancer in P1Ts not only alters their own death work, but also the grief work of their parents (who serve as proxy decision-makers).[14,41] The child's P1T participation theoretically minimized parents' ability to engage in anticipatory grieving and prepare for their child's death, potentially leading to more incidences of complicated bereavement.[41] There was some evidence that although partners of adult P1T participants did not generally regret participating in the P1T, two years after the participant's death they experienced more depression, psychological distress, complicated grief and decreased social and mental functioning compared to population norms.[126]

2.5.e Protective Factor: Social Integration

Overall, the pediatric and adult articles generally reinforced the importance of strong social support (which includes the support of friends, health care providers, and the community) to the patient's well-being.[88,90,91] There was limited evidence that adult P1T participants reported higher levels of social integration than non-participants.[101] Although the lack of pediatric research lessened an understanding of how P1T participation impacted children's social integration, there was strong evidence that pediatric P1T participants were included in decision-making discussions with healthcare providers.[24,27]

Cox described the 'therapeutic alliance' that was formed between adult P1T participants and healthcare providers, where participants benefited from the sense of everyone working together to actively fight their cancer.[4,10] There was a strong level of evidence that adult P1T participants experienced enhanced support of high-quality healthcare and valued effective communication with healthcare providers.[4,8,10,11,111,117]

Indeed, adult P1T participants who traveled to a different geographic location to participate in the P1T were adversely affected by losing the support of their original healthcare providers.[3] Adult P1T participants also experienced feelings of abandonment if their connection and shared goals with the P1T healthcare providers were lost at the end of trial participation.[4,43,111] Adult P1T participants frequently experienced gaps in support and information at trial conclusion and would have benefited from assistance coping with being removed from the trial and transitioning back to their original healthcare providers.[4,11,42,43,117] No empirical data on the impact of the therapeutic alliance with health care providers was available for children participating in P1Ts.

An important societal influence prevalent in Western culture is the expectation that people with cancer are to be brave and to fight to overcome their cancer.[10] There was some limited evidence that this societal expectation could influence adults' participation in a P1T, since stopping treatment could be socially discouraged as giving-in and losing hope.[10,11] The impact of societal influences on P1T participation was not explored in the pediatric articles, however such influences represented a potential threat to social integration as a protective factor.

2.5.f Protective Factor: Family Environment

Family environment was generally accepted as important to P1T participants' well-being, however there was minimal empirical work on the role and impact of family during the P1T experience.[11,17,21,112,113,117] There was some evidence that the inclusion of the adult participant's family when developing the P1T plan of care enhanced communication.[11,117] Adult participants expected increased support from their family during the P1T and tended to receive support beyond those expectations.[117] There was also some evidence that traveling away from family to participate in a P1T adversely affected the well-being of adult P1T participants.[3] Kessler et al.[127] found that caregivers of adult P1T participants reported high levels of distress, anxiety, and depressive symptoms, suggesting that enrollment in a P1T places a considerable burden on family and caregivers in terms of scheduling and managing the patient's care. No empirical family environment data was available for children participating in P1Ts.

Double-protection was identified in the pediatric articles, reflecting a potential threat to the protection offered by the family environment. Double-protection is a phenomenon wherein both parent and child attempt to protect each other from distress, which while based in the intention to be supportive, reflects an evasion of open communication.[128] Barrera et al. and Hinds et al. both provided empirical evidence that children who had recently been enrolled in a P1T demonstrated an awareness of the advanced state of their cancer and of their parents' emotional turmoil.[17,19] This suggested that the child's assent to participate in a P1T may not have solely reflected their own desires, but may be influenced by a desire to ease their parents' suffering or to acquiesce to their parents' wishes.[17,19]

2.5.g Protective Factor: Derived Meaning

For children and adults with cancer, there was a high level of evidence that P1T participation offered hope that positively influenced well-being.[4,7,10,11,17,28,111,113,114,121] Adult P1T participants attributed meaning to simply being offered the opportunity to participate in a P1T; the offer engendered feelings of being special and chosen because only a few individuals were extended the opportunity.[4,5,7,28,114] However, parents who were considering enrolling their child in a P1T struggled to balance hope for a cure with the potential negative impact of the P1T on their child's well-being.[17]

When prematurely removed from a P1T due to disease progression or toxicities, adult P1T participants lost hope for stabilization of cancer and / or symptom improvement.[7,11,43] Yet although adult P1T participants experienced feelings of despair at this time, there was also evidence they maintained some degree of hope that others would be helped by their participation in the P1T.[7,11,17,43] Even if not personally benefiting from the P1T, adult participants generally did not regret participating in the trial. Having the opportunity to try a novel treatment, to help themselves, to help others, and to contribute to future scientific advances, all provided meaning for adults' P1T experiences.[4,11,110,113,114,117,121] No data were available for children's experiences at trial conclusion.

Other findings related to the use of hope and spirituality to find meaning included Daugherty et al.'s findings that adult P1T participants had higher levels of spirituality than non-participants and that P1T participants most commonly used a collaborative religious style of problem-solving.[119] In addition, parents who were offered the option of a P1T for their child with cancer held onto different forms of hope, including hope for a peaceful death.[17]

2.5.h Outcome Factor: Well-Being

Well-being includes positive health outcomes like global QOL, resilience resolution, and self-transcendence, yet QOL was the only well-being outcome assessed in the articles.[88] For adult P1T participants, QOL was focused on the ability to function, be productive, and free from symptoms of disease and treatment side-effects.[3,11,112] In adult participants, no significant changes were found in overall QOL scores over one course of P1T therapy.[6,12,101,102] There was some evidence that older adults participating in P1Ts established their QOL by comparison with their own prior treatment experiences and health, and by social comparison with peers.[3,9] Even though there was minimal empirical evidence regarding whether the QOL or well-being of children or their families was impacted by P1T participation, there was a high level of evidence that QOL was a contributing factor to the decision to participate in a pediatric oncology P1T.[17-21,23,24]

2.6 DISCUSSION OF FINDINGS

2.6.a Primary Purpose: Synthesize and Appraise Evidence

Overall, this review established that there is minimal empirical evidence regarding the experiences or well-being of children with cancer or their families in a P1T, beyond the process of consenting to the P1T. This lack of pediatric-focused research restricts our understanding of the impact of pediatric oncology P1T participation on the well-being of child participants and their families. However, meta-analyses and empirical studies focused on adult P1T participants and the pediatric oncology P1T consent process provided additional insights. Although the prognosis for children enrolled in a P1T is poor, these trials are generally safe, have manageable toxicities, and offer some hope for at least stabilization of disease for several months.

The Resilience Framework highlights that risk factors impacting the well-being of children with cancer include illness-related distress and defensive coping; whereas protective factors include courageous coping, derived meaning, social integration, and family environment.[88] Per review findings, P1T-related treatment burdens may include increased hospital visits, additional medical procedures and tests, toxicities related to the novel therapy, logistical problems such as transportation and parking, and financial cost. The role of strong family and social support in fostering the patient's well-being is well-recognized. It is important to also recognize the burden that P1T participation places on family members, and that travel away from family and friends to participate in a P1T may adversely affect the well-being of P1T participants.

As P1T participation focuses providers', patients', and families' attention on survival work (courageous coping), review findings suggest participation may foster avoidance of death work (defensive coping) that could negatively impact the child's dying process and /or the family's bereavement. However, defensive coping strategies only become problematic when used exclusively for long periods of time, without development of courageous coping strategies.[91] Courageous coping strategies may be supported through P1T participation by providing a sense of trying everything, allowing participants to form a therapeutic alliance with healthcare providers, representing a contribution to cancer research, and providing a purpose and meaning for their lives.

Although not explored in the pediatric articles, further research is warranted regarding whether children or their parents feel compelled to battle their cancer heroically, to live up to societal – and perhaps familial - expectations. The unnaturalness of death in children and the fact that multiple stakeholders (i.e. child, parents, and providers) need to come to an agreement to stop curative attempts, are other potential societal influences on the decision to participate in a pediatric oncology P1T. Double-protection may be particularly influential to children's participation in a P1T as they seek to ease their parents' suffering or to acquiesce to their parents' wishes, due to the vital importance of the parent-child relationship for children.[129]

2.6.b Secondary Purpose: Gaps in Knowledge

Insights were gained from research on the experience of adult P1T participants, however adult experiences are not directly applicable to the pediatric population. As demonstrated in Table 2.2 and Table 2.3, the reviewed articles employed a wide variety of research designs. The methods used to research the experience of adult P1T participants may be helpful to guide future research with pediatric participants. A unique challenge of researching experiences of P1T participants is that poor patient prognoses and disease progression results in decreased participant retention and completion of study procedures at later timepoints. A limitation of relying solely on quantitative QOL measures is that adult P1T participants' ratings on QOL measures differed substantively from what these same participants reported during qualitative interviews.[6,111]

From the adult focused articles, the work of Dr. Karen Cox is noteworthy in that it provides an exemplar of how research on adult experiences in P1Ts proceeded from initial descriptive studies to testing an intervention in an experimental study.[4-7,42,111,130] Dr. Cox's research began with a small, longitudinal qualitative pilot study.[111] After identifying areas of potential concern in the P1T experience, she then conducted a larger-scale longitudinal study with 55 adult P1T participants.[4,6] Based on this second study, the transition off a P1T was identified as a significant area for intervention. Dr. Cox then developed a nurse-led intervention to improve patient management at the end of P1T participation, which was tested in a randomized, pre-post intervention study.[48,7]

2.6.c Limitations of the Review

Literature searches were limited to English language articles. In addition, use of a different framework than the Resilience Framework to synthesize findings would have resulted in a different organization of findings. Lastly, article evaluations were susceptible to bias as the researchers were not blinded to authors, journal, or publication year.

2.7 IMPLICATIONS FOR NURSING PRACTICE AND RESEARCH

Review findings have implications for nurses and healthcare providers who work with children and families considering pediatric oncology P1Ts. The idea that a child's assent to participate in a P1T may not solely reflect their own desires, but instead may be influenced by a desire to ease their parents' suffering or by family and societal expectations, warrants particular attention. Children should have an active voice in the decision to participate in the P1T, and be directly addressed in consent discussions at an appropriate developmental level.[129,131,132] Communication during P1T consent conversations is often inadvertently falsely reassuring.[133] The impact of P1T participation on QOL and well-being, as outlined in this review, should be included in consent discussions, as well as the option of stopping treatment and focusing solely on palliative care.[81,133]

2.8 CONCLUSIONS

The experience and effects of P1T participation on children and families need to be better understood to uphold the ethical principles outlined in the Declaration of Helsinki.[44] By understanding the impact of P1T participation on participants' well-being, P1T researchers can acknowledge participants' contributions, incorporate participants' views into P1T management, enhance future participants' preparedness, and ensure care is effectively provided throughout the P1T experience.[5] Further research is needed that focuses on understanding the impact of participating in a P1T on the well-being of children and their families, in order to address gaps in current knowledge and ensure the P1T experience does not inadvertently impact the well-being of participating children with cancer and / or their families.

FIGURE 2.1 RESILIENCE FRAMEWORK

(Reprinted with permission)[88,89]

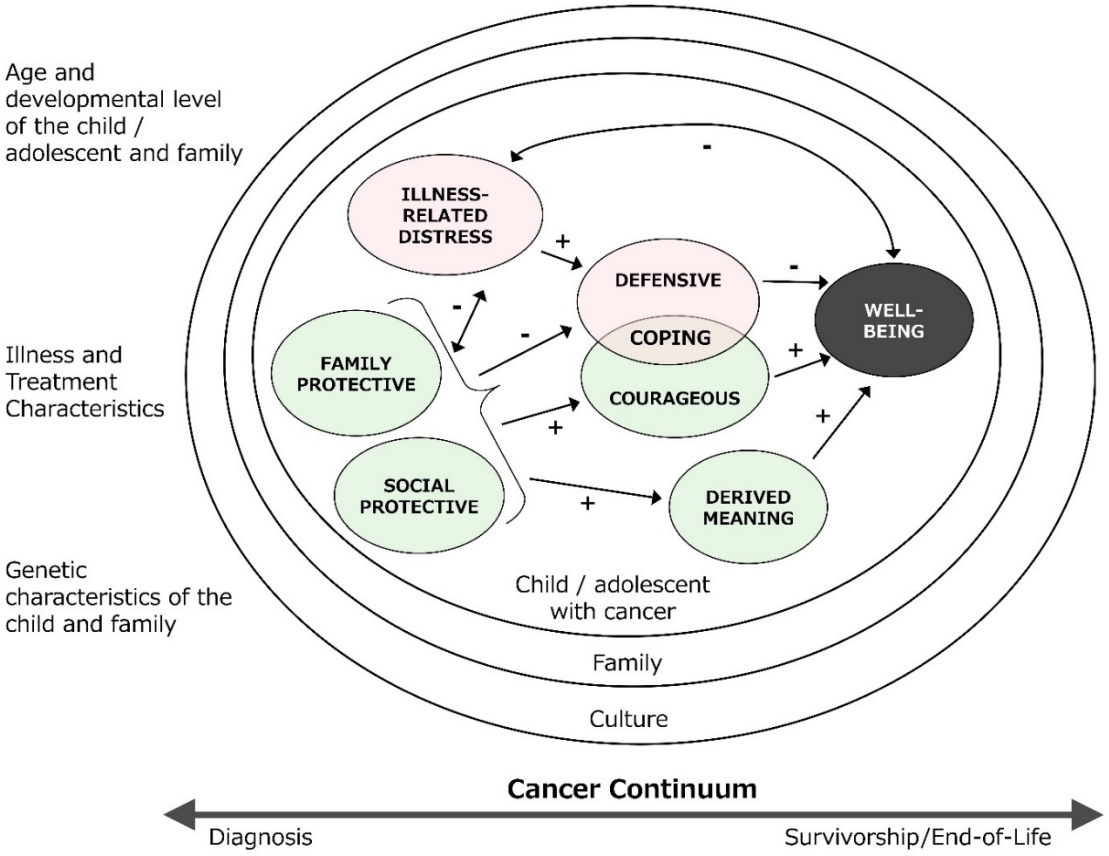

FIGURE 2.2 PRISMA FLOW DIAGRAM

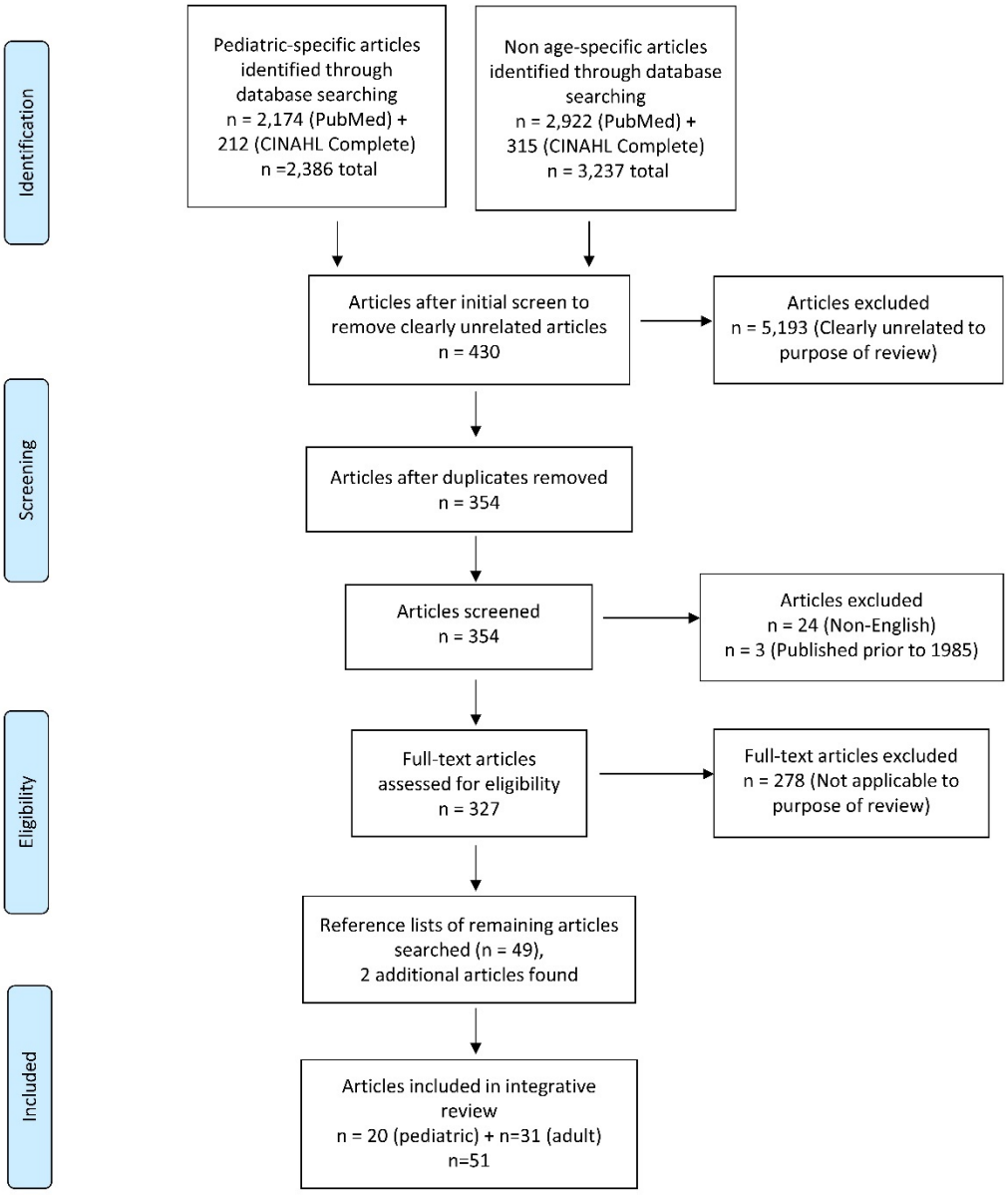

TABLE 2.1 DEFINITION OF FACTORS FROM THE RESILIENCE FRAMEWORK

(Reprinted with permission)[88]

Risk Factors	Illness- Related Distress	The degree of perceived illness-related uncertainty, disease- and symptom- related distress, and burdens associated with treatment for disease. *
	Defensive Coping	The degree to which the patient/family member uses evasive and emotive coping strategies to deal with the cancer experience.
Protective Factors	Courageous Coping	The degree to which the patient/family member uses confrontive, optimistic, and supportant coping strategies to deal with the cancer experience.
	Social Integration	The degree to which the patient/family perceives a sense of connectedness with and support from friends and healthcare providers.
	Family Environment	The degree to which the patient/family member perceives the family as adaptable, cohesive, effectively communicating, and having family strengths.
	Derived Meaning	The degree to which the patient/family member uses hope and spiritual perspective to derive meaning from the cancer experience.
Outcome Factor	Well-Being	The process of identifying or developing resources and strengths to flexibly manage stressors to gain a positive outcome, a sense of confidence/ mastery, self- transcendence, and self-esteem.

* Treatment burden was added as an additional indicator of Illness-Related Distress

TABLE 2.2 FINDINGS AND EVALUATION OF PEDIATRIC ARTICLES

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Barrera et al.[17] / Health-Related Quality of Life and Enrollment in Phase I Trials in Children with Incurable Cancer	To investigate health-related QOL in children eligible for P1Ts and the reasons why families participate in these trials	Nine families of children with cancer presented the option of a P1T at a Canadian hospital	• Qualitative study • Individual semi-structured interviews with parents and children	• Key components to health-related QOL were maintaining normalcy and control, information sharing, and having hope for life • Hope for a cure and prolonging the child's life were the main reasons for enrolling in P1Ts	Medium	High
Bautista et al.[39] / Patients in Pediatric Phase I and Early Phase II Clinical Oncology Trials at Gustave Roussy: A 13-Year Center Experience	To describe the experience in clinical new drug development in pediatric oncology at Gustave Roussy	All solid tumor patients below the age of 21 who enrolled in a phase I (n=106) or II trial (n=154) from 2000 - 2012	Meta-analysis of previously reported phase I and phase II clinical trial results	• Phase I and II pediatric oncology trials are safe, associated with clinical benefit, and can be successfully integrated in current relapse strategies	High	Medium
Carlson et al.[109] / Pediatric Phase I Drug Tolerance: A Review and Comparison of Recent Adult and Pediatric Phase I Trials	To evaluate the ratio of pediatric to adult maximum tolerated doses from P1Ts	70 P1Ts conducted from 1975 - 1995, where pediatric and adult P1Ts could be matched	Meta-analysis of previously reported P1T results	• Pediatric patients have an equal or greater medication tolerance than adult patients enrolled on matched P1Ts • Patients on adult P1Ts are significantly less heavily pretreated than patients on matched pediatric P1Ts	High	Low
Chang[15] / An Exploratory Survey of Nurses' Perceptions of Phase I Clinical Trials in Pediatric Oncology	To evaluate nurses' perceptions of P1Ts	43 nurses from a large North American hospital surveyed in 2003	Exploratory survey study using qualitative and quantitative questions	• Nurses identified benefits of P1Ts as improving future therapies, QOL, disease burden, and hope, and negative outcomes as toxicities, false hope and decreased QOL	Low	Medium

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Cousino et al.[27] / Communicating and Understanding the Purpose of Pediatric Phase I Cancer Trials	To investigate physician-parent communication during informed consent conferences and parental understanding of the P1T purpose	85 P1T informed consent conferences and 60 follow-up parent interviews conducted at six hospitals from 2008 - 2011	• Multi-site, prospective study • Quantitative analysis of qualitative data from recorded informed consent conferences and parent interviews	• After informed consent conferences, many parents do not understand the scientific purpose of P1Ts • Physician explanations during informed consent conferences did not ensure parental understanding • Child attended 83 of 85 observed informed consent conferences	High	Low
Deatrick et al.[18] / Parents' Views of their Children's Participation in Phase I Oncology Clinical Trials	To describe parents' views about their children's participation in P1Ts	21 parent interviews following a P1T decision, taken from a prospective study of end-of-life decision-making	Secondary, qualitative analysis of data from a prospective, descriptive study of pediatric oncology end-of-life decision-making	• All parents saw limited choice in the decision whether to enter their child in the P1T • Parent expectations of trial participation included providing treatment, buying time, working a miracle, being altruistic, and delaying death • Parental circumstances, including practical issues, the child's capacity and spirituality, were important to perceptions of P1T participation	High	Medium
Furman et al.[37] / Mortality in Pediatric Phase I Clinical Trials	To determine the risk of fatal toxicity and objective response rate in pediatric P1Ts	577 pediatric enrollments on 30 P1Ts at one hospital from 1967-1989	Meta-analysis of previously reported P1T results	• Well-planned phase I clinical trials do not expose children to an undue risk of fatal toxicity and offer slight hope for a therapeutic effect	High	Low

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Hinds et al.[19] / End-of-Life Care Preferences of Pediatric Patients with Cancer	To identify preferences of children / adolescents with cancer about their end-of-life care and the factors that influenced their decisions	20 pediatric patients (>10 years), their parent, and their primary oncologist interviewed after making an end-of-life decision	• Qualitative, prospective study • Individual, open-ended interviews with patient, parent and oncologist within 7 days of end-of-life decision	• Children / adolescents with cancer realized they were involved in an end-of-life decision, understood the consequences, and were capable of participating in the decision • Consideration of others' preferences was the most frequently reported decision-making factor by patients, parents, and physicians	High	Low
Hinds et al.[20] / Decision Making by Parents and Healthcare Professionals when Considering Continued Care for Pediatric Patients with Cancer	To define the treatment-related decisions considered most difficult by parents of pediatric patients and the factors that influenced decisions	39 parents of a child with cancer deceased in the previous 6-24 months and their child's primary provider	• Mixed methods retrospective study • Individual, semi-structured interviews with parent and provider	• Parents and healthcare professionals cite similar decision-making factors, but differ in their rating of the factors' importance • Once parents conclude their child cannot get better, they are more likely to choose non-curative options	High	Low
Hinds et al.[21] / "Trying to be a Good Parent" as Defined by Interviews with Parents who made Phase I, Terminal Care, and Resuscitation Decisions for their Children	To define being a good parent to a child with incurable cancer	62 parents (of 58 children) who made an end-of-life decision in the last 72 hours for their child with cancer	• Qualitative study using semantic analysis • Individual open-ended interviews with parent	• Being a good parent means making informed, unselfish decisions in the child's best interest, remaining at the child's side, showing the child they are cherished, teaching the child to make good decisions, advocating for the child with staff, and promoting the child's health	High	Low
Kim et al.[2] / Characteristics and Outcome of Pediatric Patients Enrolled in Phase I Oncology Trials	To describe the characteristics of children enrolled in P1Ts, find associations between characteristics and toxicity risk, and analyze outcomes	262 patients enrolled on 16 different P1Ts coordinated by National Cancer Institute from 1992-2005	Meta-analysis of previously reported P1T results	• Approximately 90% of P1T participants were evaluable for study endpoints • P1Ts are safe with manageable toxicities • Therapy dose was most strongly associated with dose-limiting toxicities • Median overall survival time after enrollment was 5 months	High	Medium

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Lee et al.[1] / Pediatric Phase I Trials in Oncology: An Analysis of Study Conduct Efficiency	To determine the efficacy and safety of pediatric oncology P1Ts and to analyze how efficiently these trials are conducted	69 P1Ts enrolling 1,973 patients between 1990-2004	Meta-analysis of previously reported P1T results	• P1Ts continue to be safe and relatively well-tolerated • Deriving direct benefit from a P1T should not be equated with observed response rate • Types of toxicities experienced by children were similar to those experienced by adults	High	Low
Levine et al.[26] / Does Phase 1 Trial Enrollment Preclude Quality End-of-Life Care? Phase 1 Trial Enrollment and End-of-Life Care Characteristics in Children with Cancer	To determine whether end-of-life characteristics differed between pediatric oncology patients who were and were not enrolled in a P1T	277 children with solid tumors who were (n=120) and were not (n=157) enrolled in a P1T and who died between 2001-2005	• Quantitative, cohort secondary analysis • Retrospective chart review	• No significant differences were found in use or timing of do not attempt resuscitation orders, hospice use or length of stay, forgoing life-sustaining therapies, location of death, time from first end-of-life care discussion to death, and total number of end-of-life care discussions • Enrollment on a P1T does not affect end-of-life care characteristics	High	Medium
Marshall et al.[22] / Negotiating Decisions during Informed Consent for Pediatric Phase I Oncology Trials	To identify key communication steps and factors that influence the negotiation of decisions regarding P1T participation	16 informed consent conversations selected by stratified random selection from 49 informed consent conversations from 2008-2011	Secondary, qualitative, grounded theory analysis	• During informed consent conversations, families, patients, and clinicians exercise choice and control by negotiating micro-decisions in two broad domains: drug logic and logistics, and administration / scheduling	Medium	Medium

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Maurer et al.[23] / Decision Making by Parents of Children with Incurable Cancer who Opt for Enrollment on a Phase I Trial Compared with Choosing a Do Not Resuscitate / Terminal Care Option	To compare the self-reported rationale, good parent definition and desired clinical staff behaviors of parents who decided on P1T participation with parents who chose a DNR / terminal care option	62 parents (of 58 children) who made an end-of-life decision in the last 72 hours for their child with cancer	• Qualitative study using semantic analysis • Individual open-ended interviews with parent and demographic data from chart	• Despite similar definitions of a good parent and desired staff behaviors, parents choosing to participate in a P1T reported feeling compelled to continue cancer-directed therapy, whereas parents choosing DNR and terminal care options reported an emphasis on QOL and patient wishes • No parent chose both participation in a P1T and a DNR / terminal care option	High	Medium
Miller et al.[24] / Adolescent Perspectives on Phase I Cancer Research	To examine adolescent patient perspectives on their understanding and decision-making about a P1T	20 structured interviews of adolescents with cancer who attended a P1T informed consent conversation between 2008-2011	• Prospective study • Quantitative analysis of qualitative data from recorded informed consent conferences and interviews	• Most adolescents understood P1T was voluntary, entailed risks, and they could withdraw • Reasons for enrolling were positive clinical benefit, needing an option, impact on QOL, and fewer side than other treatments • Most participants hoped or expected that P1T would provide a direct benefit and reported that they made the final decision to enroll in P1T	High	Medium
Morgenstern et al.[40] / Toxicity and Outcome of Children and Adolescents Participating in Phase I/II Trials of Novel Anticancer Drugs: The Royal Marsden Experience	To produce an overview of outcomes and toxicities for pediatric patients recruited to early phase trials from 2002 to 2011	66 patients who enrolled and were treated in a phase I (n=24) or II trial (n=42) from 2002-2011	Meta-analysis of previously reported phase I and phase II clinical trial results	• Early phase trials in children are safe and unexpected toxic side effects are infrequent, although the overall prognosis for these individuals is poor • Patients and their families are willing to travel to access novel therapies	Medium	Medium

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Oppenheim et al.[25] / Ethical Issues in Pediatric Oncology Phase I-II Trials Based on a Mother's Point of View	To present and discuss the complex relational, psychological and ethical issues regarding P1T participation	1 parent interview with a psycho-oncologist following the decision to participate in a P1T	Case report	• Decisions regarding P1T participation are easier when all parties involved are aware of motivations, expectations, and accept the inherent risks • Physicians in charge of clinical care and research should be different, to ensure child's interests take precedence over that of research	Low	Medium
Paoletti et al. [36] / A Comparative Analysis of Paediatric Dose-Finding Trials of Molecularly Targeted Agent with Adults' Trials	To assess the objectives, place and role of P1Ts in the era of molecularly targeted agents	19 single agent pediatric P1Ts of molecularly targeted agents approved in adults before 6/15/2012	Meta-analysis of previously reported P1T results	• 63% of pediatric patients are treated at suboptimal doses of molecularly targeted agents (less than the maximum tolerated dose) • Safety profiles described by pediatric P1Ts of molecularly targeted agents were usually similar to the adult population	High	Low
Shah et al. [38] / Phase I Therapy Trials in Children with Cancer	To examine the response and toxicity rates of therapies evaluated in P1Ts to identify trends in response and toxicity over time	56 P1Ts enrolling 1,606 patients between 1978 and 1996	Meta-analysis of previously reported P1T results	• P1Ts are a safe mechanism to determine the maximum tolerated dose, toxicity profile, and pharmacokinetics of new agents • Methods of assessing response do not routinely consider stable disease, improvements in pain control, or QOL, even though these are meaningful to patients and families	Medium	Medium

TABLE 2.3 FINDINGS AND EVALUATION OF ADULT ARTICLES

Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Berdel et al.[101] / Influence of Phase I Early Clinical Trials on the Quality of Life of Cancer Patients: A Pilot Study	To assess the impact of phase I trials on the QOL of cancer patients versus patients treated with low efficacy 1-2 medication regimens off-study	18 patients treated in P1Ts and 8 patients treated with low efficacy 1-2 medication regimens off-study	• Quantitative, cohort pilot study • Linear Analog Self-Assessment and Karnofsky Performance Score used to assess QOL at four timepoints	• No significant negative QOL influence in P1T group • Slight positive influence of P1T in terms of self-assessed social activity and performance score • In both groups, there was a significant positive influence of overall anticancer medication on psychological and social aspects of QOL	Medium	Medium
Campbell et al.[112] / The Quality of Life of Cancer Patients Participating in Phase I Clinical Trials Using SEIQoL-DW	To examine the QOL of cancer patients participating in P1Ts, and to determine the acceptability of the QOL instrument	15 adult cancer patients participating in a P1T during 4-week recruitment period in 1997	• Quantitative study • One individual, semi-structured interview using the Schedule for the Evaluation of Individual QOL –Direct Weighting (SEIQoL-DW)	• Health and family were particularly important to in relation to patient's QOL • QOL instrument was found to be acceptable and practical to use with P1T participants	Medium	Medium
Carlson et al.[121] / Individualized Quality of Life, Standardized Quality of Life, and Distress in Patients Undergoing a Phase I Trial of the Novel Therapeutic Reolysin	To evaluate the individualized and standardized QOL and psychological distress of patients participating in a P1T of the novel therapeutic reovirus	16 adult cancer patients interviewed prior to being accepted into the phase I trial	• Mixed methods study • One individual, semi-structured interview of health expectations where standardized QOL, distress, and spirituality instruments were completed	• Patients felt hopeful and excited about the trial, with about two thirds hoping for disease regression and one third hoping for a cure • Patients reported less psychopathology than would be expected of patients in similar disease states, but comparable to cancer patients in general, and overall mild depressive symptomatology	Low	Medium

Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Cohen et al.[3] / Phase I Participants' Views of Quality of Life and Trial Participation Burdens	To assess participants' perception of experience on P1Ts including associated QOL	First 100 adult patients referred to a specified P1T; and 16 patients enrolled in the P1T	• Qualitative study • Qualitative survey completed by referred patients • Hermeneutic phenomenological interview with enrolled patients	• Participants established their current QOL by comparison with prior cancer treatments • Indirect and procedural burdens of P1T participation had a significant impact on participants' current QOL	Medium	High
Cox[4] / Researching Research: Patients' Experiences of Participation in Phase I and II Anti-Cancer Drug Trials	To identify the psychosocial processes of participating in a phase I or II trial, ways of coping, and consequences of trial involvement	55 adult patients enrolled in a phase I or II cancer clinical trial within a 12-month recruitment period from 1996-1997	• Mixed methods, longitudinal study • Semi-structured in-depth interviews and instruments completed at four timepoints	• Trial offer meant: hope, uncertainty, and being honored • Trial involved: burdens, being in expert hands, contributing to research, being special, having a purpose, and life on hold • Trial conclusion involved feelings of disappointment, relief, fear of abandonment, uncertainty, and preparations for death	Medium	High
Cox[5] / Enhancing Cancer Clinical Trial Management: Recommend-ations from a Qualitative Study of Trial Participants' Experiences	To propose empirically-based recommendations for early phase cancer clinical trial management	55 adult patients enrolled in a phase I or II cancer clinical trial within a 12-month recruitment period from 1996-1997	• Mixed methods, longitudinal study • Semi-structured in-depth interviews and instruments completed at four timepoints	• Early phase trial participation is a dynamic process that has different meanings and impact per the stage of trial involvement • Need to enhance preparation of trial participants, establish continuing care post-trial, and incorporate patients' views	Medium	Medium
Cox[7] / The Hopes of the Dying: Examining Patients' Experience of Participation in Early Phase Cancer Clinical Trials	To present a theoretical examination of hope and dying from a longitudinal qualitative study of the experience of phase I cancer clinical trial participation	55 adult patients enrolled in a phase I or II cancer clinical trial within a 12-month recruitment period from 1996-1997	• Mixed methods, longitudinal study • Semi-structured in-depth interviews and instruments completed at four timepoints	• Hope and dying were the two major themes that emerged in relation to how patients experienced trials • By averting the immediate confrontation with death, trial involvement appeared to disturb some of the psychological processes and stages of dying	Medium	High

Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Cox[6] / Assessing the Quality of Life of Patients in Phase I / II Anti-Cancer Drug Trials: Interviews versus Questionnaires	To compare and contrast two different approaches to assessing QOL in the context of cancer clinical trial participation	55 adult patients enrolled in a phase I or II cancer clinical trial within a 12-month recruitment period from 1996-1997	• Mixed methods, longitudinal study • Semi-structured in-depth interviews and instruments completed at four timepoints	• Data obtained from QOL questionnaires revealed no statistically significant differences in scores • Interviews uncovered some of the psychological, emotional and social impact of early phase clinical trial participation from the patient's perspective	Medium	Medium
Cox et al.[111] / Psychosocial Aspects of Participation in Early Anticancer Drug Trials: Report of a Pilot Study	To present the results of a pilot study exploring the psychosocial aspects of participation in an early phase clinical trial	7 adult patients enrolled in a phase I or II cancer clinical trial during recruitment period	• Mixed methods, longitudinal study • Semi-structured in-depth interviews and instruments completed at three timepoints	• Patients consistently minimized their problems when filling in QOL questionnaires • Results suggest there were times when the process of trial participation was not acceptable to participants	Medium	High
Cox[42] / A Randomised Controlled Trial of Nurse-Managed Trial Conclusion Following Early Phase Cancer Trial Participation	To present the quantitative findings from a nurse-led strategy for improving the management of the conclusion of patients' participation in a P1T	117 patients (n=59 intervention group, n=58 control group) enrolled in any P1T at two medical centers within a 36-month recruitment period from 2001-2004	• Randomized, pre-post mixed methods intervention study • Nurse intervention included P1T exit interview, leaflet, and follow-up call • Quantitative instruments completed at two timepoints with in-depth interview at second timepoint	• No difference between groups in scores for anxiety and depression at trial conclusion • Patients in intervention group had statistically insignificant reduction in anxiety post intervention • Patients in intervention group were more satisfied with information given about the trial and with their follow up	Medium	Low

Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Daugherty et al.[119] / Trusting God and Medicine: Spirituality in Advanced Cancer Patients Volunteering for Clinical Trials of Experimental Agents	To examine the role of spirituality in terminally ill cancer patients who volunteer for P1Ts	162 cancer patients enrolled in a P1T from 1997-1999 and 156 advanced cancer patients not participating in a P1T from 1993-1996	• Quantitative, cohort study • Spirituality, QOL, and decision-making instruments were completed at one timepoint by P1T group; Control group participants and data were selected from a pre-existing data set	• P1T group had slightly higher levels of spirituality than the control group • In P1T group, spirituality was positively associated with QOL • Spirituality was not associated with P1T patients' awareness of their prognosis or decision-making preferences	High	Medium
Finlay et al.[100] / Do Phase 1 Patients Have Greater Needs for Palliative Care Compared with Other Cancer Patients?	To define the palliative care needs of phase I patients and to determine whether their needs are greater than other cancer patients	297 patients receiving cancer therapy and 69 patients enrolled in P1Ts over a period of two years	• Quantitative, cohort study • Instruments completed at one timepoint	• Compared with other patients who had cancer, patients who were participating in P1Ts were less likely to want home care services, although they experienced a greater symptom burden • Groups differed significantly with respect to race	Medium	Medium
George et al.[104] / Sleep Quality and Its Association With Fatigue, Symptom Burden, and Mood in Patients With Advanced Cancer in a Clinic for Early-Phase Oncology Clinical Trials	To describe sleep quality and its relation with fatigue, symptom burden, and mood in patients recruited from an early-phase clinic for targeted therapy	256 patients recruited from a phase clinical I trial clinic during the 16-month recruitment period	• Quantitative, cross-sectional study • Instruments completed at one timepoint	• Poor sleep quality was a significant problem in the current study and was associated with greater fatigue, symptom burden, and mood disturbance. • Sleep quality should be routinely assessed in patients with advanced cancer who are participating in early-phase clinical trials.	High	Medium

Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Godskesen et al.[114] / Phase 1 Clinical Trials in End-Stage Cancer: Patient Understanding of Trial Premises and Motives for Participation	To explore and describe patients' reasons for participation, their experiences related to P1T participation, and issues associated with the information–consent process	14 patients enrolled in one of three ongoing P1Ts during the 11-month recruitment period from 2011-2012	• Qualitative, cross-sectional study • One individual, semi-structured interview	• Patients expressed unrealistic expectations of therapeutic benefit and inadequate understanding of P1T's purpose • Patients valued the close and unique medical and psychological attention they received by participating. • Participation made patients feel unique and notable.	Medium	High
Helft et al.[115] / Associations Among Awareness of Prognosis, Hopefulness, and Coping in Patients with Advanced Cancer Participating in Phase I Clinical Trials	To examine the relationships among awareness of prognosis, hopefulness, and coping in a selected group of advanced cancer patients	179 advanced cancer patients signing consent for a P1T within the recruitment period	• Quantitative study • One individual, structured interview conducted within 7 days of the start of the P1T using both quantitative and semi-quantitative instruments	• Many patients reported an unrealistic view of their prognosis. • Having a more accurate view of prognosis in the face of terminal illness was associated with reduced hopefulness, which may be related to a poorer sense of coping.	Low	Low
Hui et al.[103] / Timing of Palliative Care Referral and Symptom Burden in Phase 1 Cancer Patients	To compare timing of referral and symptom burden between patients referred to palliative care by phase I oncologists vs. non-phase I oncologists	57 patients referred by phase I oncologists and 114 patients referred by non-phase I oncologists from 2007-2008	• Quantitative, retrospective cohort study • Secondary analysis of data extracted from chart, including QOL instruments completed on referral to palliative care services	• Patients referred by phase I oncologists had a better performance status but similar symptom burden compared to control group • Patients phase I involvement did not delay palliative care referral, but it did increase the likelihood of receiving chemotherapy in the last 30 days of life	Medium	Low
Hutchison[8] / Phase I Trials in Cancer Patients: Participants' Perceptions	To determine how cancer patients perceive P1Ts in reference to trial participation and information received	28 adult patients receiving therapy on an oncology P1T during the 3-month recruitment period	• Quantitative study • One structured interview using a questionnaire with closed questions	• Patients participated in P1Ts because they offered hope, yet expectations were still realistic • Benefits related to participating in P1Ts including amount and quality of nursing / medical care as compared to standard treatment	High	Medium

Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Jansen et al.[116] / Dispositional Optimism and Therapeutic Expectations in Early-Phase Oncology Trials	To examine expectations for personal therapeutic benefit reported by patients in early-phase oncology trials	171 patients enrolled in a phase I or II trial at one of the participating cancer centers	• Quantitative study • One structured interview using a questionnaire with closed questions	• High expectations for therapeutic benefit should not be assumed to result from misunderstanding of specific information. • Unrealistic optimism, but not dispositional optimism, was significantly associated with therapeutic misconception.	High	Low
Kessler et al.[127] / Distress Among Caregivers of Phase I Trial Participants: A Cross-Sectional Study	To assess the distress and emotion regulation of caregivers of P1T participants to inform the design of future interventions	88 caregivers of patients enrolled in a P1T during the recruitment period	• Quantitative cross-sectional pilot study • Self-administered instruments completed at one timepoint between Course 1 Day 1 and Day 15 of P1T	• Caregivers exhibited greater distress than population norms. • Emotion regulation was also moderately impaired. • Caregivers identified positive aspects of caregiving despite exhibiting moderate distress.	High	Medium
Kvale et al.[9] / The Experience of Older Patients With Cancer in Phase 1 Clinical Trials: A Qualitative Case Series	To explore the experiences of older patients with cancer in P1Ts	4 white older adults receiving treatment on a phase 1 oncology clinical trial	• Qualitative, hermeneutic phenomenology study • One in-depth semi-structured interview	• Social comparison influences decisions to enroll in P1Ts, shapes perceptions of supportive care needs, and encourages use of hope • Social comparison can inhibit articulation of pain, suffering and symptom burden	Medium	Medium
Langenberg et al.[126] / How Did Partners Experience Cancer Patients' Participation in a Phase I Study? An Observational Study After a Patient's Death	To explore partners' experience of patients' participation in P1Ts and to investigate their well-being after a patient's death	58 Partners of deceased cancer patients who participated in a P1T from 2007-2009	• Quantitative study • Instruments completed at one timepoint by hand, using standardized instruments to assess well-being and one novel instrument developed for study	• Although partners reported negative consequences on patients' quality of life, most did not regret patients' participation in the P1Ts. • Depression, psychological distress, and complicated grief were important problems for partners after the patient's death.	Medium	Medium

Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Mack[110] / The Quest for treatment: Cancer Patients' Experience of Phase I Clinical Trials	To explore, from the perspective of the patient, the essential structure of the lived experience of participating in P1Ts	20 adult patients who consented to participate in an oncology P1T	• Qualitative, longitudinal hermeneutic phenomenology study • Two in-depth unstructured interviews	• The overall theme that emerged was the Quest for Treatment • The Quest for Treatment was an active process, marked by typical steps along the way. These steps emerged as categories across the narratives: (a) Taking Charge, (b) Deciding, (c) Living on a Trial, and (d) Dealing with Uncertainty.	High	High
Melink et al.[102] / The Impact of Phase I Clinical Trials on the Quality of Life of Patients with Cancer	To evaluate the QOL of cancer patients receiving cytotoxic phase I therapy	45 patients treated in a P1T and 10 patients found ineligible to be treated in a P1T from 1983-1985	• Quantitative, longitudinal pilot study • Linear Analog Self-Assessment of QOL, performance status, and survival time assessed at two timepoints	• Cancer patients receiving treatment in a P1T had no significant changes in QOL or performance status after one course in a P1T • Patients not eligible for a P1T experienced a significant decline in overall QOL and performance status one month later	High	Medium
Meyers et al.[41] / Simultaneous Care: A Model Approach to the Perceived Conflict Between Investigational Therapy and Palliative Care	To describe the findings of a pilot study trial of the simultaneous delivery of investigational therapy and a structured program of supportive care	44 patients enrolled in a phase I or II trial along with a supportive home care program, and 20 patients enrolled in just a phase I or II trial	• Quantitative intervention pilot study • QOL assessed with instrument at five timepoints • Monitored referral to hospice and chemotherapy cycles administered	• P1Ts in patients with advanced cancer may not pay sufficient attention to QOL and supportive care issues • A statistically significant increase in referral to hospice, and mean length of stay in hospice, was seen in simultaneous care group compared to control group	High	Medium
Moore[10] / A Need to Try Everything: Patient Participation tn Phase I Trials	To describe patients' perceptions of participating in P1Ts	15 patients enrolled in any P1T within the 4-month recruitment period	• Qualitative, longitudinal study • In-depth semi-structured interview and open-stem questionnaires completed at two timepoints	• Major themes: need to try anything and everything at any cost, living with incurable cancer whilst still hoping for miracle cure, and receiving self-benefit while giving to future patients • Being in a P1T is meaningful by providing a supportive structure and enabling hope	Medium	High

Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Rouanne et al.[12] / Evaluation of Sexuality, Health-Related Quality-of-Life and Depression in Advanced Cancer Patients	To evaluate health-related QOL, depression and sexual function in advanced cancer patients treated in a P1T with molecularly targeted agents	63 patients enrolled in any P1T within the 4-month recruitment period in 2011	• Quantitative. longitudinal study • Initial consultation • Questionnaires completed at two timepoints	• Patients enrolled in molecularly targeted agent P1Ts preserved mental and physical activity, but sexual activity declined • Statistically significant difference was found between baseline and 1-month assessments for physical health, but not for mental health, on QOL questionnaire	High	Medium
Stetz[28] / Survival Work: The Experience of the Patient and the Spouse Involved in Experimental Treatment for Cancer	To describe the experiences of patients and their spouses undergoing experimental therapy for advanced cancer	Purposive sample of 24 patients enrolled in an experimental trial during recruitment period	• Qualitative, longitudinal, grounded theory study • Unstructured interviews at four timepoints	• Primary psychosocial process of participants was survival work: the work of choosing life over death. • Three phases of survival work were identified: (1) engaging, (2) monitoring, and (3) carrying on.	High	Medium
Sun et al.[108] / Feasibility of a Palliative Care Intervention for Cancer Patients in Phase I Clinical Trials	To test the feasibility of a palliative care intervention administered concurrently to cancer patients receiving treatment in a P1T.	14 patients who consented to participate in a P1T during the recruitment period	• Pre-post quantitative intervention pilot study • Intervention included baseline assessment, care conference, and two tailored patient educational sessions • Quantitative instruments completed at three timepoints	• Concurrent palliative care was feasible for cancer patients treated in Phase I clinical trial settings. • Results indicated that symptom distress, psychological distress, and QOL were somewhat stable over two months, which suggests that concurrent palliative care may have potential in preventing precipitous declines in QOL reported in other studies.	Medium	Low

Title	Purpose	Sample and Setting	Design and Method	Findings Related to P1T Experience	Rigor	Relevance
Wilson et al.[43] / Enhancing Cancer Trial Management: An Intervention Study of the Impact of Providing Information, Trial Results and Support to Patients in Phase I And II Anti-Cancer Drug Trials	To present the qualitative findings from a nurse-led strategy for improving the management of the conclusion of patients' participation in P1Ts	117 patients (n=59 intervention, n=58 control group) enrolled in any P1T at two medical centers within a 36-month recruitment period from 2001-2004	• Randomized, pre-post mixed methods intervention study • Nurse intervention included P1T exit interview, leaflet, and follow-up call • Quantitative instruments completed at two timepoints with in-depth interview at second timepoint	• Patients in the intervention group expressed fewer fears of abandonment, appreciated feedback about the trial, expressed satisfaction with the exit interview, and derived a feeling of support from the follow-up telephone call	Medium	Medium
Wooten et al.[11] / A Qualitative Assessment of the Experience of Participating in a Cancer-Related Clinical Trial	To explore the experiences of patients enrolled in a cancer-related clinical treatment trial using a focus-group methodology	14 patients who completed any cancer clinical trial within the past six months; 71.4% (n=10) were patients enrolled in P1Ts	• Qualitative, pilot study • Participants took part in one of three focus groups • Three participants did not attend a focus group (two were individually interviewed and one wrote feedback)	• Clinical trial participation is a positive experience, although there are practical and emotional burdens. • Trial participants may benefit from closer follow-up, assessment of support needs, and help in re-evaluating meaning of trial participation if initial hopes and expectations aren't met.	Medium	High
Yoder et al.[117] / Expectations and Experiences of Patients With Cancer Participating in Phase I Clinical Trials	To describe the expectations and experiences of patients enrolling in P1Ts	37 patients enrolled in any P1T during the recruitment period	• Quantitative, longitudinal pilot study • Interviews conducted with structured questionnaires pre-and post-P1T participation	• Patients' expectations for increased family support were met; expectations were not met for decreased tumor size, decreased symptoms, increased physician communication, decreased hospitalization, and increased activity.	Low	Medium

TABLE 2.4 SUMMARY OF RESULTS OF ARTICLE EVALUATIONS

		Evaluation of Rigor			
		Low	Medium	High	Totals
Evaluation of Relevance	Low	1	3	9	13
	Medium	4	11	14	29
	High	0	8	1	9
	Totals	5	22	24	51

CHAPTER 3

This chapter presents the results of the quantitative, longitudinal pilot study examining treatment burden and quality of life impact of participation during 13 parent / child dyads participation in a pediatric oncology early phase clinical trial.

3.1 INTRODUCTION

Early phase clinical trials (EPTs) are the first steps to test novel medical therapies in humans.[1,2] The process of developing therapies involves a series of clinical trials in humans; after preclinical testing, therapies are tested in phase I, phase II and/or pilot, and phase III clinical trials in order to obtain sufficient evidence of the therapy's safety and efficacy.[134] For the purposes of this study, EPTs include phase I, phase II, and pilot trials of investigational therapies that are still under development and not yet approved by the United States Food and Drug Administration. The challenge with pediatric EPTs is that, due to the investigational nature of the therapies being tested, children can only participate in an EPT when standard therapies are considered ineffective. The median life expectancy of children with relapsed cancer enrolled in a phase I clinical trial is between just 3.6 – 6.4 months.[2,39,40]

Treatment burden is defined as the physical, financial, time, psychosocial, and procedural demands that a treatment places on a patient and their family, as well as its impact on patient and family functioning.[92-94] Treatment burden is a dynamic, multidimensional concept that fluctuates over time due to severity of the patient's condition, development of toxicities, and adjustment to the treatment. Treatment burden is different from burden caused by other factors such as symptoms or disease, because it is based on treatment for the disease, and not on either the natural history or natural symptoms of the disease.[93] In adult patients, treatment burden encompasses time lost from work and other activities.[135] Although children may not work, their time lost is equally important and burdensome; they would also benefit from spending the time required for treatments with family and friends or carrying out their usual activities. Although research has yet to confirm this, experts hypothesize that for children with chronic illness, treatment demands such as injections, blood samples, and

dietary restrictions may be particularly burdensome and negatively impact children's quality of life (QOL).[95,135]

A better understanding of treatment burden in the context of EPTs may help healthcare professionals, patients, and parents to make more informed treatment decisions.[94] Although adults' participation in phase I clinical trials provides hope and a sense of purpose, there are also significant associated physical, emotional, and practical burdens.[3,4,10,11] The research with adults is not generalizable to pediatric EPTs because children are reliant on parents as providers, caregivers, teachers, moral compasses, disciplinarians, and proxy decision-makers. Some experts suggest that EPTs burden children with additional medical procedures and toxicities, negatively impact QOL, limit palliation opportunities, and disrupt dying and bereavement processes.[13,14] Recent evidence, however, has demonstrated that an active palliative care program can ensure that measures of end-of-life care (e.g., presence or timing of do not attempt resuscitation orders, hospice use or length of stay) are not impacted by enrollment in a phase I clinical trial.[26] Although research on experiences of communication and decision-making *during EPT consent processes* has been conducted, knowledge is lacking regarding parent and child experiences of treatment burden and QOL *while participating in an EPT*. Therefore, the purposes of this pilot study were to assess the feasibility and preliminary results of having children with cancer and their parents complete measures of treatment burden and QOL concurrent with EPT participation.

3.2 METHODS

This was a descriptive, longitudinal, pilot study with data collected from parents and children. Institutional Research Board approval was obtained for this study prior to enrolling participants. All parents and children aged $\geq$ 18 provided written documentation of informed consent; children 7 - 17 years of age provided verbal assent for participation. Recruitment occurred between June 2011 and May 2013.

All recruitment occurred at a large, Midwestern pediatric medical center. Parents and children were approached to participate after confirmation of their eligibility with the attending oncologist. The recruitment goal was 20 parent and child

dyads. As this was a pilot study, the sample size was based on participants available (i.e. annual EPT enrollment projections at the pediatric medical center), rather than on statistical power.[136,137] A 24-month maximum length was set on recruitment.

Child inclusion criteria were: (1) age 2 to 25 years; (2) receipt of at least one therapy prior to the EPT (i.e., phase I, phase II, or pilot clinical trial); (3) consented to participate in an outpatient-based EPT for relapsed/refractory pediatric cancer; (4) EPT therapy did not include ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) or oncolytic virotherapy; (5) enrolled within 48 hours of first dose of EPT therapy; and (6) ability to communicate in English. Parent inclusion criteria were: (1) age $\geq$ 18; (2) self-identification as biological parent or legal guardian of child; and (3) fluency in English. Eligibility criteria were established to prospectively capture the full experience of participation in a classic EPT where therapy involves either oral or intravenous agent(s) administered on a regular schedule to a child with relapsed and/or refractory cancer. To capture as full a data set as possible, an extended range of child ages was included based on ages covered by the PedsQL^{TM} modules. EPTs involving ^{131}I-MIBG therapy and oncolytic virotherapy were excluded due to the unique requirements of these studies that necessitated prolonged isolation from support systems. The first 48 hours was selected to ensure that baseline data reflected experiences at the time the EPT started.

3.2.a Procedures

Children were followed for either eight weeks (if length of treatment course was four weeks) or nine weeks (if length of treatment course was three weeks) during the EPT. This variance was due to a desire to standardize the time on study, while ensuring that children completed this study at the end of an EPT course. Assessments were completed at baseline, post-first disease evaluation, and end of this study. The baseline assessment was completed after the child was enrolled in the clinical trial, preferably before treatment started, but no more than 48 hours after the administration of the first dose of the investigational therapy. The post-disease evaluation assessment was completed after the first disease evaluation was performed, but no more than 7 days after the child/family were provided the results of the disease evaluation. The off-study

assessment was completed at the end of a course, after the child had been on the EPT for 60 (+/- 5) days. In addition, parents were asked to complete the Diary of Trial Experiences on an ongoing basis (i.e. two to three times a week) at home. To ensure completeness, a study team member reviewed diary entries with the parent every 5 to 14 days throughout the study. Table 3.1 provides a list of measures completed with each assessment, and by which participants. Participants received $25 in cash upon completion of the baseline and post-disease evaluation assessments, and $50 in cash after completing the off-study assessment.

3.2.b Measures

3.2.b.1 Family Demographics

Parents completed an investigator-designed Family and Patient Demographic form at the baseline assessment. In addition to standard demographics, data included family composition, type of central line access, whether central line access was placed specifically for the EPT, and distance from primary household to pediatric medical center in miles and minutes of travel time.

3.2.b.2 Child Performance Status

The child's Lansky or Karnofsky scale scores were evaluated at each assessment by a member of the health care team and documented in the clinical trial record. These scales are similar with the Lansky scale applicable for children less than 16 years of age and the Karnofsky for those aged 16 years and older. Both scales (1) quantify cancer patients' general well-being and activities of daily life, (2) have well-established reliability and validity, (3) are responsive to change, (4) are widely used, and (5) use a single score of 0 to 100 in increments of 10, where 0 is death and 100 is normal health with no complaints.[97-99]

3.2.b.3 EPT Data

Using an investigator-designed form, the study team extracted data from the EPT protocol, consent form, and the child's EPT records. Data captured included: length of treatment course; frequency, number and duration of required and optional blood draws, physical exams, imaging, bone marrows, lumbar punctures, clinic visits and

infusions; number of planned separate visits to a medical facility / laboratory; number of expected separate needle punctures; optional observations that the child / parent agreed to provide for the EPT (e.g. pharmacokinetic and pharmacogenetic samples); and outcomes of EPT disease evaluations.

3.2.b.4 Treatment Burden

Based on an adaptation of the Collection of Indirect and Non-medical direct costs (COIN) form,[46] the study team created the Diary of Trial Experiences to capture the treatment burden associated with EPT participation for parents and children. The COIN form was a feasible and practical method for assessing patient cost data in a study of 29 adult cancer patients being treated for prostate carcinoma.[46] Adaptations included reformatting and capturing time spent in different activities; financial costs associated with child care, lodging, and meals; venipunctures; and reasons why usual activities were missed. The additions were made by adding columns and rows as needed into the tables structuring the form, and by adding a separate section at the bottom of a page to capture venipunctures. The Diary of Trial Experiences was completed by parents on an ongoing basis and used to directly capture the number of appointments and activities related to the EPT, including time spent on and financial cost of those activities. See Table 3.2 for a listing of elements included in the diary.

3.2.b.5 QOL

The standardized and widely used PedsQL™ modules were used to assess QOL, including: the PedsQL™ Quality of Life Inventories (Standard Version), Cancer Modules, and Family Impact Module. The 21-to 23-item Quality of Life Inventories measure health-related QOL in children and adolescents, with subscales for physical, emotional, social, and school functioning. The 25- to 27-item Cancer Modules measure elements of health-related QOL specific for children and adolescents with cancer, with subscales for pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance, and communication. The 36-item Family Impact Module measures parent physical, emotional, social, and cognitive functioning; communication; worry; family daily activities; and family relationships. For all modules,

5-point response options range from 'Never' (100) to 'Almost Always' (0). The Likert scores were then transformed to a 0-100 scale; as the items in PedsQL™ modules relate to problems, higher scores indicate better QOL and less problems. The total score for each module was determined by averaging the sum of all the scores for the items answered. A change of between 4.4 to 4.5 in the total score is the standard for a minimal clinically important difference in the PedsQL™ Quality of Life Inventories.[48] Advantages to the PedsQL™ modules are their ease of completion, demonstrated internal consistency and reliability, and established responsiveness to change when repeatedly administered in short intervals.[47-53] For most children in this study (based on child's age), both parent report and child self-report versions of the PedsQL™ Quality of Life Inventories and Cancer Modules were available, allowing parent and child to separately complete these modules. The parent completed the Family Impact Module.

3.2.c Statistical Analyses

All data were analyzed using descriptive statistics. Since children were enrolled in EPTs with varying course lengths, treatment burden per week was calculated for each participant as the sum of entries in the Diary of Trial Experiences for course 1 of the EPT divided by the number of weeks per course. Descriptive statistics of treatment burden per week were then calculated.

Feasibility was assessed by the following criteria: (1) $\geq$ 75% enrollment of all eligible parent and child dyads; (2) $\geq$ 80% retention of participants at the post-disease evaluation assessment; (3) $\geq$ 90% of questions answered by parents and children on each measure. Retention was evaluated as the rate of completion of the post-disease evaluation assessment by the 13 dyads who enrolled in the study, as completion of one course in the EPT was considered the minimum to be evaluable for this study. The same instruments were completed at the post-disease evaluation and off-study assessments, so selecting the post-disease evaluation provided a full set of data to be compared with the baseline assessment and ensured that the experiences of children who were only in the EPT for one course were captured.

3.3 RESULTS

3.3.a Family Demographics, Child Performance Status, and EPT Data

The accrued sample consisted of 13 parent and child dyads. The children were mostly female (69.2%) and white (76.9% white, 15.4% black, 7.7% other). The mean age of the children was 11.4 years old (SD=4.9, range 4-20) and the mean number of children in the household was 1.8 (SD=1.2, range 0-4). More than half of the children had some sort of central venous access in place (Port 38.5%, PICC 15.4%). Parents' annual income levels were fairly evenly distributed across categories (<$20,000 15.4%; $20-$40,000 23.1%; $40-$60,000 23.1%; $60-100,000 23.1%; >$100,000 15.4%), and the majority of parents had attended college or had a professional degree (93.3%). Mean distance of the primary household from the medical center was 78.8 miles (SD=96.0, range 2-300) or 80.8 minutes (SD=70.6, range 15-240). The median baseline performance score of the children was 90 (SD=9.0, range 70-100). The children were participating on five different EPT protocols. See Table 3.3 for descriptive statistics summarizing requirements across the five EPT protocols.

3.3.b Aim 1: Feasibility

3.3.b.1 Enrollment of Eligible Parent and Child Dyads.

As shown in Figure 3.1, of the parents and children approached to participate (n = 15), only one parent and child dyad declined to participate (92.9% participation rate). However, one child was determined to be ineligible following consent due to communication difficulties resulting from a brain tumor, resulting in final enrollment of 13 of the 15 dyads approached to participate (86.7% enrollment rate). Both percentages were above the criteria of ≥75% enrollment, indicating that recruitment to this pilot study met feasibility criteria.

3.3.b.2 Retention of Eligible Parent and Child Dyads.

Per Figure 3.1, three children (23.1%) deteriorated due to disease progression or suffered sufficient toxicities to be withdrawn from the EPT prior to their first disease evaluation. Thus, the criteria of 80% of study participants remaining on this study and completing the post-disease evaluation assessment was not quite met (76.9% retention

was achieved at this time point). Overall, only seven children (53.8% completion rate) remained on this study at the off-study assessment conducted 60 (+/- 5) days after enrollment, although no parent and child dyads were lost from this study for reasons other than the child's removal from the associated EPT.

3.3.b.3 Completion of Measures.

Each review of the Diary of Trial Experiences with the parent required between 5 – 15 minutes to complete. The reviews were either done while the parent was waiting at the medical center, or a study team member contacted the parent over the telephone. The Diary of Trial Experiences was too complicated to be completed by most participants without some assistance. Thus, rather than completing the diary at home on an ongoing basis, most parents waited and completed the form during a review with the study team member. Some questions on the diary were either too uncomfortable or too difficult for most participants to answer, and many participants elected to not provide that information. See Table 3.2 for a listing of elements of the diary that were observed by study team members to be easier and more difficult to answer. Overall, the feasibility criteria of 90% of the Diary of Trial Experiences being successfully completed before the review with a study team member was not met.

QOL measures were generally all completed, with only two individual child PedsQL™ modules missed during an assessment due to study team errors. The baseline assessment required between 20 – 40 minutes to complete, and was usually completed at the medical center either prior to or during an appointment (in a waiting room, clinic appointment room, or in their own room while inpatient). Two parents elected to complete their baseline PedsQL™ modules at home and return them at the next visit. The post-disease evaluation and off-study assessments required between 15 – 30 minutes to complete and all were done while the parent and child were waiting at the medical center.

There was minimal missing data from both parents and children on individual PedsQL™ modules. One parent did not respond to any of the five questions in the PedsQL™ Quality of Life Inventory related to school functioning (78.3% completion of

that module) and two questions related to treatment anxiety on a PedsQL™ Cancer Module (92.6% completion). In addition, three other parents did not respond to one question in an individual PedsQL™ module (95.6 – 96.3% completion). Three different children did not answer one of the questions in one PedsQL™ module (95.6 – 96.3% completion). One child did not respond to five questions related to social functioning on a PedsQL™ Quality of Life Inventory (78.3% completion of that module). Overall, the children completed 99.4% of the questions on 52 individual PedsQL™ modules they were provided to complete, while the parents completed 99.5% of the questions on 87 modules. There were no detectable patterns to the questions not answered. However, many parents and children were observed by study team members as having difficulty answering questions related to school, particularly since many children were not attending school due to the advanced stage of their cancer and the PedsQL™ modules do not provide 'Not Applicable' as a response option. Thus, the school functioning subscale of the PedsQL™ Quality of Life Inventories likely resulted in inconsistent data. Overall, the feasibility criteria of 90% of the questions answered on each measure by parents and children was met.

3.3.c Aim 2: Preliminary Results

3.3.c.1 Treatment Burden.

Table 3.4 provides the descriptive statistics of per week treatment burden for parent and child dyads who completed the post disease evaluation assessment (n=10). Median data suggest that at least half of the children had an average of 3.8 appointments per week, requiring an average of 11.5 hours of time and 2.8 needle punctures per week, and resulting in an average of 9.9 hours of missed activities and $10.60 in out of pocket costs per week. Appointment hours included overnight admissions for observation experienced by 70% of the children for their first dose of EPT therapy. These overnight admissions were for monitoring and collection of timed pharmacokinetic laboratory specimens and were considered as one 24-hour long appointment. Children's missed activities included school, attending camp, and family activities, and were almost entirely due to EPT appointments, with only three children

missing activities due to not feeling well.

3.3.c.2 QOL.

Figure 3.2A shows mean child and parent PedsQL™ Quality of Life Inventories scores at each assessment. While emotional health scores reported by both parents and children increased over time, other scores did not follow a continuous pattern. In general, children self-reported higher QOL scores than their parents reported on their behalf. The exception to this was the physical health summary score at post-disease evaluation and the psychosocial health summary score at baseline, which the parents generally reported as higher than their child. Statistical comparison could not be performed due to the small sample size.

Figure 3.2B shows mean child and parent Cancer Modules scores at each assessment. While the total scores reported by both parents and children increased over time, patterns of change for the other subscales varied over time. A wide variation between parent and child reports occurred for the communication subscale at both baseline and post-disease evaluation, with children self-reporting much lower scores than their parents on their behalf. Children generally reported higher procedural anxiety subscale scores than parents did at all time points, but particularly for the post-disease evaluation assessment; higher procedural anxiety subscale scores indicate less anxiety associated with needle sticks and other procedures performed as part of the child's cancer care. Again, statistical analyses were not performed due to the small sample size.

Figure 3.2C shows the mean Family Impact Module scores as reported by parents at each assessment. Patterns of change on the worry and communication subscales varied over time, while the remaining scores continuously improved through the EPT. The overall total scores on this module were stable but low at all time points, indicating that the child's cancer had a significant impact on the family. In particular, parents reported notably lower scores on the worry subscale, indicating that parents were very worried about their child's cancer.

3.4 DISCUSSION

The first major finding of this pilot study was that feasibility was not clearly established. While the goal of $\geq$ 75% enrollment was met, the goals for recruitment and retention were not met. In particular, the overall recruitment goal of 20 dyads was not achieved despite recruiting over a 24-month period. Challenges to recruitment included a slow accrual to non-^{131}I-MIBG and oncolytic virotherapy EPTs and lack of sufficient study team members to approach all potential participants.

The primary retention challenge was that attrition was higher than expected; although the goal of $\geq$ 80% retention was not quite met, no participants opted to leave this study early. All attrition was due to the child's removal from the EPT due to either toxicity or disease progression. While this was an anticipated problem, given the limited life expectancy of children with cancer enrolled in EPTs, feasibility was impacted by this attrition [2,39,40]. An important implication for future research with this population is to ensure that data is captured at multiple time points, starting before the end of the first course of therapy in the EPT, to ensure that attrition does not prohibit capturing the experiences of participants who are unable to remain in the EPT.

In terms of measure completion, the goal of $\geq$ 90% of questions being answered on each measure was met for the PedsQL^{TM} measures, but not for the Diary of Trial Experiences. This diary proved to be overly complicated to complete without the assistance of a study team member. While treatment burden data were captured using the diary, it is clear that revisions to both the format and content are needed to enhance the diary's usability and acceptability.

To improve feasibility, the following suggestions are recommended for future studies. First, to maximize recruitment efforts and minimize bias in those approached to participate, recruitment should clearly and systematically be tasked to multiple study team members. In addition, future research should be conducted at multiple sites or within a cooperative group to enhance recruitment and generalizability of findings. Lastly, the format of the Diary of Trial Experiences should be revised to mimic EPT medication diaries (i.e. one diary per course of therapy, with one line in the diary to be

completed each day of the course).

The second major finding was that while some interesting insights were provided by completion of the PedsQL™ modules, it is less clear that the Diary of Trial Experiences has sufficient value to be worth pursuing in future research. While it may be useful to obtain quantitative results regarding EPT treatment burden, in its current form this diary only measures objective elements of treatment burden (i.e. number of medications, number of appointments, and time at appointments). The subjective elements of treatment burden, including the different perceptions patients and their family have of a treatment's burden, are not captured. These perceptions include intangible elements that significantly impact the experience of treatment burden, such as difficulty administering oral medications to a young child, the meaning attributed to side-effects of the treatment, and beliefs about a treatment's effectiveness.[93] Qualitative research would be needed to identify subjective elements for inclusion. For the Diary of Trial Experiences to be valuable, it should be able to identify children or families who would benefit from further support or allow families to specify their need for further support. However, in its current format this diary does not seem to perform any better than standard psychosocial assessments already being done by social workers and other health care providers.

The third major finding was that preliminary results suggest there is value in having parents and children complete QOL measures during EPT participation. Although the PedsQL™ measures have been widely used in a variety of settings, no evidence was found of their use in early phase pediatric oncology clinical trials, prior to this study. In particular, having both parents and children separately complete the PedsQL™ modules, provided insight that there may be time points when parents' and children's perceptions of indicators of the child's quality of life may substantively differ. An example of this is the wide variation between parent and child reports on the PedsQL™ Cancer module communication subscale at baseline and post-disease evaluation, which suggests that children may have had more difficulty communicating concerns related to their cancer at these times than their parents were aware of. This discord between child

and parent reports has been acknowledged as prevalent whenever a concern is not directly observable (e.g. when asking about pain, communication, and personal experiences).[138,139] In this population, it is unlikely that the school functioning subscale of the PedsQL™ Quality of Life Inventories will produce valid results since many children participating in EPTs do not regularly attend school and 'Not Applicable' is not a response option. In a study of the QOL of children with advanced cancer, Deborah Tomlinson, Hinds, Bartels, Hendershot, and Sung[140] also reported significant missing data for the school functioning subscale. A larger study of the use of QOL measures during EPT participation is necessary to better elucidate the value they provide. In future research, to more fully understand the impact of EPT participation on physical health, it would be helpful to capture occurrence of toxicities along with completion of QOL measures. The use of PROMIS Pediatric measures (i.e. Physical Functioning - Mobility, Physical Functioning - Upper Extremity, Pain Interference, Fatigue, Depression, Anxiety, and Peer Relationships) should also be considered in future research.[141]

An additional result was that all participants in this study reported minimal financial burden directly associated with EPT participation. In particular, the reported financial burden was not grossly observed to correlate with other data, such as distance traveled. In contrast, for adults with chronic illness financial burden has emerged as the most problematic element of treatment burden.[94] Potential explanations for this finding include: (1) Parents were unwilling to report monetary burdens; (2) Parents were unable to accurately track monetary burdens; (3) Strong levels of financial support were offered by the pediatric medical center through foundations that support families of children with cancer; and, (4) Baseline socioeconomic demographic characteristics of parents and children enrolling in a pediatric oncology EPT may differ from the general population of adults with chronic illness.

The results of this pilot study are limited by small sample size, use of a single site for recruitment, the wide inclusion age range resulting in participants aged 4 to 20 years, and attrition of study participants. In particular, only a preliminary presentation of QOL results was possible. A problem affecting all studies of this population, including

ours, is that the interpretation of results is hampered by the bias created by participant attrition. Children with the most toxicities and disease progression do not remain on study to complete follow-up assessments.

3.5 CONCLUSIONS

This avenue of research is important, and likely to be feasible if conducted at multiple sites or within a cooperative group. To date, no studies have considered the impact of EPT participation, in terms of burden and QOL impact, on children with cancer and their families. Instead, current research focuses on how QOL is impacted by the child's current health status; the impact of treatment burden on QOL has not yet been considered. While it is unclear whether the Diary of Trial Experiences, as an objective measure of treatment burden, is worthy of further research, this pilot study highlights that measures of QOL impact of EPT participation can feasibly be completed by children with cancer who are participating in an EPT and their parents, and may provide valuable insights that could guide personalized interventions.

FIGURE 3.1 STUDY RECRUITMENT AND RETENTION

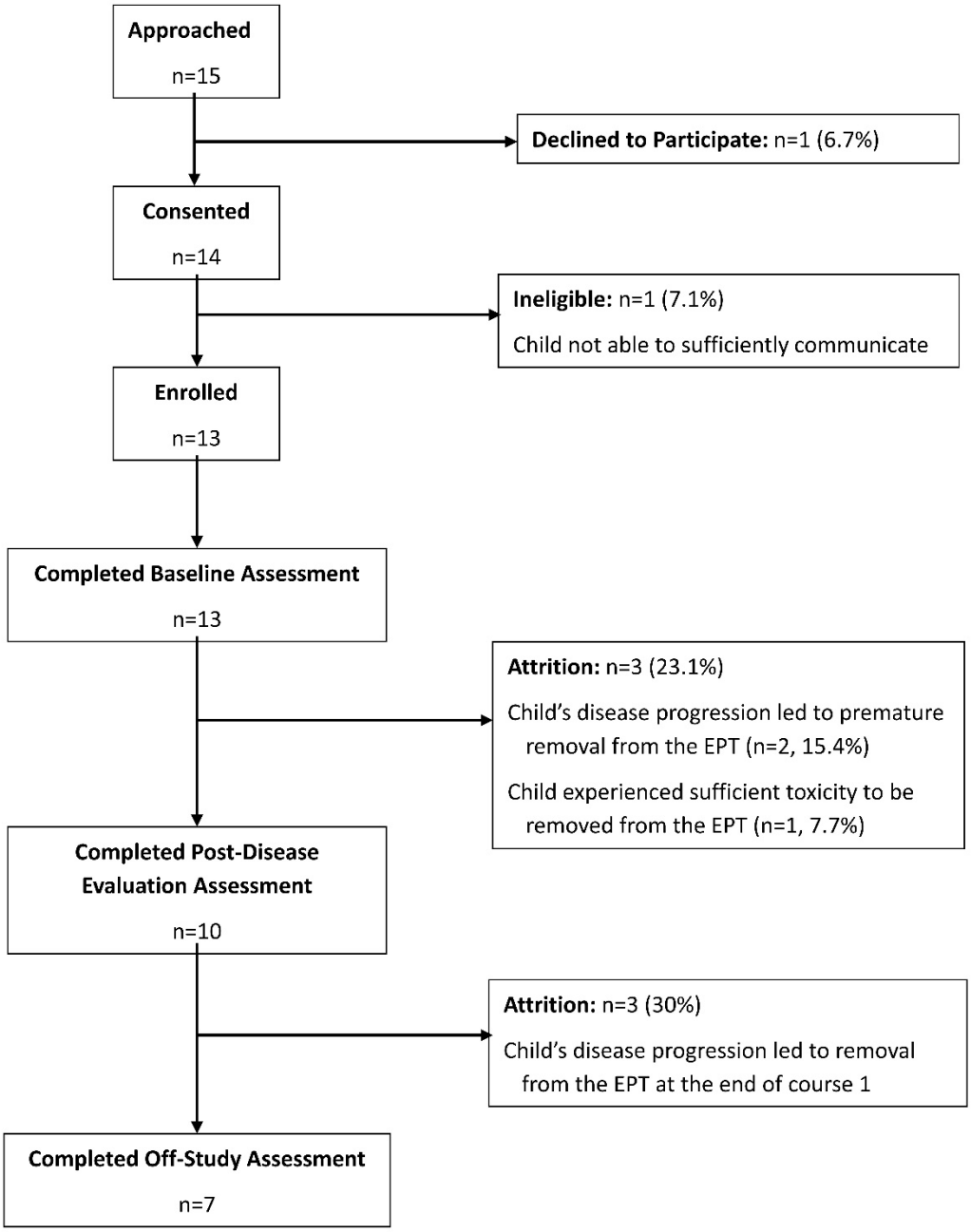

Figure 3.2 Mean PedsQL Scores at Each Assessment

Figure 2A. Quality of Life Inventories

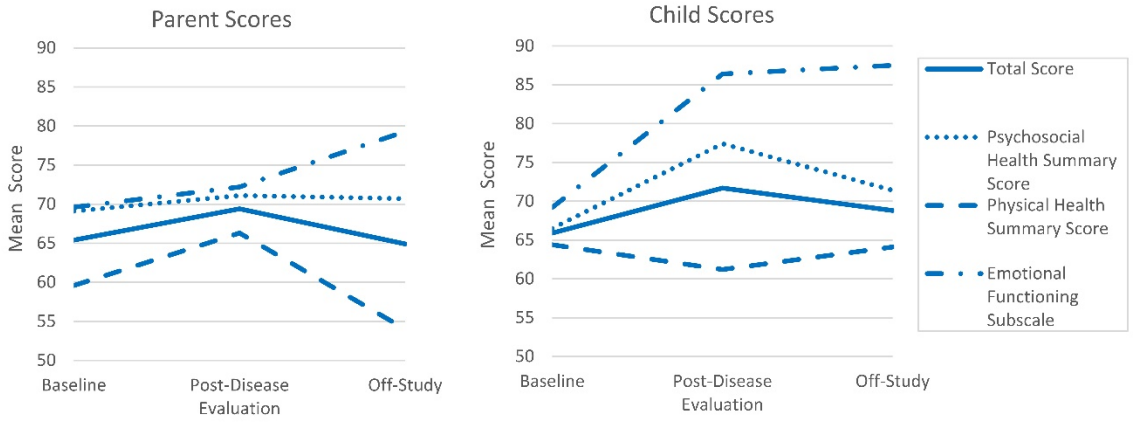

Figure 2B. Cancer Modules

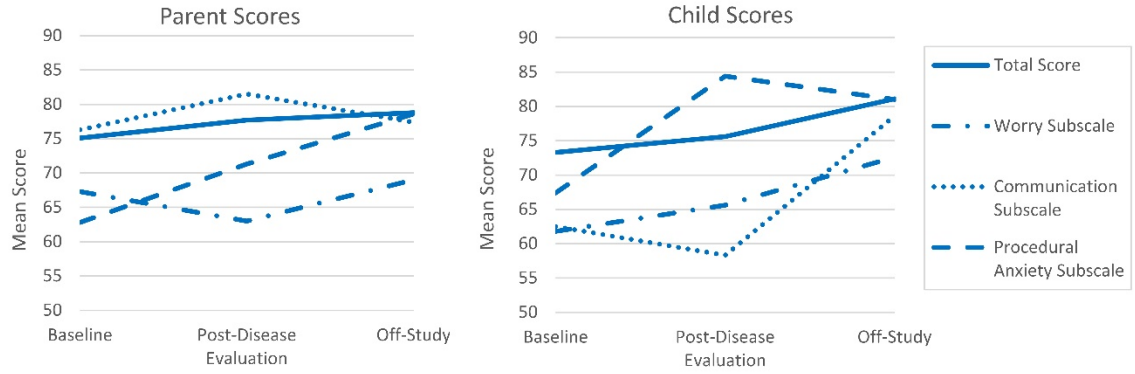

Figure 2C. Family Impact Module

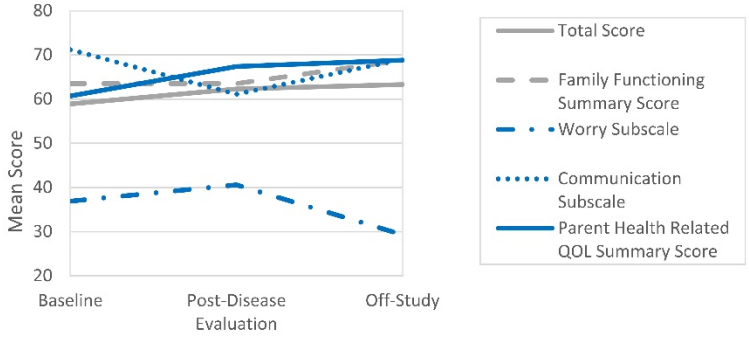

TABLE 3.1 INSTRUMENTS COMPLETED BY PARTICIPANTS AT EACH ASSESSMENT

Instrument	Baseline Assessment	Post Disease Evaluation Assessment	Off-Study Assessment
Child and Family Demographics Form	Parent	----------	----------
Diary of Trial Experiences	Completed Throughout Study by Parent		
PedsQL™ Quality of Life Inventories	Parent and Child	Parent and Child	Parent and Child
PedsQL™ Cancer Modules	Parent and Child	Parent and Child	Parent and Child
PedsQL™ Family Impact Module	Parent	Parent	Parent

TABLE 3.2 ELEMENTS FROM THE DIARY OF TREATMENT EXPERIENCES

Easily Answered	Difficult to Answer
• Type of services child used (e.g. oncology clinic, family doctor, emergency room, imaging, lab draw, parking, lodging, meals, and child care) • Number of times services used • Amount of time spent at medical service visits • Out of pocket costs associated with medical services, parking and lodging • Number of venipunctures, finger sticks, port access, and central line accesses • Type of activities child missed • Amount of time child missed at activities • Reason activities were missed by child or parent	• Out of pocket costs associated with transportation, child care, and meals • Type of activities parent missed • Amount of time parent missed at activities • Estimated loss of pay due to activities parent missed • Insurance coverage for medical services and other services • Other financial coverage for medical services and other services

TABLE 3.3 SUMMARY OF TOTAL EPT COURSE 1 PROTOCOL REQUIREMENTS*

Item	Median	Mean	SD	Range
Length of Course (weeks)	4	3.8	0.4	3 - 4
Baseline Imaging (number of scans)	2.5	2.8	1.2	2 - 5
Physical Exams (number)	4	3.8	0.4	3 - 4
Required Blood Draws (number)	12	11.3	4.7	4 - 16
Optional Blood Draws (number)	2.5	1.8	1.5	0 - 3
End of Course Imaging (number of scans)	2	1.5	1.2	0 - 3
Total Required Observations	20.5	19	5.9	10 - 26

*n=5 different EPT protocols

TABLE 3.4 DESCRIPTIVE STATISTICS FOR TREATMENT BURDEN PER WEEK DOCUMENTED*

Treatment Burden Per Week	Median	Mean	SD	Range
Number of Appointments	3.8	3.4	0.8	2.3 – 4.3
Time for Appointments (hours)	11.5	11.6	2.7	7.9 – 17.8
Activities Child Missed (hours)	9.9	15.6	13.2	2.3 – 37.5
Out of Pocket Cost ($)	10.6	15.6	16.5	0 - 50
Number of Needle Punctures	2.8	2.7	1	0.5 – 4.3

Note. Children were enrolled in EPTs with varying course lengths. Per week treatment burden was calculated for each participant as the total of entries in the Diary of Trial Experiences for course 1 of the EPT, divided by the number of weeks.

* n = 10 parent and child dyads completing the post-disease evaluation assessment

CHAPTER 4

This chapter presents the results of the phenomenological study examining 11 parents' experiences when their child with cancer participated in a P1T.

4.1 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.[29,30] 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%).[29,30] These improvements in childhood cancer outcomes are attributed to better therapies and high levels of participation in clinical trials.[142,143] Phase I clinical trials (P1Ts) are the critical first stage of clinical trials, and involve determining the recommend dosage and testing the safety of new therapies.[1,2,33,143] P1Ts are necessary for developing new therapies that will improve outcomes for children with cancer.

The Declaration of Helsinki requires that "the interests of the [research] subject must prevail over the interests of science and society".[44] The ethical conflict inherent in pediatric oncology P1Ts is that the primary aims of these trials 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.[18,39,74] The median life expectancy of children with relapsed cancer enrolled in a P1T is less than seven months.[2,39,40] 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.[17,18,25,74,143] To address the ethical concerns 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. However, research has not been

performed on the benefits, burdens, or impact of P1T participation for children with cancer or their parents outside of the process of consenting to the P1T.[17-26,144]

The purpose of this study was to identify the fundamental commonalities and 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.[54] Phenomenological research is used to describe the essence (i.e. the fundamental commonalities and meaning without which a phenomenon would not be what it is) of the lived experiences of people in similar life situations.[55-58] The specific aim was to develop a rich, in-depth, phenomenological description of parents' lived experiences of having a child with cancer participate in a P1T.

4.2 METHODS

This study was approved by the Indiana University Institutional Review Board.

4.2.a Setting

Parent recruitment occurred at two time points. First, a pilot interview was conducted with one parent recruited by the primary researcher, 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 P1Ts. Parents were also recruited for the main study from national childhood cancer support and advocacy groups that were not affiliated with either medical center.

4.2.b Sample

The purposive sample consisted of parents of children with cancer who participated in a P1T. Sample size in phenomenological studies is not determined in advance. Rather, sampling continues until data analysis yields thematic redundancy, and generally ranges between 10 and 20 participants.[64,145-149] 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.[54,150,151] 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 P1T.

Parent was defined as anyone who served in the role of primary caregiver (e.g. biological parent, guardian, grandparent). Up to two parents were interviewed for each eligible child. Parent inclusion criteria were: (1) age $\geq$ 18; (2) self-identification as primary caregiver of child; (3) fluency in English; and (4) having provided consent for child's P1T participation. In addition, the parent's child must have been: (1) enrolled in at least one pediatric oncology P1T in the United States; (2) aged < 18 during the P1T; and (3) removed from the P1T at least 60 days prior (to ensure that the off-study transition had fully been experienced). Parents were ineligible if the child had died within the previous 60 days.

4.2.c 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 primary researcher 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 P1T within the past four years. Potentially eligible participants were recruited using the method developed for research involving parents of deceased children.[68] 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 primary researcher. The primary researcher 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[152] via electronic mail that allowed participants to formally agree to participate and begin study procedures. If desired, participants could complete the agreement to participate and other REDCap™ surveys in writing.

4.2.d 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 primary researcher. The primary researcher sent the interview question via email at least one day in advance of the interview.[68] Interviews were audio-recorded and done over the telephone by the primary researcher at a time convenient to the parent. Seven to fourteen days after the interview, a follow-up call was made by another researcher to clarify any ambiguous details from the interview and to ensure no undue distress resulted from participation in this study. Lastly, the researcher 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 primary researcher 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.

4.2.d.1 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.

4.2.d.2 Phenomenological interview

The goal of empirical phenomenological interviews is to obtain clear, rich descriptions of participants' experiences.[149,153] Of particular importance is ensuring that the participant describes their experiences without analysis or interpretation, using a

small number of broad, open-ended questions.[54,56,58,149,153,154] 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.[148,153] Probes such as: "Please tell me more about that" and "What did that mean to you?" were used to enhance depth of the discussion.[148,153] 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 P1T, receiving the first dose of each P1T therapy, and transitioning off each P1T. Lastly, the parent was asked if they had any advice for parents considering enrolling their child in a P1T, and if there were any other important events or people who impacted their P1T experience.

4.2.d.3 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 researcher 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.

4.2.e Data Analysis

Interviews were audio-recorded and professionally transcribed by a contracted, Health Information Portability and Accountability Act (HIPAA)-approved provider. The

primary researcher de-identified and verified the accuracy of the transcripts, prior to beginning data analysis. Data were managed using NVivo™ software.

Steps of analysis, per the adapted Colaizzi method, included:[54] (1) repeated readings of the full interview transcript for a sense of the whole; (2) identification of substantive phrases; (3) restatement of substantive phrases in general terms; (4) formulation of derived statement meanings; (5) development of themes and organization of themes into theme clusters and categories; (6) generation of an exhaustive description of the experience; and (7) development of the essential structure of parents' experiences of having a child enrolled in a P1T. Table 4.1 provides examples of steps 2 through 4.

Data analysis occurred simultaneously with participant recruitment. Thematic redundancy was established when new themes no longer emerged from interview transcripts. After achieving thematic redundancy, two additional participants were recruited to confirm that no potential themes were left unidentified. The demographic form and clinical trial record were used to describe the sample, understand details specific to the P1T in which the child was enrolled, inform parents' descriptions of their experiences, and provide context for interpreting experiences. In addition, when more than one parent participated, the consistency and divergence of their narratives and themes was explored as part of determining the essence of the phenomenon.

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 essence of the phenomenon.[58,65,155-159] Prior to beginning this study, the primary researcher reflected in writing on personal and theoretical knowledge of the P1T experience. These reflections were used to recognize when the phenomenological attitude had been compromised. In addition, a reflexive diary of decision-making and theme emergence was kept throughout interviewing and data analysis.[66] 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 and that each step of the process was performed through discussion and consensus.

After data analysis was complete, two clinicians validated the findings. The primary researcher 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 P1Ts? Although no substantive changes were made based on feedback provided, some concepts and ideas in the exhaustive description were clarified through their feedback.

4.3 FINDINGS

4.3.a 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) at enrollment to the first P1T. Parents reported their annual household income as $40-$59,999 (27.3%); $60-99,999 (18.2%); >$100,000 (36.4%); Don't Know (18.2%). No parent reported an annual income of <$40,000 per year. Most parents had at least some college or professional degree (81.8%). Parents' reports of the distance they traveled from their household to the P1T center varied between: 10 to 29 miles (36.4%), 30 to 89 miles (18.2%), 90 to 239 miles

(27.3%), and greater than 240 miles (18.2%). 63.6% of parents were bereaved (n=7), 18.2% of parents had a surviving child who was still receiving treatment (n=2), and 18.2% of parents had a child who was a long term survivor and off treatment (n=2). Only two parents enrolled were a couple; all other participants were parents of different children. 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 4.2 for further characteristics of the sample and their P1T experiences.

4.3.b 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. See Table 4.3 for a list of theme categories, clusters, and selected sub-themes. 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.

4.3.b.1 Theme Category 1 - Being the parent of a child with high-risk cancer: "This is my child here" [P10.L283].

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." [P3.L94] 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." [P10.L203]

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." [P8.L282]

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." [P6.L267] 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'." [P6.L203]

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" [P3.L352] (see Table 4.3 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." [P1.L213]

4.3.b.2 Theme Category 2 - Contending with high-risk cancer: Fighting "this beast" [P12.L82].

Woven throughout parents' P1T 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." [P6.L95 & L101]

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." [P8.L192]

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 P1T] for good reasons." [P3.L50]

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." [P4.L424] Although parents clung to hope that the next treatment would help, they also felt challenged to begin thinking about stopping their search for treatment. Catalysts precipitating whether parents decided to stop curative treatments are listed in Table 4.3. 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" [P2.L211], 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." [P10.L119] Parents managed by finding a new norm for their child and family, i.e. by getting "to where we could all breathe" [P1.L246]. This resulted in a redefinition of what was considered truly difficult or problematic. See Table 4.3 for specific strategies used day to day.

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" [P10.L397] 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 P1T]. I mean I was not okay with it at the time, but we knew it could happen." [P8.396] 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.

4.3.b.3 Theme Category 3 - Perceptions of child's experiences: "There is something about them that is very, very different" [P10.L184].

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." [P9.L406]. 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.'" [P8.L316]

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 P1T experience as younger children were "too young to really have any conversations about what it [the cancer] meant" [P10.L204] 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" [P9.L138] and "he never complained" [P1.L230]. 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" [P10.L220] 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." [P2.L166] 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." [P2.L158] 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 [P1T participation] fit right in for him." [P12.L350]

4.3.b.4 Theme Category 4 - The nature of P1T participation: "The further you get into a poor prognosis, the easier a phase I trial becomes" [P12.L332].

This theme category reflects the elements of parents' experiences specific to the P1T, and it encompasses a broad range of theme clusters, including underlying characteristics of P1Ts, choosing to participate in a P1T, ebb and flow of P1Ts, emotional stances towards P1Ts, and the impact of P1T participation.

The underlying P1T characteristic impacting parents the most was the uncertainty of P1Ts; the sense that "nothing's ever a given" [P1.L71] 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 P1T 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 P1T] was the one that offered the most hope. And, I don't know if that was a tangible hope or not." [P1.L71]

In addition, the inherent complexity of P1Ts created challenges for parents in terms of learning about the clinical trial system and finding specific P1Ts that could work for their child. Parents specified that the primary website for finding P1Ts, Clinicaltrials.gov[160], was confusing to search. Parents were seeking more support in learning about clinical trials, e.g. "you really need to find somebody who is going to sit down with you and explain the clinical trial process from start to finish, because it's not straightforward." [P10.355]. This included a "resource to really simplify things … [to] lay everything out for people… [using] very simple language that's trust-building." [P12.L538 & L563]

Parents understood there weren't any guarantees that the P1T would help against their child's cancer. Some clearly expressed that "I knew it wouldn't help [my child]" [P5.L264], yet were still willing to participate given their child's poor prognosis. The hope that the P1T 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." [P4.L464] Altruism and leaving a legacy were only identified by parents of children ages 12 and older as reasons for participation. The appeal of P1Ts was a sense of trying something completely novel and of pursuing every possible option to help their child, as well as being part of research that potentially could lead to a cure.

Most parents described the decision to participate in a P1T as easy, and many had a sense that the P1T plan "just fell into place" [P1.L99]. Emotional stances towards P1T participation varied as the experience unfolded. That is, parents at times embraced the P1T and all of its unknowns, felt special for being asked or chosen to participate, were fearful of P1T unknowns and potential toxicities, and deemed the P1T as more burdensome than other treatments (see Table 4.3 for full list). Many parents experienced frustration with the inflexibility of the P1T protocol at some point. One parent who would later become involved in childhood cancer advocacy expressed how at the time of P1T enrollment, he had "no idea, absolutely no idea" [P10.L117] what he was getting into. Despite feeling negative emotions at times, almost without exception parents did not regret their child participating in a P1T and recommended P1Ts to other parents of children with cancer.

Overall, parents approached the P1T as "just another medicine" [P5.L138] for their child's cancer. Specific advantages parents experienced while participating in a P1T included feeling better informed and cared for during the P1T, and having access to more resources and opportunities by being at a larger P1T center. Disadvantages included having to wait to start P1T therapy, burdens of extra and longer medical appointments as well as additional procedures and venipunctures, and a sense of their lives revolving around the P1T. Parents strove to minimize the burdens of P1T participation by incorporating enjoyable activities around required P1T appointments (i.e. by making visits to the P1T center feel like "a family trip… a little get-away") [P8.L121].

Some parents described the meaning attached to blood samples taken specifically to support research. "He was all excited about doing that, … sending samples

out to wherever it needed to go." [P5.L128] However, an appreciation of the significance of research-only lab draws and procedures did not offset the additional burden they created for parents and children. Parents whose child was surviving and still involved with P1Ts described the specific burdens associated with P1T research-only lab draws and procedures.

> "We had to sit there for nine hours … because they had to draw his blood every hour. …. Just sitting there doing absolutely nothing and they weren't doing anything for us… And what sucked was he needed one blood draw 24 hours after. It was we went all the way down there, so it was over an hour drive. I counted we were in the clinic for seven minutes, and we left and drove back an hour." [P4.L389 & L393]

Parents were more receptive to research-only lab draws and procedures that occurred while their child was still participating in the P1T. When there were requirements asked of participants after the child's removal from the P1T, parents were far less willing to comply unless these procedures could be planned to coincide with other elements of the child's medical care. However, parents did feel empowered to refuse post P1T research-only labs and procedures on their child's behalf, when they felt that the burden was too great.

> "It's like you feel you aren't good enough to get the drug, but they still want to get some data from you. …. They wanted us to go in for lots of blood work and even scans, and we're like, 'No. If he can't get the drug we're not going to do it.' " [P4.L96 & L99]

Most parents were aware that the P1T protocol guided decisions made about their child's medical care during the P1T. Parents viewed the P1T protocol as mandatory, took their role as parents of a P1T participant seriously, and strove to always comply with protocol requirements. However, many parents struggled with a sense of not being in control, feeling compelled to comply with the P1T protocol, and a sense that their child's medical care was not the primary priority of the P1T. Parents' frustration with the P1T protocol flourished when they deemed that their child's best interests were not in line with protocol requirements. "If the doctors don't even blink an eye because there's really nothing wrong with those [lab] numbers, why are we getting kicked [out of the P1T]?" [P4.L341] Although most parents continued to comply with the

P1T protocol requirements even when they were frustrated, one parent described defying the protocol requirements when they felt their child's medical care and well-being was being significantly compromised. This episode occurred in response to the requirement that treatment for the child's progressing cancer stop for several weeks before starting the P1T, in order to avoid medication interactions:

> "I was not about to sit back during that watch period and not administer any treatment to her. We still had drug left over from the first phase I and I will go on record as saying, we administered some of that drug to her. ... I was not going to sit idly by." [P10.L285 & L292]

There was evidence that P1T 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." [P4.L343] This resulted from an overriding fear that additional medications could exacerbate toxicities (e.g. liver or renal dysfunction) and cause the child's premature removal from the P1T. In addition, some parents were not educated about palliative care and hospice services until 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 it was a very good decision." [P10.449]

There were unique aspects of participating in a P1T related to the use of oral medications. Although parents appreciated not having to go to the medical center for therapy, they struggled with their child's dislike of oral medications and difficulty swallowing pills (e.g. "taking [oral] medicine is the worst" [P8.L255]). They also struggled with restrictions on when their child could eat and drink (i.e. due to the need to ensure the oral medication is absorbed properly eating and drinking is restricted for 1 to 2 hours before and after each dose). "It felt worse, the extra fasting and then trying to support her emotions, and 'I'm so hungry'." [P3.L334]. One parent's experience was that the eating and drinking restrictions exacerbated the nausea and vomiting her child experienced with the oral medication. "She wasn't able to eat anything, and then she had to take this medicine, and then she had to wait an hour afterwards before she could eat anything. It would just really make her extremely sick." [P6.L82] P1T protocols with

oral medications could also be more problematic to manage when the child experienced toxicities and the medication was given daily without a break. “This is just every day take the pill, feel like crap. Take the pill, feel like crap, you know?” [P3.L266]

4.3.b.5 Theme Category 5 - Remembering and forgetting: “Sometimes your brain kind of blocks things” [P6.L12].

All parents described a fogginess in their memories of their child’s participation in a P1T and cancer treatments in general, e.g. “a lot of it is a blur.” [P10.109] 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.” [P9.L413]

Parents whose child was surviving and continuing to pursue P1Ts remembered the specific challenges of P1T 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 health care providers. Parents reported that younger children who were long-term survivors did not “remember anything about … cancer treatments” [P11.L382] in the long run, although they “remember some of the happy things” [P11.L351] associated with the cancer treatment (i.e. playing with child life specialists). Most parents were not concerned with their challenges remembering P1T details, and even took comfort in not remembering.

4.3.c The Essential Structure

Pervasive throughout parents’ descriptions of their lived experiences during P1T 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 P1T participation, parents’ experiences were not focused on the P1Ts 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 P1T reflected what stood out in the experience, and how parents managed the P1T experience. Particularly important aspects of the P1T experience included the connection with the health care providers who managed the child's care during the P1T, making the choice to continue trying to slow or stop the child's cancer by participating in a P1T, and being burdened by additional requirements when participating in a P1T.

4.4 DISCUSSION

The purpose of this study was to address the gap in our understanding of P1T participation for children with cancer or their parents, by identifying the fundamental commonalities and meaning of the P1T experience. The overarching thread throughout parents' descriptions of their experiences was "we don't have time to waste" [P12.L557]. 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." [P12.L455] 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 P1T, in other situations it was a reason to stop. Further research is needed to better understand parents' decision-making related to stopping curative 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 P1T participation may include improved QOL and hope.[13-16,77,85-87] Although this study did not attempt to assess QOL benefits associated with P1T participation, it did find some hope benefit. Study findings confirmed that P1T participation fosters hope to slow or stop the cancer. A potential risk of P1T participation posited in the literature was the fostering of unrealistic hope.[13-15,85-87] Findings did not indicate parents had unrealistic hope. arents were able to be realistic in their expectations of direct benefit for their child from the P1T 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 P1T 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 P1T participation.

Another risk of P1T participation identified in the literature was the burdening of children with additional medical procedures and toxicities.[13-16,77,85-87] This study found the burdens of P1T participation for children and parents included additional medical procedures, toxicities, and medical appointments. This study also added to our understanding of the unique burdens associated with oral medications, which was not previously identified in the literature. It is important to be aware of the potential issues with oral medications when presenting treatment options to parents and children, as clinicians and P1T researchers may overestimate the burdens of intravenous therapy administered in a medical clinic or hospital. P1Ts with oral medications that involved eating and drinking restrictions were particularly burdensome for parents, as they had at times to deny the requests of their child with cancer for food and drink. Parents took the requirements of the P1T protocol seriously and strove to comply, even when compliance was burdensome.

Inconveniences associated with research-only specimens and procedures were also described in detail, suggesting that for some parents P1T-specific tests and procedures caused significant burden. Interestingly, no parent mentioned the incentive that was provided to participants to acknowledge the burdens associated with research-only lab draws. This suggests that the incentive was not coercive but raises questions of whether the amount of the incentive was sufficient to reflect the burden experienced by parents and children, and whether the distribution of the incentive could be enhanced. It is also possible that no incentive would ever sufficiently reimburse families for time lost. Currently, there are no recommended guidelines for incentive distribution, beyond what is required by institutional review boards. Many centers may logistically provide the incentive to P1T participants with the first research-only lab draw, rather than waiting until the completion of the lab draws. In addition, parents tended to be reluctant to continue with research-only lab draws and procedures after their child was

removed from the P1T, unless these coincided with other medical care provided to the child. P1T researchers should consider the importance of post P1T research-only lab draws and procedures and consider providing additional incentives to acknowledge and offset the additional burden created for parents and children.

A final risk of pediatric oncology P1T participation identified in the literature was limitations on opportunities for palliation.[13,14,85] The study findings provided evidence that P1T participation could impact how parents managed their child's symptoms. The need to ensure the child could continue in the P1T, without held doses of therapy, for parents sometimes overrode 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. The latter does not seem to reflect the impact of P1T 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 curative 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.[161-163] These findings highlight the need to simultaneously provide effective palliative care throughout the child's P1T participation.[41,164]

P1T decision-making and consent processes were demonstrated in this study to be impacted by the quality of communication between the child, parent, and health-care providers. Empiric research has previously identified challenges educating potential participants about pediatric oncology clinical trials and lapses in pediatric oncology P1T consent processes.[27,132,133,165,166] This study confirmed that parents need more support and better education regarding the clinical trial system, e.g. regarding intricacies of and motivations behind each phase of clinical trials. Parents in this study also described challenges identifying appropriate P1Ts. ClinicalTrials.gov is the database which provides information about all clinical trials conducted throughout the United States.[160] Clinicaltrials.gov was recognized by parents as containing the most comprehensive information available on existing trials; however, parents struggled with obtaining information on P1Ts from the site. In addition to what is described in the literature,

parents in this study also 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.[128] This warrants clinicians and P1T researchers paying particular attention during P1T consent conversations to the transparency of communication.

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 distress.

Overall, parents did not regret their child participating in a P1T and would recommend P1Ts to other parents of children with cancer. There was a notable exception as one parents' experience with the P1T was substantively more negative, despite their child having prolonged stable disease with tumor shrinkage from the P1T therapy. This parents' P1T experience was fraught with a sense of disconnectedness from the medical team from beginning to end, the child fighting taking the oral 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 a P1T and described an ethically problematic situation related to trial participation. It is important to not dismiss this one parent's experience as an outlier, as it may reflect other previously unreported problematic P1T experiences. The researchers recommend that in future research, an in-depth multiple case study be conducted when any ethically problematic situations are identified, in order to capture the perspectives of the parent, medical team, and child. In addition, P1T researchers and clinicians should explore with parents the reasons behind hesitancies to participate or continue in a P1T. It is particularly important that P1T researchers and clinicians are aware of the significance of an offer of a P1T for parents of children with high-risk cancer, and

the impact that a pre-existing parent / provider relationship has on parents' ability to decline a P1T offer or to share concerns with providers during a P1T.

4.4.a Limitations

The primary limitations of this study were the lack of racial, ethnic, and social 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 P1T experiences would include the child's perspective. Due to the shortened life expectancy of children enrolled in P1Ts, 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.

4.5 CONCLUSIONS

Study findings are generally reassuring to P1T researchers and pediatric oncologists who consider recommending P1Ts for children with cancer. For parents of a child with high-risk cancer, a P1T represents a novel treatment option with potentially more acceptable toxicities. Although some concerns were raised regarding the experiences of parents and children in P1Ts, these reflect opportunities for improvement. Parents who describe burdens in P1Ts would not dissuade other parents of children with high-risk cancer from participating, and indeed would continue to pursue other P1Ts for their own child with cancer.

TABLE 4.1 EXAMPLES OF SIGNIFICANT STATEMENTS, RESTATEMENTS, AND FORMULATED MEANINGS DEVELOPED DURING DATA ANALYSIS

ID	Significant Statements (From Original Interview Transcript)	Restatements (Developed by the Researchers)	Formulated Meanings (Developed by the Researchers)
P3.L55	We just kept telling ourselves that even if we have these hesitancies 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 hesitancies 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.
P5.L128	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.
P8.L256	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 4.2 CHARACTERISTICS OF THE SAMPLE AND THEIR P1T EXPERIENCES*

Item	n (%)
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)
Child's Status (N=10 children)	
Deceased	6 (60)
Surviving and on Treatment	2 (20)
Surviving and in Extended Remission	2 (20)
Timing of Removal from P1Ts (N=15 trials)	
Middle of Course 1	3 (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 P1Ts (N=15 trials)	
Adverse Events / Toxicities	5 (33.3)
Disease Progression	8 (53.3)
Death	1 (6.7)
Completed Trial	1 (6.7)
Best Overall Response to P1Ts (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.

TABLE 4.3 LISTING OF IDENTIFIED THEME CATEGORIES, THEME CLUSTERS, AND THEMES WITH SELECTED SUB-THEMES

Theme Categories	Theme Clusters	Themes	Selected Sub-Themes
Being a parent of a child with high-risk cancer: "This is my child here" [P10.L283]			
	• Being fully responsible for child's well-being: "It's all on our shoulders" [P3.L94]		
		• Child fully relying on parent	
		• Advocating for child when needed: "If you don't, then your child's going to get pushed around" [P10.L382]	
		• 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" [P1.L205]	
		• 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" [P10.L434]	
		• Doing everything possibly can for child	
	• Aligning with child: "We would quit whenever she wanted to" [P8.L15]		
		• Looking to child for direction: "If that's what she wants to do ... she knows how she feels" [P6.L259]	
		• Striving for open communication with child: "We don't surprise her with anything. We talk about things." [P3.L253]	
		• Needing child to agree with plan: "I was just very hopeful that she would say, yeah mom, let's do this" {P6.L205]	
		• Being on the same page: "She was willing to do it and we were willing to do it, so we tried whatever" [P8.L53]	
		• Becoming misaligned: "When she started resisting it was very weird for us because she's always been so accepting" [P3.L272]	
	• Parental suffering		
		• 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" [P1.L213]	
		• Feeling overwhelmed with what have to handle: Trying to keep up with moving treadmill as speed is being increased	
Contending with high-risk cancer: Fighting "this beast" [P12.L82]			
	• Continuum of the cancer journey: The life cycle of cancer		
		• Beginning the journey: Life altering diagnosis of cancer	
		• The insidious nature of cancer	
			• Cancer not going away
			• A time bomb ticking beneath the surface
			• Cancer becoming a visible or tangible reality

Theme Categories	Theme Clusters	Themes	Selected Sub-Themes
			• Trapped in unrelenting cycle of remission and relapse • Cancer relentlessly taking over
		• Enduring endless treatments	
		• Perception of wellness muddying the waters: “Cancer kids can get sick” [P4.L147]	
			• Dichotomy of having cancer and being well: “You would not look at her and know that she had a terminal diagnosis” [P10.L233] • Becoming unwell during cancer journey • Recovering from being unwell
		• The journey ending	
			• Entering hospice • Deciding that child was just ready to go • Child dying from cancer or complications of cancer • Child dying unexpectedly • Sadness of child missing out on good parts of life • Family disintegrating after child died • Child being a long-term survivor
	• Forming a team		
		• Establishing and maintaining connections with medical team	
			• Getting the right medical team • Having expectations of medical team • Connecting with members of medical team • Disconnecting with medical team • Unconnected with medical team members
		• Managing family dynamics	
			• Aligning • Misaligning • Managing misalignment
		• Being supported by other parents and children with high-risk cancer	
			• Child taking comfort in presence of other children with cancer • Finding other parents who understood and had a similar point of view
	• Leaving no stone unturned: Searching for tolerable and effective treatment options		
		• Looking everywhere for the best treatment option	
			• Being supported by others in search for options • Needing to always be ready with other treatment options • Traveling when needed to find treatment options: “Then you've got to travel” [P10.L149] • Trying complementary therapies and herbal supplements along with other treatments • Struggling to find a treatment option that meets their requirements
		• Having requirements for treatment options	

Theme Categories	Theme Clusters	Themes	Selected Sub-Themes
			• Making exceptions in certain circumstances • Turning down treatment options that don't meet requirements
		• Vicious cycle of trying to find an effective treatment that child can tolerate: “Hoping that one works, one that we can stay on” [P4.L461]	
		• Role of doctors in search for treatment options	• Relying on doctors to provide treatment options • Doctors continuing to provide treatment options • Discussing treatment options together with medical team • Seeking input from different trusted medical team members
	• To stop or not to stop: Stopping point as a moving target		
		• Moving onto next treatment	• Needing to do something to stop cancer • Not ready to quit: “We didn't want to give up yet” [P9.252] • Not willing to waste time in search for an effective and tolerable treatment
		• Deciding to stop curative treatments	• Recognizing at some point, when cancer is taking over, have to stop treatment • Passively making decision to stop curative treatment • Accepting child is going to die
		• Catalysts precipitating or hindering decisions at potential stopping points	• Availability of good or reasonable options • Child's quality of life • Level of understanding of seriousness of child's condition • Effectiveness of last treatment • Tolerability of last treatment • Believing there is a treatment out there that's going to work • Wanting to be able to explore all possibly effective treatment options
	• Bearing burden of tough decisions		
		• No choice but to make a choice	• Between a rock and a hard place: Start another cancer treatment or let child die
		• Ways of decisioning	• Being decisive: “Let's do it” [P1.L269] • Being hesitant or uncertain • Needing time to make a decision • Conscientiously thinking everything through before making a decision • Seeking input from others

Theme Categories	Theme Clusters	Themes	Selected Sub-Themes
			• Wanting to be told what to do • Taking ownership of decisions related to child's care • Taking risks • Trusting gut instincts • Spirituality in decision-making
		• Angst of having to make a decision	• Wondering if doing the right thing • Becoming desperate • Being overwhelmed • Being unprepared • Feeling defeated • Questioning own ability to make a decision • Not knowing what to do: “We just didn't know” [P10.L512]
		• Living with choices made	
	• Managing day to day - Doing the best you can day to day		
		• Facing constant challenges or problems	• Having to do things that were difficult or unpleasant: “It was tough!” [P10.L324] • Having to be self-reliant • Compelled to juggle responsibilities • Compelled to make compromises • Unable to enjoy life • Becoming swept up in tide of negativity
		• Living with uncertainty	• Having to wait: “We'll have to see” [P10.442] • Experiencing unexpected interruptions to plans • Not being able to plan too far into the future
		• Finding a new norm: “It all just started to click a little bit better” [P1.266]	• Seeking normalcy • Finding comfort in routine: “That was just our routine” [P8.L143] • Redefining what is considered difficult or a real problem: “Hard... it's all relative I think” [P10.L277]
		• Strategies for managing day to day	• Focusing on the present • Trying to solve or prevent problems • Following a plan diligently • Having transcendent goals • Rolling with the punches • Gaining expertise and knowledge over time: “Now I know a lot more” [P10.L145] • Accepting help • Maintaining connections with family, friends, and social network • Relying on pre-existing strengths

Theme Categories	Theme Clusters	Themes	Selected Sub-Themes
			• Setting boundaries • Being proactive • Being realistic with expectations • Finding time and space to recover • Avoiding information and difficult discussions
		• Transcending the struggle against cancer	
			• Finding meaning
			• Using time well • Sense of achievement or pride in cancer journey • Being a part of something bigger than own journey • Valuing research and participation in research • Believing that treatments helped child in some way • Continuing bonds with child after child's death: "That's a part of her so we'll just leave it there" [P8.L151]
			• Being grateful for how things went: "We've been very fortunate" [P10.L397]
			• Being better off than others • Having resources and people available • Having special moments and memories • Child maintaining a good quality of life
			• Having hope
			• Hoping to slow or stop cancer • Hoping for quality of life in time remaining • Hoping can help others • Hoping P1T participation was meaningful
			• Relying on faith and spirituality
Nature of P1T participation: "The further you get into a poor prognosis, the easier a phase I trial becomes" [P12.L332]			
		• Underlying characteristics of P1Ts	
			• Uncertainty of P1Ts: "Nothing's ever a given" [P1.L71]
			• Having to qualify for a P1T • No guarantee P1T will work: "It's a crapshoot" [P10.L138] • Not knowing what P1T therapy would do to or for child • Abnormal lab values having the potential to remove child from P1T
			• Complexity of P1Ts
			• Trying to become fluent in the clinical trial system • Understanding complexity and logistics of P1Ts • Not understanding full complexity of P1Ts
			• Having a clear plan
			• Therapy given in outpatient setting
			• P1Ts having the most requirements in the first cycle(s)
			• P1Ts being administered the same, regardless of institution

Theme Categories	Theme Clusters	Themes	Selected Sub-Themes
		• Institutions and medical teams influencing or determining how the P1T experience unfolds for families	
	• Choosing to participate in a P1T		
		• Reasons for participating in a P1T	
			• Hoping that P1T will help slow or stop child's cancer: "It is your hope!" [P10F.L42]
			• Believing that research will find cures for cancer
			• Wanting to try something completely novel: "We wanted to try something that had not been tried before" [P10.L33]
			• Altruism
			• Participating in research as legacy: "You're leaving something behind" [P12.L325]
			• Doctor recommending or suggesting P1T
			• P1T available when needed
			• P1T anticipated to have minimal impact on quality of life
			• Other parents of children with cancer commending their experiences with clinical trials
			• Being willing by nature to take risks
		• Child having to assent to participate in P1T	
		• Many steps involved with enrolling in a P1T	
	• Ebb and flow of P1Ts		
		• P1T plan "just fell into place" [P1.L99]	
		• Interruptions to P1T plan	
			• Holding P1T therapy so child could recover from side effects
		• Restarting P1T, even after things went wrong	
			• Trying again at a lower dose of P1T therapy
		• Trial conclusion	
			• Being removed prematurely from P1T
			• Deciding to stop participating in P1T
			• Reasons for leaving or being removed from P1T
			• Being concerned only with continuing child's cancer treatment as soon as possible
			• Being asked for child to have additional lab work and tests done after removal from P1T
		• Outcomes of P1T participation	
			• Cancer improving
			• Cancer remaining essentially stable
			• Cancer getting worse
			• Having clinical improvements
			• Dying unexpectedly during P1T
	• Emotional stances towards P1Ts		
		• Embracing P1T, including unknowns	
			• P1T as an easy or obvious decision
			• Being unafraid: "There really was no fear" [P1.L284]
			• Taking comfort in what is known about P1T drugs

Theme Categories	Theme Clusters	Themes	Selected Sub-Themes
			• Not regretting participating • Relief in doing something to stop the cancer • Seeing only risk as potentially wasting time on an ineffective treatment • Sense of security in knowing can withdraw from P1T at any time and get backup chemotherapy
		• Feeling special for being asked or chosen to be in P1T	
		• Initial resistance to participating in a P1T	• P1Ts as least desirable type of treatment option • Not wanting child to be a guinea pig
		• Being fearful	• Fearing P1T unknowns • Fearing side effects • Overriding fear of child being prematurely removed from P1T: “People can get sick, and if we had just been in that perfect timing once again we could've got kicked off, but a week later he's going to feel just fine” [P4.L334] • Being afraid that P1T didn't or won't work against child's cancer • Worrying about child having long term health damage from P1T therapy
		• Appreciating that P1T experience could be even harder	
		• Deeming P1T as being more burdensome than other treatments including conventional chemotherapy, other clinical trials, or stem cell transplant	• Child hating to take the P1T drug • Feeling used as a means to an end • Believing in the end that P1T was worth burdens experienced
		• Frustration with inflexibility of P1T protocol	• Seeing child as not being the priority of the P1T • Feeling that P1T protocol focuses on lab values that don't matter • Viewing P1T protocol as mandatory • Trying unsuccessfully to bend the rules • Defiantly breaking the rules: “I was not going to sit idly by” [P10.L292]
		• Not understanding at the time what getting into when enrolling in P1T: “Back then, I had no idea, absolutely no idea” [P10.L117]	• Becoming doubtful regarding effectiveness of P1Ts and clinical trial system after P1T completed: “The paradigm has to be shifted” [P10.L143]
		• Not caring about P1T complexities or logistics	
		• Not blaming P1T for bad experiences	
		• Others having negative opinions about P1Ts	
	• Impact of P1T participation		• P1T as “just another medicine” [P5.L138]

Theme Categories	Theme Clusters	Themes	Selected Sub-Themes
		• Advantages of P1T	
			• Feeling well informed during P1T
			• Feeling well cared for during P1T
			• More resources and opportunities available at P1T center
		• Disadvantages of P1T	
			• Having to wait to be able to go onto a P1T
			• Being burdened by participating in P1T
			• Life revolving around P1T
			• P1T protocol and decisions beyond parent's control
			• Child not being the priority during the P1T
			• Family's insurance not covering P1T
		• Unique aspects of oral P1T therapy regimens	
			• Disliking taking oral medications
			• Having to work around child's difficulty swallowing pills
			• Being restricted on when child can eat or drink
			• Not ever getting a break from taking the P1T drug or experiencing its side effects
			• Not having to go to the hospital to get the P1T therapy
		• Experiencing side effects or complications during P1T therapy	
			• Side effects being intolerable
			• Becoming critically ill during P1T
			• Vital organs being impacted by P1T therapy
			• Not really being burdened by side effects
			• Importance of timing of onset of side effects during P1T
			• P1T protocol exacerbating side effects
			• Experiencing side effects from supportive medications in addition to side effects from P1T therapy
		• Not feeling burdened by P1T participation	
		• Short part of cancer journey: “This is a really short story” [P4.L8]	
Perceptions of child's experiences: “There is something about them that is very, very different from kids who deal with non-life-threatening illnesses” [P10.L184]			
	• Seeing child as special		
			• Child having special needs
			• Perceiving child as medically complex: “She is a very complex person … with all her conditions” [P3.L183]
			• Seeing child in a very positive light - brave, optimistic, resilient: “She was amazing!” [P10.L271]
			• Seeing child as stronger and more resilient than parent: “I couldn't have done half the stuff she did” [P8.L293]
			• Deriving strength from child: “I drew my strength from her” [P6.L240]

Theme Categories	Theme Clusters	Themes	Selected Sub-Themes
			• Having pride as a parent for who child is or was: "That makes a parent proud!" [P6.L275]
		• Child's age impacting their P1T experience: "She was too young" [P10.L205]	
			• Child being too young to understand meaning of having cancer or to ask difficult questions: "She was too young to have any conversations about what it meant" [P10.L204]
			• Child being very young and not knowing any other way of living: "This was what was normal for her" [P10.L353]
		• Child not protesting against treatments or procedures: "He never complained" [P1.L230]	
		• Child being very active in decision-making: "We would leave it up to her: [P6.L264]	
		• Child mature beyond years because of what went through in cancer journey: "Very mature for her age" [P6.L33]	
		• Adolescent's willingness to take risks impacting decision-making: "He was a risk-taker so that fit right in for him" [P12.L350]	
		• Child playing the cancer card: "She knew how to get what she wanted" [P10.L220]	
		• Being uncertain of child's understanding of their own cancer: "I don't think he realized the extent of how things had gotten at that point" [P2.L166]	
Remembering and forgetting: "Sometimes your brain kind of blocks things out after certain things happen" [P6.L12]			
		• Fogginess and uncertainty: "A lot of it is a blur" [P10.109]	
			• Not remembering specific details
			• Remembering incorrectly
		• What is remembered by parents	
			• Remembering some details: "I do remember that" [P1.L101]
			• Remembering important moments in particular: "I'll never forget this" [P10.L455]
		• What is remembered by children	
			• Child only remembering happy times: "She remembers some of the happy things" [P11.L351]
			• Child not remembering cancer treatments in the long run: "She doesn't remember any of the pain" [P11.L351]
		• Emotional stances towards remembering and forgetting	
			• Lack of concern over difficulties remembering: "Of course I don't remember a lot of the details" [P2.L40]
			• Taking comfort in not remembering: "I don't remember it being a big deal" [P12.L245]
			• Wanting to remember more: "I wish I could remember better" [P2.L187]
			• Wishing could forget experience of treatment completely: "I'm not really interested in remembering" [P9.L416]

CHAPTER 5

This chapter summarizes the overall findings of this dissertation, discusses strengths and limitations of the dissertation, and provides recommendations for future research and pediatric oncology P1T design and management.

5.1 INTRODUCTION

The purpose of this dissertation was to investigate the phase I clinical trial (P1T) participation experience for children with cancer and their parents by: (1) assessing what is currently known about the participation experience, (2) exploring ways to understand and assess treatment burden and QOL during participation, and (3) interviewing parents about the experience of having a child participate in a P1T. Following a review of the literature, two studies were conducted: a longitudinal pilot study of 13 parent and child dyads who enrolled in a pediatric oncology early phase clinical trial at the recruiting institution, and a phenomenological study of 11 parents of children with cancer who participated in pediatric oncology P1T. Findings are formulated in three chapters (Chapters 2 through 4). This chapter synthesizes the key findings from those chapters, discusses strengths and limitations of the dissertation, and provides recommendations for future research and pediatric oncology P1T design and management.

5.2 SUMMARY OF FINDINGS

The first key finding was that participants in pediatric oncology P1Ts overall had positive experiences during their participation. Parents whose child with cancer participated in a P1T strove to use the time they had remaining with their child well. Although the prognosis for children enrolled in a P1T is poor, in general these trials were safe, had manageable toxicities, and offered slight hope for at least stabilization of disease for several months.[1,2,37-40] P1T participation fostered hope to slow or stop the child's cancer, provided a sense of trying everything to fight the child's cancer, supported a therapeutic alliance with healthcare providers, contributed to cancer research, and provided meaning for participants' lives. Even though potential harm could be created by unrealistic optimism or hope during P1T participation, the findings

of this dissertation indicated that parents were able to be realistic in their hope of direct benefit for their child.[15,18,41,80,115] Overall, parents did not regret their child's participation in a P1T and would recommend P1Ts to other parents of children with cancer, regardless of the child's outcome.

The second key finding was that participants in P1Ts were burdened to varying extents by their participation. These burdens included increased hospital visits, additional medical procedures and tests, toxicities related to the P1T therapy, and additional time in hospital and / or clinic that detracted from time at home and usual activities. These burdens extended to other family members who supported the child and parents through the trial. Participants' experiences of burdens varied based on the specific circumstances and child / family demographics including: distance from P1T center, age of child and other siblings, child's level of wellness, level of external support, and alignment with health care providers. Parents of children participating in a P1T particularly felt burdened by research-only procedures that otherwise wouldn't be needed. In this dissertation, the burdens associated with participation in an early phase clinical trial were preliminarily quantified at one site in terms of out of pocket costs, needle punctures, time spent at medical appointments, and time lost at other activities. However, it was difficult to interpret that data given that comparative information was not available for children with high-risk cancer not participating in an early phase clinical trial.

The third key finding was that communication issues between the child and parent and between parent / child and health-care providers impacted P1T decision-making. Preliminary evidence in this dissertation indicates that parents may not be aware of the difficulty their children, including older children, had in communicating concerns related to their cancer. In addition, double-protection (i.e. the desire to protect each other from distress) was found in this dissertation, and may in particular hinder open communication between parents and their child.[128] Double-protection raised concerns that a child's assent to participate in a P1T was based on a desire to ease their parents' suffering or to acquiesce to their parents' wishes, rather than on

their own preferences.[129] Parent and child communication with their providers was particularly important during P1T decision-making because parents simultaneously struggled to understand the intricacies of P1Ts while dealing with the reality of their child's persistent or advancing cancer. The child's presence during these difficult discussions facilitated their full participation in decision-making; however, it also impeded open communication regarding the child's condition. Study findings indicated that the decision to participate in a P1T is influenced by the relationship and trust the family has in the oncologist, in that it was more difficult for parents to express hesitancy or decline participation in an offered P1T when there was a pre-existing relationship with the oncologist.

The fourth finding was that parents struggled during the on-study process to understand the clinical trial system and identify P1Ts for their child. This finding highlighted gaps in the education provided to potential participants, and supported empiric research which identified challenges educating potential participants about pediatric oncology clinical trials and lapses in pediatric oncology P1T consent processes.[27,132,133,165,166] In particular, parents specified that the primary website for finding P1Ts anywhere in the United States, Clinicaltrials.gov[160], was confusing to search. Parents would also like a tool that would lay out the clinical trial system for them as simply as possible.

The final key finding was that while the dissertation study conducted concurrent with P1T participation was feasible, there were specific challenges related to participant recruitment and attrition. No instances of undue participant distress or negative feedback from participants occurred during either study. However, when a child with a poor prognosis had disease progression during the P1T, there was decreased retention of participants and completion of study procedures at later time points. An important implication for future research with this population is to ensure that data are captured at multiple time points, starting before the end of the first course of therapy in the P1T, to ensure that attrition does not prohibit capturing the experiences of participants who are unable to remain in the P1T. In addition, recruitment challenges existed due to the

limited number of pediatric oncology P1T participants at each P1T center. These recruitment and retention challenges necessitate that future research with this population be conducted at multiple sites.

5.3 STRENGTHS AND INNOVATION

This dissertation is innovative in several ways. It was the first synthesis of existing evidence on the impact of participation in a pediatric oncology P1T on participants' well-being. Beyond the process of consent, minimal empirical evidence was found in the integrative review regarding the experiences or well-being of children with cancer or their families while participating in a P1T. As a result, both the pilot and phenomenological studies conducted in this dissertation were the first to directly elucidate the experiences of children and parents during their participation in a pediatric oncology P1T.

5.4 LIMITATIONS

Findings of this dissertation should be considered with respect to the following limitations. The first study was a longitudinal, pilot study with a small sample, conducted at a single site. As a result, a full statistical analysis of results was not possible. Although the second study accrued a sufficient sample to achieve thematic redundancy, the accrued sample lacked racial, ethnic, and social diversity. In addition, lower-than-anticipated response rates to recruitment attempts at the medical centers created concerns for self-selection bias by those who chose to participate in the second study.

5.5 IMPLICATIONS FOR PEDIATRIC ONCOLOGY PHASE I CLINICAL TRIALS

The findings of this dissertation are relevant to the design and management of phase I clinical trials by providing insights to improve consent processes. Communication during pediatric oncology P1T consent conversations is often inadvertently falsely reassuring.[133] This dissertation provides evidence of the impact of P1T participation on child and parent QOL and well-being that can help to inform potential participants during consent discussions.[81,133] In addition, by identifying challenges parents had understanding the clinical trial system and finding P1Ts for their child, this dissertation highlights gaps in education provided to potential participants

during recruitment and consent processes.

Although the prevalence of P1T participants who have profoundly negative experiences during the trial is likely very low, P1T researchers should remain aware that some participants are unduly burdened by P1T participation. Hesitancies expressed by potential participants during consent and enrollment processes should be investigated before proceeding with P1T enrollment. Participant concerns expressed during the trial should be fully explored to ensure alignment is maintained between participants and health care providers throughout the P1T. In addition, providing palliative care services simultaneously with P1T participation could help to enhance children's QOL during the P1T.

The findings of this dissertation indicate that participants may feel particularly burdened by research-only lab draws and procedures required as part of the P1T. Incentives are provided to participants to acknowledge the burdens of P1Ts, however greater care should be taken in the distribution of incentives. By ensuring that incentives are provided at the point when the most burdensome procedures are completed, and by thoughtfully expressing the importance of the procedures and the gratitude of the study team with the disbursement, participants may more definitively feel that their sacrifices are appreciated.

5.6 RECOMMENDATIONS FOR FUTURE RESEARCH

Two recommendations for future research on P1T participation are proposed. First, it is important to prospectively capture the experiences of both children and parents as they undertake participation in a P1T. To date, no attempt has been made to understand the experiences of children with cancer who participate in pediatric oncology P1Ts. Due to the shortened life expectancy of children enrolled in P1Ts, obtaining the child's perspective necessitates a prospective study. In addition, a limitation of the phenomenological study was reliance on parents' retrospective reflections of their previous experiences during their child's P1T participation. A prospective study of parents' experiences will allow direct examination of their experiences and will highlight how parents' perceptions of their experiences alters over

time. Quantitative QOL measures used in this dissertation were feasible and provided some insights into the experiences of pediatric oncology P1T participants. However, research with adult P1T participants identified that participants' ratings on quantitative QOL measures differed substantively from what these same participants reported during qualitative interviews.[6,111] Thus, it is recommended that this future prospective research use mixed methods.

Second, research needs to be conducted on how to better prepare potential participants for P1T participation. Johnson's self-regulation theory of coping with stressful experiences highlights how knowledge and preparation prior to threatening health care events increases cooperation and decreases anxiety.[167] A pediatric oncology P1T educational tool needs to be developed and prospectively tested as part of an intervention to improve P1T recruitment and consent processes, and to better prepare future P1T participants. This educational tool should be designed collaboratively, using community-based participatory research methods, with past P1T participants. It could be based on the tool initially designed by Johnson et al.[165] The latter tool is a one-page generic cover sheet for P1T consent forms that provides the purpose, risks and benefits, and voluntary nature of P1Ts, as well as definitions of common P1T terms (i.e. dose escalation, dose-limiting toxicity, and maximum tolerated dose), and contact information for further support.[165]

5.7 CONCLUSIONS

This dissertation provides insight into the experiences of participation in pediatric oncology P1Ts. Findings contributed to the understanding of the impact of P1T participation on participants' well-being and were reassuring that overall parents did not regret their child's participation in a P1T. Further research is needed into children's experiences during P1Ts and to address challenges identified by parents. Understanding the impact of P1T participation on participants' well-being allows clinicians and P1T researchers to incorporate participants' views into P1T management, enhance the preparedness of future participants, and minimize any inadvertently negative impact on participants' well-being.[5]

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167. Johnson, J. E. (1999). Self-regulation theory and coping with physical illness. *Research in Nursing and Health, 22*(6), 435-448.

CURRICULUM VITAE

STACEY M. CRANE

EDUCATION

2013–2017	PhD in Nursing Science Dissertation Title 'Participant Experiences in Phase I Pediatric Oncology Clinical Trials' Anticipated Completion Date: Fall 2017 Indiana University, Indianapolis, IN
2014-2015	Graduate Certificate in Bioethics, Focus in Research Ethics Indiana University, Indianapolis, IN
2010-2013	Master of Science in Nursing, Nursing Informatics Focus Graduated with Distinction Chamberlain College of Nursing, Columbus, OH
1996-2001	Bachelor of Science in Nursing Ryerson University, Toronto, ON, Canada
1991-1996	Bachelor of Science in Engineering (not completed), Engineering Science, Biomedical Engineering Focus University of Toronto, Toronto, IN, Canada

PROFESSIONAL EXPERIENCE

2015–2016	Teaching Assistant Qualitative Research Methods, Graduate Level Course Indiana University School of Nursing, Indianapolis, IN
2014–Present	Research Project Manager Indiana University School of Nursing, Indianapolis, IN
2007–2014	Developmental Therapeutics Oncology Research Nurse III Cincinnati Children's Hospital Medical Center, Cincinnati, OH
2005–2007	Pediatric Oncology Travel Nurse Cross Country TravCorps and American Mobile Nursing Healthcare
2001–2005	Pediatric Oncology Staff Nurse Children's Hospital of Michigan, Detroit, MI
1996–2001	Electronic Brokerage Services Operations Officer TD Waterhouse Investor Services, Toronto, ON, Canada

CLINICAL EXPERIENCE

2007–2014	Developmental Therapeutics Oncology Research Nurse III Served in dual role of nursing care manager and research nurse for pediatric oncology patients participating in early phase

	clinical trials. Cincinnati Children's Hospital Medical Center, Cincinnati, OH
2005–2007	Pediatric Oncology Travel Nurse Jan. 2007 – June 2007: Cincinnati Children's Hospital Medical Center, Cincinnati, OH Apr. 2006 – Dec. 2006: Providence Alaska Medical Center, Anchorage, AK Jun. 2005 – Mar. 2006: Kapiolani Medical Center for Women and Children, Honolulu, HI Jan. 2005 – May 2005: Children's Hospital of Orange County, Orange, CA Cross Country TravCorps and American Mobile Nursing Healthcare
2001–2005	Pediatric Oncology Staff Nurse Children's Hospital of Michigan, Detroit, MI

RESEARCH EXPERIENCE

2015-Present	Reviewer for the Journal of Pediatric Oncology Nursing
2014–Present	Research Project Manager Title: Writing to Improve Self in Intimate Relationships Principal Investigator: Claire Draucker, PhD RN FAAN Online narrative therapy intervention study, Funded by Indiana University School of Nursing Pilot Grant
2014-2015	Background Literature Reviewer and Participant Nursing Ethics for the 21st Century Summit
2013–2016	Quality Assurance Monitor Title: Palliative Cancer Care: Music Video for AYA-Parent Communication and Resilience (ANUR1131) Principal Investigators: Joan Haase, PhD RN FAAN and Sheri Robb, PhD MT-BC Children's Oncology Group Nursing Discipline Study, Funded by NCI R01 Research Grant
2013–Present	Predoctoral Trainee Research in Palliative and End of Life Care (RESPECT) Signature Center
2012–Present	Nursing Committee Representative and Study Protocol Nurse Children's Oncology Group Phase I and Pilot Consortium Study Protocols: ADVL1013, ADVL1014, ADVL1111, ADVL1221, ADVL1412, ADVL1414 and ADVL1515
2012–2014	Study Protocol Nurse Pediatric Brain Tumor Consortium Study Protocol: PBTC036

2011–2013	Co–Principal Investigator Title: Incorporation of a Direction of Care Note into the Electronic Medical Record of High–Risk Pediatric Oncology Patients
2010–2015	Principal Investigator Title: Measuring the Patient and Family Experience while Participating in an Early Phase Pediatric Oncology Investigational Therapy Clinical Trial: Direct Costs, Indirect Costs and Impact on Quality of Life Funded by Carolyn Stoll Nursing Research Grant from Cincinnati Children's Hospital Medical Center

CONSULTATIONS

May 2016	Dr. Joan Haase's Smart II Program A Manuscript – Database Designer
Apr. 2016	Oncology Nursing Society (ONS) – Expert Reviewer of the Oncology Clinical Trial Nurse Competencies
Feb. 2016	Dr. Sheri Robb's Multisite Music Intervention Systematic Review – Database Designer
Oct. 2015 – May 2016	Pediatric Brain Tumor Foundation – Parent Educational Materials
Oct. 2015	Pediatric Brain Tumor Consortium Nursing Committee
Aug. 2013	Onyx Pharmaceuticals Advisory Board

GRANTS AND FELLOWSHIPS

2016-2018	Oncology Nursing Society Foundation Dissertation Grant $5,000
2016-2017	Midwest Nursing Research Society Founder's Circle Endowment Grant $2,500
2016	Nurses in Washington Internship through the Nursing Organizations Alliance $1,000 Scholarship awarded by the Association of Pediatric Hematology Oncology Nurses (APHON)
2015-2018	National Research Service Award F31 Individual Predoctoral Fellowship $100,725 including stipend, tuition, and training support NIH/NINR (1F31 NR015393A)
2013–2015	National Research Service Award T32 Institutional Training Grant Fellowship in Health Behaviors Research $135,503.97 including stipend, tuition, travel, and training

	support NIH/NINR (2T32 NR007066)
2013–2016	Research Incentive Fellowship $35,000 IU School of Nursing
2013	Pediatric Oncology Student Training Program Grant $6,000 Alex's Lemonade Stand Foundation
2011	Carolyn Stoll Nursing Research Grant $5,000 to evaluate cost and quality of life of phase I pediatric oncology clinical trials Cincinnati Children's Hospital Medical Center
2004	Nursing Research Grant $5,000 to compare the effectiveness of antiemetics for inpatient chemotherapy in children with cancer Children's Hospital of Michigan

HONORS AND AWARDS

2016 & 2017	IUPUI Elite 50 Graduate Student. In 2017, selected as second overall and best in School of Nursing.
2016	Nursing Graduate Student Scholarship from Walther Cancer Foundation ($800)
2016	Oncology Nursing Society Foundation Congress Scholarship ($1,200)
2016	Sigma Theta Tau International (STTI) Honor Society of Nursing Rising Star of Research and Scholarship
2016	International Learning Experience Scholarship from the Indiana University Alumni Foundation ($800)
2015	Association of Pediatric Hematology Oncology Nurses (APHON) Novice Nurse Researcher Award ($250)
2015	William & Doris Rodie Dissertation Scholarship Award from IU School of Nursing ($2,000)
2013–2017	American Cancer Society Doctoral Degree Scholarship in Cancer Nursing ($60,000) (DSCN–13–267–01—SCN)
2014	Association of Pediatric Hematology Oncology Nurses (APHON) Writing Award ($100)
2014	Oncology Nursing Society Foundation Doctoral Nursing Scholarship ($5,000)
2013	Michelle A. White Scholarship from IU School of Nursing ($1,000)
2013	Oncology Nursing Society Foundation Masters Nursing Scholarship ($3,000)
2009	Poster chosen in top three by Children's Oncology Group Clinical Research Professional Committee

2001	Sigma Theta Tau International Nursing Honor Society
2001	Golden Key Honor Society at Ryerson University
2001	Canadian Scholars Press Award for Highest Academic Standing in Nursing Research Course ($100)
1991	Undergraduate Engineering Canada Scholarship
1991	University of Toronto Entrance Scholarship

PUBLICATIONS - REFEREED

2017	Understanding Ethical Issues of Research Participation from the Perspective of Participating Children and Adolescents: A Systematic Review Crane, S. and Broome, M. Worldviews on Evidence-Based Nursing, 3(14), 200-209.
2017	Designing an Internet Intervention for Emerging Adults Who Experience Troubled Relationships Draucker, C. B., Martsolf, D. S., Crane, S., Romero, L., & McCord, A. L. Archives of Psychiatric Nursing, 3(31), 296-301.
2017	Understanding Treatment Burden and Quality of Life Impact of Participating in an Early Phase Pediatric Oncology Clinical Trial: A Pilot Study Crane, S., Backus, L., Stockman, B., Carpenter, J., Lin, L., and Haase, J. Journal of Pediatric Oncology Nursing. Retrievable from http://journals.sagepub.com/eprint/NtD2ZUtnvUmKXh86CCPQ/full.
Under review	Well-Being of Child and Family Participants in Phase I Pediatric Oncology Clinical Trials: An Integrative Review Crane, S., Haase, J., and Hickman, S.
In preparation	Parental Experiences of Child Participation in a Phase I Pediatric Oncology Clinical Trial: “We Don’t Have Time to Waste” Crane, S., Haase, J., and Hickman, S.
In preparation	Evaluation of Follow-Up Calls to Measure Research Related Parental Burden and Benefit Hopper, A., Crane, S., and Haase, J.
In preparation	Beyond Data Capture: An Innovative Use of REDCap to Facilitate Web-Based Therapeutic Intervention Research Crane, S., Comer R. S., Arenson, A., and Draucker, C.
In preparation	Experiences of Nurse Interveners in the Smart II Study Haase, J., Stegenga, K., Cherven, B., Nance, S., Butrum, K., Howard, J., Perez–Perado, L., Beacham, B., Crane, S., Landon, L., and Phillips–Salimi, C.

PUBLICATIONS – NON-REFEREED

2016 Health Care Disparities in Phase I Clinical Trials
Crane, S.
APHON Counts, 30(4), 8.

2016 Advocacy is an Extension of Nursing Practice
Crane, S.
APHON Advocacy Correspondent: 2016 Nurses in Washington Internship Edition

2014 A Blueprint for 21st Century Nursing Ethics: Report of the National Nursing Summit
Rushton, C.H., Broome, M., Adams, M., Badzek, L., Barden, C., Barton–Burke, M., Brown–Saltzman, Caldwell, M., Catlin, A., Christensen, L., Cipriano, P., Cox, C., Crane, S., Daly, B., Davidson, P., Erdman, L., Fowler, M., Gallagher, A., Gordon, V., Grady, C., Haddad, A., Hamric, A., Harris, K.T., Hatmaker, D., Ivory, C., Kiss, T., Knodel,L., Kovacikova, I., Kub, J., Kurtz, M., Liaschenko, J., Mancino, D., Miller, J., Mitchell, C., Olsen, D., Ramsey, G., Reller, N., Scanlon, C., Shannon, S., Stutzer, K., Sullivan, C., Sullivan, M.C., Tang, C., Tarzian, A., Taylor, C., Thompson, P., Trautman, D., Ulrich, C., Walton, M., Weisfeld, V., Wise, B., and Wocial, L.
Retrievable from http://www.bioethicsinstitute.org/nursing–ethics–summit–report

2013 Blinatumomab: Nursing Challenges for Children with ALL
Crane, S.
APHON Counts, 27(3), 4 & 15.

2013 Oncolytic Virotherapy for Pediatric Cancer Patients
Crane, S., & Stockman, B.
In Renewal Program for APHON Pediatric Chemotherapy and Biotherapy Providers. Retrievable from http://www.aphon.org/education/renew.cfm.

PUBLICATIONS – ABSTRACTS

2013 Iodine–131–Metaiodobenzylguanidine Therapy for Neuroblastoma: A Nursing Perspective
Crane, S., Richardson, K., Morris, V., Gelfand, M., Turpin, B., and Weiss, B.
Pediatric Blood & Cancer, 60(S3), 156–157.

2013 Building a Therapeutic 131–Iodine–Metaiodobenzylguanidine Program: A Multidisciplinary Approach
Weiss, B., Crane, S., Perentesis, J., Sharp, S., Gelfand, M., Morris, V., Nagarajam, R., Geller, J., and Turpin, B.

Pediatric Blood & Cancer, 60(S3), 112.

PRESENTATIONS

Sept. 2016	Beyond Data Capture: An Innovative Use of REDCap to Facilitate Web-Based Therapeutic Intervention Research Crane, S., Comer R. S., and Arenson, A. Oral presentation at the Council for the Advancement of Nursing Science (CANS) state of the science congress in Washington, DC	National
Sept. 2016	Improving the Efficiency and Rigor of Systematic Literature Reviews with Microsoft Access Crane, S. and May, L. Oral presentation at the CANS state of the science congress in Washington, DC	National
July 2016	Understanding Ethical Issues of Research Participation from the Perspective of Participating Children and Adolescents: A Systematic Review Crane, S. and Broome, M. Poster presentation at the STTI nursing research congress in Cape Town, South Africa	International
Sept. 2015	What is Taking so Long? Understanding Pediatric Oncology Drug Approval Crane, S. Oral presentation at the APHON annual conference in Providence, RI	National
Sept. 2015	Time, Cost, and Procedural Distress: Understanding Burdens of Clinical Trials Crane, S. and Haase, J. Oral presentation at the APHON annual conference in Providence, RI	National
Jan. 2015	Exploring Experience in Phase I Pediatric Oncology Clinical Trials Crane, S. Oral presentation for COG Nursing Scholars Group	National
Dec. 2014	131I–MIBG therapy: Unveiling the Mystery for Patients with Neuroblastoma Crane, S. Oral presentation at the APHON Indiana Chapter meeting in Indianapolis, IN	Regional

Sept. 2014	Processes and Practicalities of Designing AYA and Family Interventions Haase, J., Robb, S., and Crane, S. Oral concurrent session presentation at the APHON annual conference in Portland, OR	National
Sept. 2014	Disillusionment in the Experience of Phase I Pediatric Oncology Clinical Trials: A Concept Analysis Crane, S. and Haase, J. Poster presentation at the APHON annual conference in Portland, OR	National
May 2014	Adolescents and Young Adults with Cancer Beacham, B. and Crane, S. Oral presentation for the Smart II site initiation at Cincinnati Children's Hospital Medical Center	Local
Mar. 2014	It's All About Us: Improving Multi–Disciplinary Palliative Care Communication Within the Electronic Medical Record Crane, S. and Simpson–Bennethum, A. Poster presentation at the Research in Palliative and End–of–Life Communication and Training (RESPECT) Center annual conference in Indianapolis, IN	Regional
Feb. 2014	Pediatric Research Isn't Just About the Children Crane, S. Evidence Based Inquiry Grand Rounds at Cincinnati Children's Hospital Medical Center	Local
Oct. 2013	Palliative Care in the Setting of the PBTC Crane, S. and Gilger, E. Oral presentation at the Pediatric Brain Tumor Consortium (PBTC) Nursing Committee annual meeting in Chicago, IL	National
Oct. 2013	Patient and Family Experience on Phase I Pediatric Oncology Clinical Trials: An Early View of a Doctoral Program of Research Crane, S. Poster presentation at the Children's Oncology Group (COG) Young Investigator's session in Dallas, TX	National
Sept. 2013	Iodine–131–Metaiodobenzylguanidine Therapy for Neuroblastoma: A Nursing Perspective. Crane, S., Richardson, K., Morris, V., Gelfand, M.,	International

	Turpin, B., and Weiss, B. Poster presentation at the International Society of Paediatric Oncology annual congress in Hong Kong	
Sept. 2013	Building a Therapeutic 131–Iodine–Metaiodobenzylguanidine Program: A Multidisciplinary Approach Weiss, B., Crane, S., Perentesis, J., Sharp, S., Gelfand, M., Morris, V., Nagarajam, R., Geller, J., and Turpin, B. Poster presentation at the International Society of Paediatric Oncology annual congress in Hong Kong	International
Sept. 2013	131I–MIBG therapy: Unveiling the Mystery for Patients with Neuroblastoma. Richardson, K.D., and Crane, S. Oral concurrent session presentation at the APHON annual conference in Louisville, KY	National
Sept. 2013	End of Life / Palliative Care Town Hall Simpson–Bennethum, A., Crane, S., Black, S., and Shields, J. Session moderator at the APHON annual conference in Louisville, KY	National
Oct. 2012	Staff Perceptions of Palliative Care: Themes from the Pediatric Oncology Palliative Care Assessment Survey Crane, S., Gallagher, M., Black, S., and McKenna, L. Poster presentation at the APHON annual conference in Pittsburgh, PA	National
Oct. 2012	Evaluating Patient and Family Experience During an Early Phase Clinical Trial Crane, S. Oral presentation for the Nursing Professional Inquiry Council meeting at Cincinnati Children's Hospital Medical Center	Local
Jun. 2012	Evaluating Patient and Family Experience During an Early Phase Clinical Trial Crane, S. Oral presentation for the Nursing Grand Rounds at Cincinnati Children's Hospital Medical Center	Local
Sept. 2011	Oncolytic Virotherapy: Implications for the Pediatric Oncology Nurse	National

Crane, S., & Kramer, C.
Oral concurrent session presentation at the
APHON annual conference in Anaheim, CA

CERTIFICATIONS

2010–2016	Certified Clinical Research Professional (CCRP)
2010	End of Life Nursing Education Consortium–Pediatric Palliative Care
2005–Present	APHON Pediatric Chemotherapy and Biotherapy Provider
2005–2009	Pediatric Advanced Life Support Certification
2003–Present	Certified Pediatric Oncology Nurse (CPON)
2003–2008	Certified Pediatric Nurse
2002	Commission on Graduates of Foreign Nursing Schools (CGFNS) Certification

REGISTERED NURSE LICENSURE

2015–Present	Indiana Professional Licensing Agency
2007–2015	Ohio Board of Nursing
2006-2008	Alaska Board of Nursing
2005-2007	Hawaii Professional and Vocational Licensing Division
2005-2008	California Board of Registered Nursing
2002-2007	Connecticut Department of Public Health
2002-2007	Michigan Board of Nursing
2001-2002	Minnesota Board of Nursing
2001-2002	College of Nurses of Ontario. Ontario, Canada.

PROFESSIONAL MEMBERSHIPS

2014–Present	Midwest Nursing Research Society (MNRS) Member
2014–Present	Council for the Advancement of Nursing Science (CANS) Member
2012–2014	Cancer and Blood Diseases Institute Nursing Research Seminar Series Cincinnati Children's Hospital Medical Center Active Representative
2011–2014	Childhood Oncology Palliative Care Improvement Group (COPING) Cincinnati Children's Hospital Medical Center Active Representative
2010–2016	Society of Clinical Research Associates (SOCRA) Member

2007–Present	Children's Oncology Group (COG) Nursing Representative to the COG Phase I and Pilot Consortium Study Nurse on the Following National Phase 1 COG protocols: ADVL1013, ADVL1014, ADVL1111, ADVL1221, ADVL1314, ADVL1412, and ADVL1414 Founder of the COG Phase I Nursing Discussion Group Active Member of the COG Nursing Scholars Group Poster Reviewer for COG CRP Committee
2001–Present	Association of Pediatric Hematology and Oncology Nurses (APHON) Active Reviewer for the Journal of Pediatric Oncology Nursing Active Member of the APHON Advocacy Committee Consultant to the Chemotherapy and Biotherapy Provider Committee Annual Conference Paper and Poster Abstract Reviewer
2001–Present	Sigma Theta Tau International (STTI) Nursing Honor Society Member

VOLUNTEER SERVICE

2016-Present	PhD Student Advisory Group at Indiana University School of Nursing Advisory Group Member
2011–2012	Camp Joy in Clarksville, OH Volunteer Registered Nurse
2004–Present	Make a Wish Foundation Volunteer Wish Grantor
2004–2014	American Red Cross Disaster Health Services Volunteer Registered Nurse
2002–2004	Hole in the Wall Gang Camp in Ashford, Connecticut Volunteer Registered Nurse