Published in final edited form as:

Oncol Nurs Forum. 2018 September 01; 45(5): E67–E97. doi:10.1188/18.ONF.E67-E97.

Understanding the Impact of Participation in a Phase I Clinical Trial on the Well-Being of Children with Cancer: An Integrative Review of the Pediatric and Adult Literature

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Abstract

Problem Identification: Pediatric oncology phase I clinical trials (PITs) are essential to developing new anti-cancer therapies, yet they raise complex ethical concerns about balancing the need for this research with the well-being of participating children. The purpose of this integrative review was to synthesize and appraise the evidence of how PIT participation, which begins with consent and ends with the transition off the PIT, can impact the well-being (either positively or negatively) of children with cancer. The Resilience in Individuals and Families Affected by Cancer Framework, which has an outcome of well-being, was used to synthesize findings.

Literature Search: Articles on the experiences of child ($n = 21$) and adult ($n = 31$) PIT participants were identified through systematic searches of PubMed and CINAHL Complete (EBSCO).

Data Evaluation: Articles were evaluated on both rigor and relevance to PIT participant experiences as either 'High', 'Medium', or 'Low'.

Synthesis: Minimal empirical evidence was found regarding the impact of PIT participation on the well-being of children with cancer. Adult PIT participant experiences provide insights that could also be important to children's PIT experiences.

Implications for Nursing Practice and Research: To achieve a balanced approach in PIT consent discussions, nurses and healthcare providers who work with children considering participation in a PIT should share the potential impact of PIT participation on participants' well-being.

Conclusions: Further research is needed that focuses on understanding the impact of PIT participation to ensure the PIT experience does not inadvertently negatively impact the well-being of participating children with cancer.

Introduction

Cancer remains the leading cause of death due to disease in children under 14 years of age (Siegel, Miller, & Jemal, 2016). Although five-year survival rates for pediatric cancers

have improved overall to 83%, for some pediatric cancers the five year survival rate is only 67% (Siegel et al., 2016). New therapies are needed to continue to improve outcomes for children with cancer. Phase I clinical trials (PITs) 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 (Kim et al., 2008; Lee, Skolnik, & Adamson, 2005).

Although the need for PITs is generally accepted, PITs raise ethical concerns (Agrawal & Emanuel, 2003; Berg, 2007; Crites & Kodish, 2013; de Vries et al., 2011; Ekert, 2013; Estlin, Cotterill, Pratt, Pearson, & Bernstein, 2000; Hazen, Zyzanski, Baker, Drotar, & Kodish, 2015; Kearns & Morland, 2014; Miller & Joffe, 2008; Oberman & Frader, 2003; Weinfurt et al., 2012). Goals of PITs are traditionally to: (1) determine the maximum-tolerated dose of the therapy, (2) describe the action of the therapy in humans, and (3) reveal side effects (Kim et al., 2008; Lee et al., 2005). Recently the National Cancer Institute updated PIT templates to include preliminary determination of efficacy as a secondary trial objective (Weber et al., 2014). PITs are primarily conducted to determine how innovative therapies may safely be given. Although not intended to directly benefit participants, healthcare providers and researchers hope that PITs will directly benefit at least some participants. The Declaration of Helsinki requires that “while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects” (World Medical Association, 2013). The ethical challenge of PITs is to assure the well-being of participants is supported throughout.

Ethical concerns regarding PITs are more complex in children with cancer, in part because children are only eligible for PITs when no known curative therapy remains for their cancer. Furthermore, children must rely on their parents as proxy decision-makers (Ekert, 2013; Estlin et al., 2000; Kearns & Morland, 2014; Oberman & Frader, 2003). Enrolling a child in a PIT provides the child access to a novel investigational therapy of promising, albeit uncertain, efficacy (Bluebond-Langner, Belasco, Goldman, & Belasco, 2007; Mack et al., 2008; Tomlinson et al., 2011). Parents enroll their children in PITs primarily based on hope of a cure for their child from the novel therapy (Barrera, D’Agostino, Gammon, Spencer, & Baruchel, 2005; Crites & Kodish, 2013; Deatrck, Angst, & Moore, 2002; Oppenheim, Geoerger, & Hartmann, 2005). However, the median life expectancy of children after enrollment in pediatric oncology PITs is 3.6 – 6.4 months (Bautista et al., 2015; Kim et al., 2008; Morgenstern et al., 2014). Consequently, children with cancer enrolled in PITs spend part of what could be limited time remaining being treated in a PIT that is not focused on directly benefiting them, although healthcare providers and researchers hope that they will indeed benefit. Ethicists and healthcare providers identify the potential benefits of pediatric oncology PIT participation as including improved quality of life (QOL) and hope, although the risks include fostering unrealistic hope, burdening children with additional medical procedures and toxicities, and limiting the opportunity for palliation (Barnes, Pressey, Adams, Hensler, & Madan-Swain, 2014; Beardsmore & Fitzmaurice, 2002; Carlson, Reilly, & Hitchens, 2005; Chang, 2008; Estlin et al., 2000; Gilliam, Madan-Swain, Adams, & Pressey, 2013; Oberman & Frader, 2003; Ulrich, Grady, & Wendler, 2004). To avoid inadvertently negatively impacting the well-being of children with cancer near end-of-life and provide evidence to inform future pediatric oncology PIT participants, a better

understanding of how PIT participation impacts the well-being of children with cancer is needed.

The purpose of this integrative review was to synthesize and appraise the evidence of how PIT participation can positively or negatively impact the well-being of children with cancer. PIT participation is defined as beginning at the start of the informed consent process, extends through enrollment and receiving therapy, and ends at transition off the PIT. Due to the substantially greater number of PITs for adults with cancer, the similar structure and requirements of PITs in the pediatric and adult populations, the dearth of pediatric literature, and the possibility of gaining insights from adults' PIT experiences, this review included both pediatric and adult literature searches.

The Resilience in Individuals and Families Affected by Cancer 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) (Kelly, Hooke, Ruccione, Lanier, & Haase, 2014; Landier, Leonard, & Ruccione, 2013). This framework is used to facilitate an understanding of how children and families sustain or regain well-being after a pediatric cancer diagnosis, and to guide interventions that can promote child and family well-being (see Figure 1) (Haase, Kintner, Monahan, & Robb, 2014; Haase et al., 2017; Kelly et al., 2014; Landier et al., 2013). The framework was developed from Haase's Resilience in Illness model, which was empirically-derived from research with pre-adolescents and adolescents with cancer (Haase, Heiney, Ruccione, & Stutzer, 1999; Haase et al., 2014; Haase et al., 2017). For children participating in PITs, the Resilience Framework can provide an organizing structure for understanding how PIT experiences impact the children's overall well-being.

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) (Kelly et al., 2014; Landier et al., 2013). The risk factors are negatively associated with well-being, and the protective factors are positively associated with well-being. See Table 1 for definitions of these factors. The well-being outcome factor includes positive health outcomes of global QOL, resilience, a sense of confidence and mastery, and self-transcendence (Kelly et al., 2014). Social integration includes the support of family, friends, healthcare providers and the community (Haase et al., 2014; Haase et al., 2017; Kelly et al., 2014).

To ensure burdens associated with PIT participation were captured, treatment burden was an additional indicator of the illness-related distress risk factor. Treatment burden refers to the physical, financial, time, psychosocial, and procedural demands that a treatment places on a patient and/or their family (Eton et al., 2012; Sav, Kendall, et al., 2013; Sav, King, et al., 2013; Ziaian et al., 2006).

Per the Resilience Framework, courageous and defensive coping are not mutually exclusive; some coping strategies encompass elements of both factors (Kelly et al., 2014). Work

undertaken in the development of the Resilience Framework (i.e. Haase's Resilience in Illness Model) confirms that defensive coping strategies are normal responses to high-threat situations that are used until courageous coping strategies are developed to address the threat (Haase et al., 2017). Defensive coping strategies are problematic only when used exclusively and for prolonged periods of time, without development of courageous coping strategies (Haase et al., 2017).

Literature Search

This integrative review was conducted using the Whittemore and Knafl method (Whittemore & Knafl, 2005). This method guides each stage of the review (i.e. problem identification, literature search, data evaluation, data analysis, and presentation of findings). Two literature searches were performed in December 2016 in PubMed and CINAHL Complete (EBSCO) databases, as summarized in Figure 2. The first search focused on pediatric literature while the second focused on adult literature.

The first search used the key words (1) 'cancer' or 'oncology'; (2) 'child' or 'pediatric'; and, (3) 'phase I', 'phase I', 'clinical trials, phase 1 (as topic)', 'therapies, investigational', 'early phase' or 'early trials'. In total, 2,386 articles were identified. For this review, children were defined as individuals less than 18 years of age. Excluded articles were: expert opinions and/or theoretical discussions, non-English, published prior to 1985, lacking an abstract, or not relevant to the purpose of the review. The date range was selected to obtain a large sample focused on more recent pediatric oncology PITs, which tend to use more molecularly targeted therapies and involve more efficient trial designs. Articles concentrating solely on clinical trial procedures (e.g. the quality of the PIT consent process) rather than the experiences of participants were excluded. The reference lists of the included articles were examined using the criteria above, resulting in a total of 21 remaining articles. Only one of these articles was highly relevant to the purpose of this review.

The second search focused on adult PIT participants and was conducted after the pediatric search was completed. Although the findings had to be interpreted cautiously, the authors felt that this search was particularly important given the dearth of highly relevant articles in the pediatric literature. Key words were as above, excluding 'child' and 'pediatric'. Since 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 the PIT consent experience were excluded. After screening and reviewing the reference lists, 31 empirical articles that described the experience or well-being of adults during their participation in oncology PITs were identified.

Data Evaluation

Per the Whittemore and Knafl method, all articles were evaluated by the authors based on: 1) relevance to the review's purpose and 2) empirical rigor (i.e. the description of the

research methods) (Whittemore & Knafl, 2005). Scores were ranked 'High', 'Medium', or 'Low' for both relevance and rigor (see Tables 2 and 3 for a listing of articles with their evaluations) (Whittemore & Knafl, 2005). The first author assessed all articles in the sample, then the second author 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 (Whittemore & Knafl, 2005). Tables 4a and 4b summarize the article evaluation results.

Findings from the Pediatric Literature

Of the 21 pediatric articles (listed in Table 2), 12 were empirical research studies, one was a case report, and eight were meta-analyses of results from multiple PITs. Considering just the 12 empirical studies, two analyzed the end-of-life care provided to PIT participants, one considered nurses' perceptions of PITs, and the remaining nine examined experiences during PIT consent processes. With the exception of PIT consent processes, minimal empirical evidence regarding the experiences or well-being of children with cancer during their PIT participation was found. In particular, no studies directly examined the experiences of children with cancer throughout a PIT. Findings from the pediatric literature are synthesized and presented herein by the factors of the Resilience Framework.

Risk Factor: Illness-Related Distress

For children with cancer and their parents considering participation in a PIT, 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 (Barrera et al., 2005). Performance scores are a measure of general well-being and ability to complete activities of daily living (Lansky, List, Lansky, Ritter-Sterr, & Miller, 1987; Mor, Laliberte, Morris, & Wiemann, 1984). Since PITs have performance status eligibility requirements, as expected, at enrollment children had high performance scores overall despite being heavily pretreated for their cancer (Kim et al., 2008).

Regarding outcomes of PIT participation, the pediatric meta-analyses established that for most children, their cancer did not improve. The combined partial and complete response rate for children enrolled in PITs was 3.8–9.6%, with reports of 17–24.5% prolonged disease stabilization (i.e. more than three or four months) (Bautista et al., 2015; Furman et al., 1989; Kim et al., 2008; Lee et al., 2005; Morgenstern et al., 2014; Shah et al., 1998). Although the median overall survival time of children with relapsed cancer after enrollment in a PIT was between 3.6 and 6.4 months, Morgenstern et al. (2014) reported 16% of children survived longer than 12 months and Kim³ reported 5% survived longer than 36 months (Bautista et al., 2015; Kim et al., 2008; Morgenstern et al., 2014). The median time in a PIT was 1.3–1.8 months or 1 cycle (Bautista et al., 2015; Kim et al., 2008; Morgenstern et al., 2014). 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 PIT (Bautista et al., 2015; Furman et al., 1989; Kim et al., 2008; Lee et al., 2005; Morgenstern et al., 2014;

Shah et al., 1998). Although overall death rates of children participating in P1Ts ranged from 7–21%, progressive disease accounted for most of the deaths during P1Ts (Furman et al., 1989; Shah et al., 1998). Despite being more heavily pretreated, children had a similar or greater medication tolerance than adults enrolled on matched P1Ts (Carlson, Ho, Smith, Reisch, & Weitman, 1996; Paoletti et al., 2013). No other symptom experience data was found for pediatric P1T participants.

Illness-related uncertainty was not well explored in pediatric P1Ts. Parents considering having their child participate in a P1T spoke of high uncertainty related to unknowns and the extra testing needed to verify eligibility (Barrera et al., 2005). Although empiric research was not found on children's experiences during P1Ts, there was some evidence that P1T logistics and potential impact on QOL contributed to parents' and children's P1T decision-making (Deatrick et al., 2002; Marshall et al., 2012; Maurer et al., 2010; Miller et al., 2013).

Risk Factor: Defensive Coping

No data were found regarding how P1T participation impacted or related to the use of defensive coping strategies. Experts 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 (Beardsmore & Fitzmaurice, 2002; Brock, Steineck, & Twist, 2016; Chang, 2008).

Protective Factor: Courageous Coping

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 (Barrera et al., 2005; Hinds et al., 2005). No other specific data were found on how courageous coping strategies were used by children participating in P1Ts.

Interaction of Defensive and Courageous Coping

Although the optimism associated with clinical trial participation was potentially beneficial for P1T participants (a courageous coping strategy), potential harm could be created by unrealistic optimism (a defensive coping strategy) (Chang, 2008; Deatrick et al., 2002; Helft, Hlubocky, Wen, & Daugherty, 2003; Kearns & Morland, 2014; Meyers et al., 2004). Unrealistic optimism is the 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 (Crites & Kodish, 2013; Jansen et al., 2016). 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 substantial evidence that pediatric P1T participants and families thought and acted like the P1T therapy would improve, or even cure, their cancer (Cousino et al., 2012; Deatrick et al., 2002; Hinds et al., 2005; Maurer et al., 2010; Miller et al., 2013).

In two studies conducted in medical centers with active palliative care programs, there was mixed evidence regarding the impact of P1T participation and coping on end-of-life care. One found that P1T participants more frequently enrolled in hospice and were more likely to

die at home or in hospice (Brock et al., 2016). The second study found that the end-of-life care provided to pediatric P1T participants did not differ from non-P1T participants (Levine et al., 2015).

Protective Factor: Social Integration

Although the pediatric articles generally reinforced the importance of strong social support to the patient's well-being, the lack of pediatric empiric research prohibited an understanding of how P1T participation impacted children's social integration. However, regarding healthcare providers' role in social integration, there was strong evidence that pediatric P1T participants were included in decision-making discussions with providers (Cousino et al., 2012; Miller et al., 2013).

Protective Factor: Family Environment

Family environment was generally important to P1T participants' well-being; however, there was minimal empiric data on the role and impact of family during the P1T experience. Double-protection was identified in the pediatric articles, reflecting a potential threat to the protection offered by the family environment. Double-protection occurs when both parent and child avoid open communication, in an attempt to protect each other from distress (Last, 1992). While based on an intention to be supportive, double-protection results instead in isolation and lack of support (Last, 1992). Barrera et al. (2005) and Hinds et al. (2005) both provided empirical evidence that children recently been enrolled in a P1T were aware of their advanced cancer and of their parents' emotional turmoil. This suggests that the child's P1T assent may be influenced by a desire to ease their parents' suffering or to acquiesce to their parents' wishes (Barrera et al., 2005; Hinds et al., 2005).

Protective Factor: Derived Meaning

There was some evidence that for children with cancer P1T participation offered hope that positively influenced well-being (Barrera et al., 2005; Carlson, Bultz, & Morris, 2005). However, parents 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 (Barrera et al., 2005). 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 (Barrera et al., 2005).

Outcome Factor: Well-being

Although there was minimal empirical evidence regarding how well-being (i.e. QOL) can be impacted by P1T participation, there was a high level of evidence that well-being was a contributing factor to pediatric oncology P1T decision-making (Barrera et al., 2005; Deatrck et al., 2002; Hinds et al., 2005; Hinds et al., 1997; Hinds et al., 2009; Maurer et al., 2010; Miller et al., 2013).

Findings from the Adult Literature

All 31 adult-focused articles (listed in Table 3) were empirical articles exploring adult patient experiences during a P1T. Findings from the adult literature are used to provide

insights into children's experiences in P1Ts, and are also synthesized and presented per the factors of the Resilience Framework.

Risk Factor: Illness-Related Distress

Similar to children, adult P1T participants had high performance scores overall at enrollment (Berdel et al., 1988; Finlay, Lu, Henderson, O'Dwyer, & Casarett, 2009; Rouanne et al., 2013). No significant changes in performance or overall QOL scores were found in adult participants who completed one course of P1T therapy (Berdel et al., 1988; Cox, 2003; Melink, Clark, & Von Hoff, 1992), although Rouanne et al. (2013) found that physical health of adult participants significantly decreased during one course of P1T therapy.

In terms of distress due to symptoms of disease, adult P1T participants had similar or higher levels of symptom burden than non-participants (Finlay et al., 2009; Hui et al., 2010). However, George et al. (2016) found that adult P1T participants experienced poor sleep quality, which was connected to increased symptom burden and disturbances in temperament. 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 (Cox, 2003; Kvale, Woodby, & Williams, 2010). Interestingly, Rouanne et al. (2013) found that 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 a high level of evidence for incorporating palliative care and / or hospice simultaneously with adults' P1T participation, to enhance supportive care and symptom management and to decrease psychological distress (Agrawal & Danis, 2002; Bluebond-Langner et al., 2007; Casarett, Karlawish, Henry, & Hirschman, 2002; Cassel et al., 2016; Hui et al., 2010; Kapo & Casarett, 2002; Meyers et al., 2004; Sun et al., 2014).

For adults, P1T treatment burdens had a significant impact on their overall QOL (Cohen et al., 2007; Mack, 1998). 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 (Cohen et al., 2007; Cox, 1999; Cox & Avis, 1996; Mack, 1998). Although these burdens were manageable and became routine for some participants, others continuously struggled with them and feared they would become more than they could handle (Cox, 1999). 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 (Cohen et al., 2007; Cox, 1999). 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 (Cohen et al., 2007; Cox, 1999; Cox & Avis, 1996; Mack, 1998; Wootten, Abbott, Siddons, Rosenthal, & Costello, 2011). 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 (Cox, 1999; Cox & Avis, 1996; Stetz, 1993; Wootten et al., 2011).

The role of illness-related uncertainty (which includes both complexity and ambiguity) was not well explored in the P1T experience of adults (Haase et al., 2014; Kelly et al., 2014). For adults there may be more uncertainty experienced during P1T participation than during

standard treatments, due to the investigational nature of the novel therapy (Cox, 1999; Wootten et al., 2011). 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 (Cox & Avis, 1996; Mack, 1998; Moore, 2001; Wilson, Cox, & Elkan, 2005). 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 (Cox & Avis, 1996; Mack, 1998; Wilson et al., 2005).

Risk Factor: Defensive Coping

There was some evidence that adult P1T participants employed evasive coping strategies. Adult P1T participants who avoided transitioning to end-of-life care demonstrated the strongest evidence of evasive coping (Cox, 2002; Cox & Avis, 1996; Meyers et al., 2004). 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 (Cox, 2000). 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 (Cox, 2000).

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' sense 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 (Campbell & Whyte, 1999; Cox, 1999; Cox & Avis, 1996; Godskesen, Nygren, Nordin, Hansson, & Kihlstrom, 2013; Hutchison, 1998; Moore, 2001; Wootten et al., 2011). The stories of adults participating in a P1T consistently reflected courageous coping in attempting the unknown as well as in managing any resulting consequences (Cox & Avis, 1996; Moore, 2001; Stetz, 1993). For many adult patients, P1T participation fulfilled their need to have tried everything to fight their cancer (Cox, 2002; Cox & Avis, 1996; Moore, 2001; Stetz, 1993).

Interaction of Defensive and Courageous Coping Factors

Adult P1T participants, similar to pediatric participants, expressed an expectation that the P1T therapy would improve, or even cure, their cancer (Godskesen et al., 2013; Helft et al., 2003; Jansen et al., 2016). Unfortunately, for adult participants, expectations for tumor response and symptom improvement were not generally met during P1Ts (Campbell & Whyte, 1999; Mack, 1998; Wootten et al., 2011; Yoder, O'Rourke, Etnyre, Spears, & Brown, 1997). That said, it is unclear how significant a problem unrealistic optimism was for adult P1T participants (Helft et al., 2003; Jansen et al., 2016; Weinfurt et al., 2012). 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 theory that patients may simultaneously accept and deny the dying experience (Carlson, Bultz, et al., 2005; Daugherty et al., 2005; Godskesen et al., 2013; Moore, 2001; Stetz, 1993; Weisman, 1972).

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 adult P1T participants because it frequently signaled cancer progression and was accompanied by a loss of optimism (Cox, 1999, 2002; Cox & Avis, 1996; Moore, 2001; Wilson et al., 2005; Wootten et al., 2011). Despite this, there was evidence that adult P1T participants at trial conclusion maintained hope that others would be helped by their participation in the P1T (Cox, 2002; Wilson et al., 2005; Wootten et al., 2011). 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 that had been caring for them (Cox, 1999; Cox & Avis, 1996; Moore, 2001; Wilson et al., 2005; Wootten et al., 2011).

The articles describing adults' P1T experiences included discussion regarding whether P1T participation represented 'survival work' that detracted from 'death work' (Cox, 2002; Meyers et al., 2004; Moore, 2001). 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 the disease take its natural course (Stetz, 1993). Death work consists of the tasks involved with preparing for one's death practically, emotionally, socially and spiritually (Schou, 1992). 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 (Campbell & Whyte, 1999; Cox, 2002; Stetz, 1993). This trade-off in survival and death work was another example of the interaction between courageous and defensive coping strategies, as for 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 grounded in Glaser and Strauss' findings 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 (Glaser & Strauss, 1965, 1968). 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 (Cox, 2002; Moore, 2001). There was no evidence that adult P1T participants would have engaged in death work had they not enrolled in a P1T (Cox, 2002; Moore, 2001).

Protective Factor: Social Integration

Overall, the adult articles reinforced the importance of strong social support. There was limited evidence that adult P1Ts participants reported higher levels of social integration than non-participants (Berdel et al., 1988).

Cox described the 'therapeutic alliance' formed between adult P1T participants and healthcare providers, wherein P1T participants benefited from the sense of the alliance working together to actively fight their cancer (Cox, 1999; Moore, 2001). There was strong evidence that adult P1T participants experienced enhanced support of high-quality

healthcare and valued effective communication with healthcare providers (Cox, 1999; Cox & Avis, 1996; Hutchison, 1998; Moore, 2001; Wootten et al., 2011; Yoder et al., 1997). However, adult PIT participants who traveled to a different geographic location to participate in the PIT were adversely affected by losing the support of their original healthcare providers (Cohen et al., 2007). Adult PIT participants also experienced feelings of abandonment if their connection and shared goals with the PIT healthcare providers was lost at the end of trial participation (Cox, 1999; Cox & Avis, 1996; Wilson et al., 2005). Adult PIT 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 (Cox, 1999; Cox, Wilson, Arthur, Elkan, & Armstrong, 2005; Wilson et al., 2005; Wootten et al., 2011; Yoder et al., 1997).

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 (Moore, 2001). There was some limited evidence that this societal expectation could influence adults' participation in a PIT, since stopping treatment could be viewed as giving-in and losing hope (Moore, 2001; Wootten et al., 2011). The impact of societal influences on PIT participation was not explored in the pediatric articles.

Protective Factor: Family Environment

Family environment was generally important to adult PIT participants' well-being (Campbell & Whyte, 1999; Ulrich et al., 2012; Wootten et al., 2011; Yoder et al., 1997). In particular, the inclusion of the adult participant's family regarding the PIT plan of care enhanced communication (Wootten et al., 2011; Yoder et al., 1997). Adult participants expected increased support from their family during the PIT and tended to receive support beyond those expectations (Yoder et al., 1997). There was also some evidence that traveling away from family to participate in a PIT adversely affected the well-being of adult PIT participants (Cohen et al., 2007). Kessler et al. (2014) found that caregivers of adult PIT participants reported high levels of distress, anxiety, and depressive symptoms, suggesting that enrollment in a PIT places a considerable burden on family and caregivers in terms of scheduling and managing the patient's care.

Protective Factor: Derived Meaning

There was strong evidence that PIT participation offered hope that positively influenced well-being in adults. (Cox, 1999, 2002; Cox & Avis, 1996; Godskesen et al., 2013; Moore, 2001; Stetz, 1993; Ulrich et al., 2012; Wootten et al., 2011). Adult PIT participants attributed meaning to simply being offered the opportunity to participate in a PIT; the offer engendered feelings of being special and chosen because only a few individuals were extended the opportunity (Cox, 1999, 2000, 2002; Godskesen et al., 2013; Stetz, 1993).

When prematurely removed from a PIT due to disease progression or toxicities, adult PIT participants lost hope for stabilization of cancer and / or symptom improvement (Cox, 2002; Wilson et al., 2005; Wootten et al., 2011). Despite losing hope for self, there was also evidence that participants maintained hope that others would be helped by their PIT

participation (Barrera et al., 2005; Cox, 2002; Wilson et al., 2005; Wootten et al., 2011). Even if they did not personally benefit, adult P1T 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 (Carlson, Bultz, et al., 2005; Cox, 1999; Godskesen et al., 2013; Mack, 1998; Ulrich et al., 2012; Wootten et al., 2011; Yoder et al., 1997).

Outcome Factor: Well-being

QOL was the only well-being outcome assessed in the articles (Kelly et al., 2014). For adult P1T participants, QOL was focused on the ability to function, be productive, and free from symptoms of disease and treatment side-effects (Campbell & Whyte, 1999; Cohen et al., 2007; Wootten et al., 2011). In adult participants, no significant changes were found in overall QOL scores over one course of P1T therapy (Berdel et al., 1988; Cox, 2003; Melink et al., 1992; Rouanne et al., 2013). There was some evidence that older adults participating in P1Ts evaluated their QOL in comparison with their own prior treatment experiences and health, as well as in comparison with peers (Cohen et al., 2007; Kvale et al., 2010).

Discussion of Findings

Overall, this review established that there is minimal empirical evidence in the pediatric literature regarding the experiences or well-being of children with cancer 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 children. Findings from the adult literature provide insights into adults' P1T experiences that could be similar for child participants and suggest areas for consideration in future research. Table 5 compares the findings from the pediatric and adult literature for each factor of the Resilience Framework.

The highest level of evidence in the pediatric literature is from the meta-analyses of P1T outcomes (Bautista et al., 2015; Carlson et al., 1996; Furman et al., 1989; Kim et al., 2008; Lee et al., 2005; Morgenstern et al., 2014; Paoletti et al., 2013; Shah et al., 1998). Although the prognosis for children with cancer enrolled in a P1T is poor, pediatric oncology P1Ts historically are generally safe, have manageable toxicities, and offer the potential for at least stabilization of disease for several months. Findings from the adult literature that appear to be relevant to children participating in a P1T include the following: 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 P1T participants' well-being was 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.

One idea from the adult literature that could be important for child participants is that since P1T participation focuses providers', patients', and families' attention on survival work (courageous coping), P1T participation may foster avoidance of death work (defensive coping) that could negatively impact the patient's dying process and/or the family's

bereavement. However, it is unclear that adult PIT participants would have chosen to engage in death work had they not participated in a PIT. In addition, defensive coping strategies only become problematic when used exclusively for long periods of time, without development of courageous coping strategies (Haase et al., 2017). The adult literature findings in fact include that PIT participation supported courageous coping strategies 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.

In the pediatric literature, the impact of PIT participation on death work was only 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 (Hinds et al., 1997; Maurer et al., 2010). Ethicists and healthcare providers hypothesized that the participation of children with cancer in PITs not only alters their own death work, but also the grief work of their parents (who serve as proxy decision-makers) (Meyers et al., 2004; Oberman & Frader, 2003). In particular, Meyers et al. (2004) proposed that a child's PIT participation could theoretically minimize parents' ability to engage in anticipatory grieving, potentially leading to more incidences of complicated bereavement. However, no empiric evidence exists that supports this theory.

A second idea from the adult literature that could be important for child participants is that external influences could impact the decision to participate in a PIT. Although not explored in the pediatric articles, further research is warranted regarding whether children might 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 cancer-focused therapy, are potential influencers on the decision to participate in a pediatric oncology PIT. Double protection was briefly explored in two of the pediatric articles. Due to the vital importance of the parent-child relationship for children, double-protection may also be particularly influential in children's assent to participate in a PIT as they seek to ease their parents' suffering or to acquiesce to their parents' wishes (Broome & Richards, 2003).

Limitations

Literature searches were limited to articles in the English language and with an abstract. The experiences of adults are likely different in some important ways than the experiences of children, requiring that the conclusions derived from the adult literature must be interpreted with caution. However, the dearth of articles focused on the experiences of children necessitated this approach and highlights the need for future research focused on children's experiences. In addition, many of the articles in the sample were published more than ten years ago and would not have reflected recent advances in molecularly targeted therapies and / or trial designs. Lastly, article evaluations were susceptible to bias as authors were not blinded to authors, journal, or publication year.

Implications for Nursing Practice and Research

Review findings have implications for nurses who work with children and families considering participation in a pediatric oncology P1T. First, the findings provide reassurance that historically P1Ts are generally safe and may indeed provide direct benefit for children with cancer. Second, 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 nurses' attention. Children should have an active voice in P1T decision-making, and be directly addressed in consent discussions at an appropriate developmental level (Baker et al., 2013; Broome & Richards, 2003; Miller, Baker, Leek, Drotar, & Kodish, 2014). Third, communication during pediatric oncology P1T conversations is often falsely reassuring (Miller, Cousino, Leek, & Kodish, 2014). Including the potential impact of P1T participation on children's well-being, per the findings of this review, will help to achieve a balanced approach when presenting risks and potential benefits of participation during P1T consent discussions, and will help to ensure pediatric oncology P1T participants are well-informed when making decisions about P1T enrollment.

The methods used to research the experience of adult P1T participants may be helpful to guide future research with pediatric participants. In particular, the work of nurse scientist Dr. Karen Cox is noteworthy in that it provides an exemplar of how research into adult experiences in P1Ts developed from initial descriptive studies into testing of an intervention to improve the transition off a P1T (Cox, 1998, 1999, 2000, 2002, 2003; Cox & Avis, 1996; Cox et al., 2005).

Conclusions

Although research on how P1T participation may impact the well-being of children with cancer is limited, the adult literature provides insight into adults' P1T experiences that could be similar for child participants and suggests areas for consideration in future research. The experience and effects of P1T participation on children's well-being needs to be understood to assure the ethical principles outlined in the Declaration of Helsinki are upheld (World Medical Association, 2013). Understanding the impact of P1T participation on participants' well-being provides nurses and other healthcare providers with the opportunity to incorporate participants' experiences into the management of P1Ts and the preparedness of future participants (Cox, 2000). Future research needs to focus on achieving a better understanding of the impact of P1T participation on children's well-being, in order to address significant gaps in our understanding of this experience and ensure that P1T participation does not inadvertently negatively impact the well-being of children with cancer.

Funding:

Research reported in this publication was supported by: 1) the National Institute of Nursing Research under award numbers F31 NR015393 and T32 NR007066; 2) the National Cancer Institute under award number T32 CA117865; 3) the American Cancer Society under grant numbers DSCN-13-267-01-SCN and DSCNR-15-081-03-SCN; 4) an Oncology Nursing Society Foundation Dissertation Research Grant; and 5) a Midwest Nursing Research Society Founder's Circle Endowment Grant. The content is solely the responsibility of the authors and does not necessarily

represent the official views of the National Institutes of Health, American Cancer Society, Oncology Nursing Society, or Midwest Nursing Research Society.

References

- Agrawal M, & Danis M (2002). End-of-life care for terminally ill participants in clinical research. *Journal of Palliative Medicine*, 5(5), 729–737. [PubMed: 12572972]
- Agrawal M, & Emanuel EJ (2003). Ethics of phase 1 oncology studies: Reexamining the arguments and data. *Journal of the American Medical Association*, 290(8), 1075–1082. doi:10.1001/jama.290.8.1075 [PubMed: 12941681]
- Baker JN, Leek AC, Salas HS, Drotar D, Noll R, Rheingold SR, & Kodish ED (2013). Suggestions from adolescents, young adults, and parents for improving informed consent in phase 1 pediatric oncology trials. *Cancer*, 119(23), 4154–4161. doi:10.1002/cncr.28335 [PubMed: 24006119]
- Barnes MJ, Pressey J, Adams J, Hensler MA, & Madan-Swain A (2014). Physician and nurse beliefs of phase 1 trials in pediatric oncology. *Cancer Nursing*, 37(5), E48–E52. doi:10.1097/ncc.0000000000000099
- Barrera M, D'Agostino N, Gammon J, Spencer L, & Baruchel S (2005). Health-related quality of life and enrollment in phase 1 trials in children with incurable cancer. *Palliative & Supportive Care*, 3(3), 191–196. [PubMed: 16594458]
- Bautista F, Di Giannatale A, Dias-Gastellier N, Fahd M, Valteau-Couanet D, Couanet D, ... Geoerger B (2015). Patients in pediatric phase I and early phase II clinical oncology trials at Gustave Roussy: A 13-year center experience. *Journal of Pediatric Hematology Oncology*, 37(2), e102–110. doi: 10.1097/mph.0000000000000237
- Beardsmore S, & Fitzmaurice N (2002). Palliative care in paediatric oncology. *European Journal of Cancer*, 38(14), 1900–1910. [PubMed: 12204672]
- Berdel WE, Knopf H, Fromm M, Schick HD, Busch R, Fink U, ... Rastetter J (1988). Influence of phase I early clinical trials on the quality of life of cancer patients: A pilot study. *Anticancer Research*, 8(3), 313–321. [PubMed: 3389737]
- Berg SL (2007). Ethical challenges in cancer research in children. *Oncologist*, 12(11), 1336–1343. [PubMed: 18055854]
- Bluebond-Langner M, Belasco JB, Goldman A, & Belasco C (2007). Understanding parents' approaches to care and treatment of children with cancer when standard therapy has failed. *Journal of Clinical Oncology*, 25(17), 2414–2419. [PubMed: 17557955]
- Brock KE, Steineck A, & Twist CJ (2016). Trends in end-of-life care in pediatric hematology, oncology, and stem cell transplant patients. *Pediatric Blood & Cancer*, 63(3), 516–522. doi: 10.1002/pbc.25822 [PubMed: 26513237]
- Broome ME, & Richards DJ (2003). The influence of relationships on children's and adolescents' participation in research. *Nursing Research*, 52(3), 191–197. [PubMed: 12792260]
- Campbell S, & Whyte F (1999). The quality of life of cancer patients participating in phase I clinical trials using SEIQoL-DW. *Journal of Advanced Nursing*, 30(2), 335–343. doi:10.1046/j.1365-2648.1999.01079.x [PubMed: 10457235]
- Carlson C, Reilly M, & Hitchens A (2005). An innovative approach to the care of patients on phase I and phase II clinical trials: The role of the experimental therapeutics nurse. *Journal of Pediatric Oncology Nursing*, 22(6), 353–364. doi:10.1177/1043454205281763 [PubMed: 16216897]
- Carlson L, Ho P, Smith M, Reisch J, & Weitman S (1996). Pediatric phase I drug tolerance: A review and comparison of recent adult and pediatric phase I trials. *Journal of Pediatric Hematology/Oncology*, 18(3), 250–256. [PubMed: 8689336]
- Carlson LE, Bultz BD, & Morris DG (2005). Individualized quality of life, standardized quality of life, and distress in patients undergoing a phase I trial of the novel therapeutic Reolysin (reovirus). *Health and quality of life outcomes*, 3, 7. doi:10.1186/1477-7525-3-7 [PubMed: 15676074]
- Casarett DJ, Karlawish JH, Henry MI, & Hirschman KB (2002). Must patients with advanced cancer choose between a phase I trial and hospice? *Cancer*, 95(7), 1601–1604. doi:10.1002/cncr.10820 [PubMed: 12237931]

- Cassel JB, Del Fabbro E, Arkenau T, Higginson IJ, Hurst S, Jansen LA, ... Miller FG (2016). Phase I cancer trials and palliative care: Antagonism, irrelevance, or synergy? *Journal of Pain and Symptom Management*, 52(3), 437–445. doi:10.1016/j.jpainsymman.2016.02.014 [PubMed: 27233136]
- Chang A (2008). An exploratory survey of nurses' perceptions of phase I clinical trials in pediatric oncology. *Journal of Pediatric Oncology Nursing*, 25(1), 14–23. doi:10.1177/1043454207311742 [PubMed: 18187597]
- Cohen MZ, Slomka J, Pentz RD, Flamm AL, Gold D, Herbst RS, & Abbruzzese JL (2007). Phase I participants' views of quality of life and trial participation burdens. *Supportive Care in Cancer*, 15(7), 885–890. doi:10.1007/s00520-007-0216-0 [PubMed: 17252219]
- Cousino MK, Zyzanski SJ, Yamokoski AD, Hazen RA, Baker JN, Noll RB, ... Drotar D (2012). Communicating and understanding the purpose of pediatric phase I cancer trials. *Journal of Clinical Oncology*, 30(35), 4367–4372. [PubMed: 23071225]
- Cox K (1998). Investigating psychosocial aspects of participation in early anti-cancer drug trials: towards a choice of methodology. *Journal of Advanced Nursing*, 27(3), 488–496. [PubMed: 9543033]
- Cox K (1999). Researching research: patients' experiences of participation in phase I and II anti-cancer drug trials. *European Journal of Oncology Nursing*, 3(3), 143–152.
- Cox K (2000). Enhancing cancer clinical trial management: recommendations from a qualitative study of trial participants' experiences. *Psycho-Oncology*, 9(4), 314–322. [PubMed: 10960929]
- Cox K (2002). The hopes of the dying: Examining patients' experience of participation in early phase cancer clinical trials. *Nursing Times Research*, 7(1), 60–74.
- Cox K (2003). Assessing the quality of life of patients in phase I and II anti-cancer drug trials: interviews versus questionnaires. *Social Science and Medicine*, 56(5), 921–934. [PubMed: 12593867]
- Cox K, & Avis M (1996). Psychosocial aspects of participation in early anticancer drug trials: Report of a pilot study. *Cancer Nursing*, 19(3), 177–186. [PubMed: 8674026]
- Cox K, Wilson E, Arthur A, Elkan R, & Armstrong S (2005). A randomised controlled trial of nurse-managed trial conclusion following early phase cancer trial participation. *British Journal of Cancer*, 93(1), 41–45. [PubMed: 15986032]
- Crites J, & Kodish E (2013). Unrealistic optimism and the ethics of phase I cancer research. *Journal of Medical Ethics*, 39(6), 403–406. doi:10.1136/medethics-2012-100752 [PubMed: 23118468]
- Daugherty CK, Fitchett G, Murphy PE, Peterman AH, Banik DM, Hlubocky F, & Tartaro J (2005). Trusting God and medicine: Spirituality in advanced cancer patients volunteering for clinical trials of experimental agents. *Psycho-Oncology*, 14(2), 135–146. doi:10.1002/pon.829 [PubMed: 15386780]
- de Vries MC, Houtlosser M, Wit JM, Engberts DP, Bresters D, Kaspers GJ, & van Leeuwen E (2011). Ethical issues at the interface of clinical care and research practice in pediatric oncology: A narrative review of parents' and physicians' experiences. *BMC Medical Ethics*, 12(18). Retrieved from Retrieved from <http://www.biomedcentral.com/1472-6939/12/18> doi: 10.1186/1472-6939-12-18
- Deatrick JA, Angst DB, & Moore C (2002). Parents' views of their children's participation in phase I oncology clinical trials. *Journal of Pediatric Oncology Nursing*, 19(4), 114–121. [PubMed: 12203190]
- Ekert H (2013). Can phase I cancer research studies in children be justified on ethical grounds? *Journal of Medical Ethics*, 39(6), 407–407. doi:10.1136/medethics-2012-101125 [PubMed: 23175460]
- Estlin EJ, Cotterill S, Pratt CB, Pearson AD, & Bernstein M (2000). Phase I trials in pediatric oncology: Perceptions of pediatricians from the United Kingdom Children's Cancer Study Group and the Pediatric Oncology Group. *Journal of Clinical Oncology*, 18(9), 1900–1905. [PubMed: 10784630]
- Eton DT, de Oliveira DR, Egginton JS, Ridgeway JL, Odell L, May CR, & Montori VM (2012). Building a measurement framework of burden of treatment in complex patients with chronic conditions: A qualitative study. *Patient Related Outcome Measures*, 3, 39–49. [PubMed: 23185121]

- Finlay E, Lu HL, Henderson H, O'Dwyer PJ, & Casarett DJ (2009). Do phase 1 patients have greater needs for palliative care compared with other cancer patients? *Cancer*, 115(2), 446–453. doi: 10.1002/cncr.24025 [PubMed: 19107769]
- Furman WL, Pratt CB, Rivera GK, Krischer JP, Kamen BA, & Vietti TJ (1989). Mortality in pediatric phase I clinical trials. *Journal of the National Cancer Institute*, 81(15), 1193–1194. [PubMed: 2746673]
- George GC, Iwuanyanwu EC, Anderson KO, Yusuf A, Zinner RG, Piha-Paul SA, ... Hong DS (2016). 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. *Cancer*, 122(21), 3401–3409. doi:10.1002/cncr.30182 [PubMed: 27412379]
- Gilliam MB, Madan-Swain A, Adams JM, & Pressey JG (2013). Physician perceptions and beliefs of phase I trials in pediatric oncology. *Pediatric Blood & Cancer*, 60(8), E67–69. doi:10.1002/pbc.24522 [PubMed: 23512880]
- Glaser B, & Strauss AL (1965). *Awareness of dying: A study of social interaction*. Chicago, IL: Aldine Publishing.
- Glaser B, & Strauss AL (1968). *Time for dying*. Chicago, IL: Aldine Publishing.
- Godskesen T, Nygren P, Nordin K, Hansson M, & Kihlbom U (2013). Phase 1 clinical trials in end-stage cancer: Patient understanding of trial premises and motives for participation. *Supportive Care in Cancer*, 21(11), 3137–3142. doi:10.1007/s00520-013-1891-7 [PubMed: 23864288]
- Haase JE, Heiney SP, Ruccione K, & Stutzer C (1999). Research triangulation to derive meaning-based quality-of-life theory: adolescent resilience model and instrument development. *International Journal of Cancer*, 12, 125–131. [PubMed: 10679883]
- Haase JE, Kintner EK, Monahan PO, & Robb SL (2014). The Resilience in Illness Model, part 1: Exploratory evaluation in adolescents and young adults with cancer. *Cancer Nursing*, 37(3), E1–E12. doi:10.1097/NCC.0b013e31828941bb
- Haase JE, Kintner EK, Robb SL, Stump TE, Monahan PO, Phillips C, ... Burns DS (2017). The Resilience in Illness Model Part 2: Confirmatory evaluation in adolescents and young adults with cancer. *Cancer Nursing*. Retrieved from <http://insights.ovid.com/crossref?an=00002820-900000000-99271#>
- Hazen RA, Zyzanski S, Baker JN, Drotar D, & Kodish E (2015). Communication about the risks and benefits of phase I pediatric oncology trials. *Contemporary Clinical Trials*, 41, 139–145. doi: 10.1016/j.cct.2015.01.015 [PubMed: 25638751]
- Helft PR, Hlubocky F, Wen M, & Daugherty CK (2003). Associations among awareness of prognosis, hopefulness, and coping in patients with advanced cancer participating in phase I clinical trials. *Supportive Care in Cancer*, 11(10), 644–651. doi:10.1007/s00520-003-0496-y [PubMed: 12883963]
- Hinds PS, Drew D, Oakes LL, Fouladi M, Spunt SL, Church C, & Furman WL (2005). End-of-life care preferences of pediatric patients with cancer. *Journal of Clinical Oncology*, 23(36), 9146–9154. [PubMed: 16172453]
- Hinds PS, Oakes L, Furman W, Foppiano P, Olson MS, Quargnenti A, ... Strong C (1997). Decision making by parents and healthcare professionals when considering continued care for pediatric patients with cancer. *Oncology Nursing Forum*, 24(9), 1523–1528. [PubMed: 9348593]
- Hinds PS, Oakes LL, Hicks J, Powell B, Srivastava DK, Spunt SL, ... Furman WL (2009). “Trying to be a good parent” as defined by interviews with parents who made phase I, terminal care, and resuscitation decisions for their children. *Journal of Clinical Oncology*, 27(35), 5979–5985. doi: 10.1200/jco.2008.20.0204 [PubMed: 19805693]
- Hui D, Parsons H, Nguyen L, Palla SL, Yennurajalingam S, Kurzrock R, & Bruera E (2010). Timing of palliative care referral and symptom burden in phase 1 cancer patients: A retrospective cohort study. *Cancer*, 116(18), 4402–4409. doi:10.1002/cncr.25389 [PubMed: 20564164]
- Hutchison C (1998). Phase I trials in cancer patients: participants' perceptions. *European Journal Of Cancer Care*, 7(1), 15–22. [PubMed: 9582747]
- Jansen LA, Mahadevan D, Appelbaum PS, Klein WM, Weinstein ND, Mori M, ... Sulmasy DP (2016). Dispositional optimism and therapeutic expectations in early-phase oncology trials. *Cancer*, 122(8), 1238–1246. doi:10.1002/cncr.29908 [PubMed: 26882017]

- Kapo J, & Casarett D (2002). Palliative care in phase 1 trials: An ethical obligation or undue inducement? *Journal of Palliative Medicine*, 5(5), 661–665. [PubMed: 12572963]
- Kearns P, & Morland B (2014). New drug development in childhood cancer. *Current Opinion in Pediatrics*, 26(1), 37–42. doi:10.1097/mop.0000000000000054 [PubMed: 24362409]
- Kelly KP, Hooke MC, Ruccione K, Lanier W, & Haase J (2014). Children's Oncology Group Nursing Research Framework. *Seminars in Oncology Nursing*, 30(1), 17–25. [PubMed: 24559776]
- Kessler ER, Moss A, Eckhardt SG, Laudenslager ML, Kilbourn K, Mauss IB, ... Kutner JS (2014). Distress among caregivers of phase I trial participants: A cross-sectional study. *Supportive Care in Cancer*, 22(12), 3331–3340. doi:10.1007/s00520-014-2380-3 [PubMed: 25120010]
- Kim A, Fox E, Warren K, Blaney SM, Berg SL, Adamson PC, ... Widemann BC (2008). Characteristics and outcome of pediatric patients enrolled in phase I oncology trials. *Oncologist*, 13(6), 679–689. doi:10.1634/theoncologist.2008-0046 [PubMed: 18586923]
- Kvale EA, Woodby L, & Williams BR (2010). The experience of older patients with cancer in phase 1 clinical trials: a qualitative case series. *American Journal of Hospice and Palliative Care*, 27(7), 474–481. doi:10.1177/1049909110365072 [PubMed: 20388935]
- Landier W, Leonard M, & Ruccione KS (2013). Children's Oncology Group's 2013 blueprint for research: Nursing discipline. *Pediatric Blood & Cancer*, 60(6), 1031–1036. [PubMed: 23255369]
- Lansky SB, List MA, Lansky LL, Ritter-Sterr C, & Miller DR (1987). The measurement of performance in childhood cancer patients. *Cancer*, 60(7), 1651–1656. [PubMed: 3621134]
- Last BF (1992). The phenomenon of double protection In Last BF & Van Veldhuizen AM (Eds.), *Developments in Pediatric Psychosocial Oncology* (pp. 39–51). Amsterdam: Swets & Zeitlinger.
- Lee DP, Skolnik JM, & Adamson PC (2005). Pediatric phase I trials in oncology: An analysis of study conduct efficiency. *Journal of Clinical Oncology*, 23(33), 8431–8441. doi:10.1200/jco.2005.02.1568 [PubMed: 16293874]
- Levine DR, Johnson LM, Mandrell BN, Yang J, West NK, Hinds PS, & Baker JN (2015). 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. *Cancer*, 121(9), 1508–1512. [PubMed: 25557437]
- Mack CH (1998). The quest for treatment: Cancer patients' experience of Phase I clinical trials. (Doctoral dissertation), University of California, Los Angeles, Retrieved from <http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=2004133283&site=ehost-live>
- Mack JW, Joffe S, Hilden JM, Watterson J, Moore C, Weeks JC, & Wolfe J (2008). Parents' views of cancer-directed therapy for children with no realistic chance for cure. *Journal of Clinical Oncology*, 26(29), 4759–4764. [PubMed: 18779605]
- Marshall PA, Magtanong RV, Leek AC, Hizlan S, Yamokoski AD, & Kodish ED (2012). Negotiating decisions during informed consent for pediatric phase I oncology trials. *Journal of Empirical Research on Human Research Ethics*, 7(2), 51–59. doi:10.1525/je.2012.7.2.51 [PubMed: 22565583]
- Maurer SH, Hinds PS, Spunt SL, Furman WL, Kane JR, & Baker JN (2010). 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. *Journal of Clinical Oncology*, 28(20), 3292–3298. doi:10.1200/jco.2009.26.6502 [PubMed: 20498399]
- Melink TJ, Clark GM, & Von Hoff DD (1992). The impact of phase I clinical trials on the quality of life of patients with cancer. *Anti-Cancer Drugs*, 3(6), 571–576. [PubMed: 1288727]
- Meyers FJ, Linder J, Beckett L, Christensen S, Blais J, & Gandara DR (2004). Simultaneous care: A model approach to the perceived conflict between investigational therapy and palliative care. *Journal of Pain and Symptom Management*, 28(6), 548–556. doi:10.1016/j.jpainsymman.2004.03.002 [PubMed: 15589080]
- Miller FG, & Joffe S (2008). Benefit in phase 1 oncology trials: Therapeutic misconception or reasonable treatment option? *Clinical Trials*, 5(6), 617–623. doi:10.1177/1740774508097576 [PubMed: 19029210]
- Miller VA, Baker JN, Leek AC, Drotar D, & Kodish E (2014). Patient involvement in informed consent for pediatric phase I cancer research. *Journal of Pediatric Hematology/Oncology*, 36(8), 635–640. doi:10.1097/mp.0000000000000112 [PubMed: 24487916]

- Miller VA, Baker JN, Leek AC, Hizlan S, Rheingold SR, Yamokoski AD, ... Kodish E (2013). Adolescent perspectives on phase I cancer research. *Pediatric Blood & Cancer*, 60(5), 873–878. doi:10.1002/pbc.24326 [PubMed: 23034985]
- Miller VA, Cousino M, Leek AC, & Kodish E (2014). Hope and persuasion by physicians during informed consent for phase I trials. *Journal of Clinical Oncology*, 32(29), 3229–3235. [PubMed: 25199753]
- Moore S (2001). A need to try everything: Patient participation in phase I trials. *Journal of Advanced Nursing*, 33(6), 738–747. doi:10.1046/j.1365-2648.2001.01715.x [PubMed: 11298211]
- Mor V, Laliberte L, Morris J, & Wiemann M (1984). The Karnofsky performance status scale. *Cancer*, 53, 2002–2007. [PubMed: 6704925]
- Morgenstern DA, Hargrave D, Marshall LV, Gatz SA, Barone G, Crowe T, ... Moreno L (2014). Toxicity and outcome of children and adolescents participating in phase I/II trials of novel anticancer drugs: The Royal Marsden experience. *Journal of Pediatric Hematology/Oncology*, 36(3), 218–223. doi:10.1097/mp.000000000000003 [PubMed: 24322496]
- Oberman M, & Frader J (2003). Dying children and medical research: Access to clinical trials as benefit and burden. *American Journal of Law and Medicine*, 29(2–3), 301–317. [PubMed: 12961809]
- Oppenheim D, Geoerger B, & Hartmann O (2005). Ethical issues in pediatric oncology: Phase I-II trials based on a mother's point of view. *Bulletin du Cancer*, 92(11), E57–60.
- Paoletti X, Geoerger B, Doz F, Baruchel A, Lokiec F, & Le Tourneau C (2013). A comparative analysis of paediatric dose-finding trials of molecularly targeted agent with adults' trials. *European Journal of Cancer*, 49(10), 2392–2402. doi:10.1016/j.ejca.2013.02.028 [PubMed: 23540589]
- Rouanne M, Massard C, Hollebecque A, Rousseau V, Varga A, Gazzah A, ... Soria JC (2013). Evaluation of sexuality, health-related quality-of-life and depression in advanced cancer patients: A prospective study in a phase I clinical trial unit of predominantly targeted anticancer drugs. *European Journal of Cancer*, 49(2), 431–438. doi:10.1016/j.ejca.2012.08.008 [PubMed: 22959468]
- Sav A, Kendall E, McMillan SS, Kelly F, Whitty JA, King MA, & Wheeler AJ (2013). 'You say treatment, I say hard work': Treatment burden among people with chronic illness and their carers in Australia. *Health and Social Care in the Community*, 21(6), 665–674. [PubMed: 23701664]
- Sav A, King MA, Whitty JA, Kendall E, McMillan SS, Kelly F, ... Wheeler AJ (2013). Burden of treatment for chronic illness: A concept analysis and review of the literature. *Health Expectations*. Retrieved from <http://onlinelibrary.wiley.com/doi/10.1111/hex.12046/pdf>
- Schou KC (1992). Awareness contexts and the construction of dying in the cancer treatment setting: 'Micro' and 'macro' levels in narrative analysis. *The Sociological Review*, 40(S1), 238–263.
- Shah S, Weitman S, Langevin AM, Bernstein M, Furman W, & Pratt C (1998). Phase I therapy trials in children with cancer. *Journal of Pediatric Hematology/Oncology*, 20(5), 431–438. [PubMed: 9787315]
- Siegel RL, Miller KD, & Jemal A (2016). Cancer statistics, 2016. *CA: A Cancer Journal for Clinicians*, 66(1), 7–30. [PubMed: 26742998]
- Stetz KM (1993). Survival work: The experience of the patient and the spouse involved in experimental treatment for cancer. Paper presented at the Seminars in Oncology Nursing.
- Sun V, Cooke L, Chung V, Uman G, Smith TJ, & Ferrell B (2014). Feasibility of a palliative care intervention for cancer patients in phase I clinical trials. *Journal of Palliative Medicine*, 17(12), 1365–1368. doi:10.1089/jpm.2014.0108 [PubMed: 25014572]
- Tomlinson D, Bartels U, Gammon J, Hinds PS, Volpe J, Bouffet E, ... Sung L (2011). Chemotherapy versus supportive care alone in pediatric palliative care for cancer: comparing the preferences of parents and health care professionals. *Canadian Medical Association Journal*, 183(17), E1252–1258. doi:10.1503/cmaj.110392 [PubMed: 22007121]
- Ulrich CM, Grady C, & Wendler D (2004). Palliative care: A supportive adjunct to pediatric phase I clinical trials for anticancer agents? *Pediatrics*, 114(3), 852–855.
- Ulrich CM, Knafl KA, Ratcliffe SJ, Richmond TS, Grady C, Miller-Davis C, & Wallen GR (2012). Developing a model of the benefits and burdens of research participation in cancer clinical trials. *AJOB Primary Research*, 3(2), 10–23. doi:10.1080/21507716.2011.653472 [PubMed: 24748992]

- Weber JS, Levit LA, Adamson PC, Bruinooge S, Burris HA, Carducci MA, ... Postow MA (2014). American Society of Clinical Oncology policy statement update: the critical role of phase I trials in cancer research and treatment. *Journal of Clinical Oncology*, 33(3), 278–284. [PubMed: 25512456]
- Weinfurt KP, Seils DM, Lin L, Sulmasy DP, Astrow AB, Hurwitz HI, ... Meropol NJ (2012). Research participants' high expectations of benefit in early-phase oncology trials: Are we asking the right question? *Journal of Clinical Oncology*, 30(35), 4396–4400. doi:10.1200/jco.2011.40.6587 [PubMed: 23091107]
- Weisman AD (1972). *On dying and denying: A psychiatric study of terminality*. Pasadena, CA: Behavioral Publications.
- Whittemore R, & Knafl K (2005). The integrative review: Updated methodology. *Journal of Advanced Nursing*, 52(5), 546–553. doi:10.1111/j.1365-2648.2005.03621.x [PubMed: 16268861]
- Wilson E, Cox K, & Elkan R (2005). 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 at trial conclusion. *Clinical Effectiveness in Nursing*, 3(3–4), 119–132.
- Wooten AC, Abbott JM, Siddons HM, Rosenthal MA, & Costello AJ (2011). A qualitative assessment of the experience of participating in a cancer-related clinical trial. *Supportive Care in Cancer*, 19(1), 49–55. doi:10.1007/s00520-009-0787-z [PubMed: 19960208]
- World Medical Association. (2013). Declaration of Helsinki: Ethical principles for medical research involving human subjects. *Journal of the American Medical Association*, 310(20), 2191–2194. doi: 10.1001/jama.2013.281053 [PubMed: 24141714]
- Yoder LH, O'Rourke TJ, Etnyre A, Spears DT, & Brown TD (1997). Expectations and experiences of patients with cancer participating in phase I clinical trials. *Oncology Nursing Forum*, 24(5), 891–896. [PubMed: 9201741]
- Ziaian T, Sawyer MG, Reynolds KE, Carbone JA, Clark JJ, Baghurst PA, ... Staugas RE (2006). Treatment burden and health-related quality of life of children with diabetes, cystic fibrosis and asthma. *Journal of Paediatrics and Child Health*, 42(10), 596–600. [PubMed: 16972965]

Knowledge Translation:

- Although the prognosis for children with cancer enrolled in a PIT is poor, pediatric oncology PITs historically are generally safe, have manageable toxicities, and offer some hope for at least stabilization of disease for several months.
- Adult PIT participants report significant PIT treatment burdens that extend to family members and 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.
- Participating in a PIT was generally a positive experience that supported courageous coping and optimism in adults with cancer.

Figure 1.
Resilience Framework (Kelly et al., 2014; Landier et al., 2013) (Reprinted with permission)

Figure 2.
PRISMA Flow Diagrams

Table 1**Definition of Factors from the Resilience Framework** (Kelly et al., 2014) (Reprinted with permission)

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

Findings and Evaluation of Pediatric Articles

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
Barrera et al. (2005) / 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 PITs and the reasons why families participate in these trials	Nine families of children with cancer presented the option of a PIT at a Canadian hospital	<ul style="list-style-type: none"> Qualitative study Individual semi-structured interviews with parents and children 	<ul style="list-style-type: none"> 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 PITs 	<ul style="list-style-type: none"> 75% (n=12) participation rate Both parents and children were individually interviewed 	<ul style="list-style-type: none"> Interview questions not provided Length of time elapsed between phase I consent and interviews not disclosed Insufficient detail to validate or evaluate data analysis processes (Creswell, 2013) Clear definition of health-related QOL not provided Small sample recruited from one Canadian hospital 	Medium	High
Bautista et al. (2015) / 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	<ul style="list-style-type: none"> Phase I and II pediatric oncology trials are safe, associated with clinical benefit, and can be successfully integrated in current relapse strategies 	<ul style="list-style-type: none"> Well-conducted analysis Analysis performed at the largest cancer center in Europe 	<ul style="list-style-type: none"> Inclusion of both phase I and phase II trials limited the applicability of the findings to this review Patients were all enrolled at one hospital in France 	High	Medium
Brock et al. (2016) / Trends in End-of-Life Care in Pediatric Hematology, Oncology, and Stem Cell Transplant Patients	To explore the associations between demographic variables and end-of-life characteristics (including PIT enrollment)	445 pediatric hematology, oncology, and stem cell transplant patients less than 35 years of age who died between 2002 – 2014	Retrospective, chart review study	<ul style="list-style-type: none"> PIT participants more often enrolled in hospice, an association that persisted after multivariate adjustment for age at death, religion, diagnosis, relapse number, and stem cell transplant status Patients who received phase I therapy died at home or an inpatient hospice facility more frequently, although this association was confounded by diagnosis 	<ul style="list-style-type: none"> Well-conducted analysis Robust sample size 	<ul style="list-style-type: none"> Study was conducted at one site in the United States Data collected retrospectively, limiting data available Thirty-three patients (7.4%) were greater than 18 years of age (range 18–25) at diagnosis 	High	Medium
Carlson et al. (1996) / Pediatric Phase I Drug Tolerance: A	To evaluate the ratio of pediatric to adult maximum	70 PITs conducted from 1975 – 1995, where pediatric and	Meta-analysis of previously reported PIT results	<ul style="list-style-type: none"> Pediatric patients have an equal or greater medication tolerance than adult 	<ul style="list-style-type: none"> Maximum tolerated dose clearly defined Pediatric and adult PITs were matched on 	<ul style="list-style-type: none"> Literature review method and inclusion criteria not discussed 	High	Low

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
Review and Comparison of Recent Adult and Pediatric Phase I Trials	tolerated doses from PITs	adult PITs could be matched		patients enrolled on matched PITs • Patients on adult PITs are significantly less heavily pretreated than patients on matched pediatric PITs	both medication and dosing regimen	• Heavily pre-treated patients were defined as simply having one prior course of both chemotherapy and radiation therapy, without consideration of specific details		
Chang (2008) / An Exploratory Survey of Nurses' Perceptions of Phase I Clinical Trials in Pediatric Oncology	To evaluate nurses' perceptions of PITs	43 nurses from a large North American hospital surveyed in 2003	Exploratory survey study using qualitative and quantitative questions	• Nurses identified benefits of PITs as improving future therapies, QOL, disease burden, and hope, and negative outcomes as toxicities, false hope and decreased QOL	• Included discussion of positive and negative outcomes of participation in PIT, from a nursing perspective	• Development and origins of survey weren't discussed • Reliability and validity of survey questions and options weren't addressed • Small sample (45% response rate) recruited from one hospital	Low	Medium
Cousino et al. (2012) / 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 PIT purpose	85 PIT 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 PITs • Physician explanations during informed consent conferences did not ensure parental understanding • Child attended 83 of 85 observed informed consent conferences	• Well-conducted, large-scale study completed at six different hospitals in the United States • 80.2% (n=106) participation rate • Included direct observation of conferences with a follow-up interview to assess parental comprehension	• Informal communications and earlier informed consent conversations between families and medical team weren't captured • Quantitative analysis of qualitative data limited to numeric scores	High	Low
Deatrick et al. (2002) / Parents' Views of their Children's Participation in Phase I Oncology Clinical Trials	To describe parents' views about their children's participation in PITs	21 parent interviews following a PIT 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 PIT • 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	• Primary study was well-conducted by a recognized expert researcher • Sufficient detail provided to validate and evaluate methods and findings (Creswell, 2013)	• Inclusion / exclusion criteria for the subset of included parent interviews only briefly described; unclear why only interviews from prospective study were included when two primary studies were described (one retrospective and one prospective) • Primary study was conducted at one hospital in the United States	High	Medium

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
perceptions of PIT participation								
Furman et al. (1989) / Mortality in Pediatric Phase I Clinical Trials	To determine the risk of fatal toxicity and objective response rate in pediatric PITs	577 pediatric enrollments on 30 PITs at one hospital from 1967–1989	Meta-analysis of previously reported PIT results	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Analysis conducted at a large, very active PIT center in the United States 	<ul style="list-style-type: none"> Limited description of data analysis techniques and inclusion criteria for patient enrollments / PITs Patient enrollments were all from one hospital in the United States 	High	Low
Hinds et al. (2005) / 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 (PIT enrollment, initiation of DNR order or terminal care)	<ul style="list-style-type: none"> Qualitative, prospective study Individual, open-ended interviews with patient, parent and oncologist within 7 days of end-of-life decision 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Well-conducted study employing quality assurance measures Study was conducted at two hospitals - one in the United States and one in Australia Multiple perspectives captured 	<ul style="list-style-type: none"> 55.6% participation rate (n=36), which could have resulted in some self-selection bias 	High	Low
Hinds et al. (1997) / 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	<ul style="list-style-type: none"> Mixed methods retrospective study Individual, semi-structured interviews with parent and provider 	<ul style="list-style-type: none"> Deciding between a PIT or no further treatment, maintaining or withdrawing life support, and giving more chemotherapy or no further treatment were the most frequently reported difficult decisions 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 	<ul style="list-style-type: none"> Well-conducted study employing quality assurance measures Parent and provider perspectives were captured Sufficient detail to validate and evaluate methods and findings (Creswell, 2013) 	<ul style="list-style-type: none"> Study was conducted at one site in the United States Retrospective design may have enhanced the probability that later decisions were selected as most difficult 45% participation rate (n=83), which could have resulted in some self-selection bias 	High	Low
Hinds et al. (2009) / "Trying to be a Good Parent"	To define being a good parent to a child in an end-of-life decision	62 parents (of 58 children) who made an end-of-life decision in	<ul style="list-style-type: none"> Qualitative study using semantic analysis 	<ul style="list-style-type: none"> Being a good parent means making informed, unselfish 	<ul style="list-style-type: none"> Well-conducted study employing 	<ul style="list-style-type: none"> Parents assessed by child's clinicians as being too vulnerable to 	High	Low

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
as Defined by Interviews with Parents who made Phase I, Terminal Care, and Resuscitation Decisions for their Children	child with incurable cancer	the last 72 hours for their child with cancer	<ul style="list-style-type: none"> Individual open-ended interviews with parent 	<p>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</p>	<p>quality assurance measures</p> <ul style="list-style-type: none"> 77.3% participation rate (n=58 of 75 eligible families) Interview questions provided 	<p>participate were excluded, potentially introducing selection bias</p> <ul style="list-style-type: none"> Study was conducted at one site in the United States 		
Kim et al. (2008) / Characteristics and Outcome of Pediatric Patients Enrolled in Phase I Oncology Trials	To describe the characteristics of children enrolled in PITs, find associations between characteristics and toxicity risk, and analyze outcomes	262 patients enrolled on 16 different PITs coordinated by National Cancer Institute from 1992–2005	Meta-analysis of previously reported PIT results	<ul style="list-style-type: none"> Approximately 90% of PIT participants were evaluable for study endpoints PITs are safe with manageable toxicities Therapy dose was most strongly associated with dose-limiting toxicities Median overall survival time after enrollment was 5 months 	<ul style="list-style-type: none"> PITs categorized based on inclusion of myelosuppressive agents Analysis conducted at a large, very active PIT center in the United States 	<ul style="list-style-type: none"> Included PITs were all performed at one site in the United States 	High	Medium
Lee et al. (2005) / Pediatric Phase I Trials in Oncology: An Analysis of Study Conduct Efficiency	To determine the efficacy and safety of pediatric oncology PITs and to analyze how efficiently these trials are conducted	69 PITs enrolling 1,973 patients between 1990–2004	Meta-analysis of previously reported PIT results	<ul style="list-style-type: none"> PITs continue to be safe and relatively well-tolerated Deriving direct benefit from a PIT should not be equated with observed response rate Types of toxicities experienced by children were similar to those experienced by adults 	<ul style="list-style-type: none"> Well-conducted, large scale analysis Children's Oncology Group database included in searches Distinguished between PITs with cytotoxic and biologic drugs 	<ul style="list-style-type: none"> No substantive weaknesses identified 	High	Low
Levine et al. (2015) / Does Phase I Trial Enrollment Preclude Quality End-of-Life Care? Phase I 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 who were not enrolled in a PIT	277 children with solid tumors who were (n=120) and were not (n=157) enrolled in a PIT and who died between 2001–2005	<ul style="list-style-type: none"> Quantitative, cohort secondary analysis Retrospective chart review 	<ul style="list-style-type: none"> No significant differences were found in use or timing of do not attempt resuscitation orders, hospice use or length of stay, foregoing 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 	<ul style="list-style-type: none"> Well-conducted analysis Analysis performed at a large, very active PIT center in the United States Demographics were compared between groups to ensure similarity, and differences in age at death were controlled for statistically 	<ul style="list-style-type: none"> Study was conducted at one site in the United States Data collected retrospectively, limiting data available 	High	Medium

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
<ul style="list-style-type: none"> • Enrollment on a PIT does not affect end-of-life care characteristics 								
Marshall et al. (2012) / 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 PIT participation	16 informed consent conversations (ICCs) selected by stratified random selection from 49 ICCs from 2008–2011	Secondary, qualitative, grounded theory analysis	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Inclusion of both English and Spanish-speaking families • Attempts were made to ensure that 16 analyzed informed consent conversations were a representative sample 	<ul style="list-style-type: none"> • In grounded theory studies, researcher compares data with the emerging theory, gathering new data as needed to fill in gaps; a secondary analysis prohibits this and impacts credibility of outcome (Creswell, 2013) • Insufficient methodological detail to validate or evaluate data analysis procedures (Creswell, 2013) 	Medium	Medium
Maurer et al. (2010) / 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 PIT 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	<ul style="list-style-type: none"> • Qualitative study using semantic analysis • Individual open-ended interviews with parent and demographic data from chart 	<ul style="list-style-type: none"> • Despite similar definitions of a good parent and desired staff behaviors, parents choosing to participate in a PIT 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 PIT and a DNR / terminal care option 	<ul style="list-style-type: none"> • Well-conducted study employing quality assurance measures • 77.3% participation rate (n=58 of 75 eligible families) • Almost equal representation of parents choosing PIT versus parents choosing a DNR / terminal care option 	<ul style="list-style-type: none"> • Parents who were assessed by one of the child's clinicians as being emotionally or mentally unable to participate were excluded, which likely impacted representativeness of the sample • Study was performed at a single site 	High	Medium
Miller et al. (2013) / Adolescent Perspectives on Phase I Cancer Research	To examine adolescent patient perspectives on their understanding and decision-making about a PIT	20 structured interviews of adolescents with cancer who attended a PIT informed consent conversation between 2008–2011	<ul style="list-style-type: none"> • Prospective study • Quantitative analysis of qualitative data from recorded informed consent conferences and interviews 	<ul style="list-style-type: none"> • Most adolescents understood PIT was voluntary, entailed risks, and they could withdraw • Reasons for enrolling were positive clinical benefit, needing an option, impact on QOL, and fewer side effects than other treatments • Most participants hoped or expected that PIT would provide a 	<ul style="list-style-type: none"> • Well-conducted, large-scale study completed at six different hospitals • 74.1% (n=27) adolescent participation rate • Included direct observation of informed consent conferences with a follow-up interview 	<ul style="list-style-type: none"> • Predominance of white males in sample • Likely adolescents who were more distressed or less-involved declined participation, which could have resulted in some self-selection bias • Quantitative analysis of qualitative data limited analysts to numeric scores 	High	Medium

Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
				direct benefit and reported that they made the final decision to enroll in PIT				
Morgenstern et al. (2014) / 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	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Well-conducted analysis • Analysis performed at one of the largest cancer centers in Europe 	<ul style="list-style-type: none"> • Patients were all enrolled at one hospital in the United Kingdom • Inclusion of both phase I and phase II trials limited the applicability of the findings to this review • Small sample size 	Medium	Medium
Oppenheim et al. (2005) / 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 PIT participation	1 parent interview with a psycho-oncologist following the decision to participate in a PIT	Case report	<ul style="list-style-type: none"> • Decisions regarding PIT participation are easier when all parties involved are aware of motivations, expectations, and accepts 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 	<ul style="list-style-type: none"> • Primary author is an experienced psycho-oncologist • Interview presented is particularly profound 	<ul style="list-style-type: none"> • Single case report • Formal qualitative analysis was not performed 	Low	Medium
Paoletti et al. (2013) / A Comparative Analysis of Paediatric Dose-Finding Trials of Molecularly Targeted Agent with Adults' Trials	To assess the objectives, place and role of PITs in the era of molecularly targeted agents	19 single agent pediatric PITs of molecularly targeted agents approved in adults before 6/15/2012	Meta-analysis of previously reported PIT results	<ul style="list-style-type: none"> • 63% of pediatric patients are treated at suboptimal doses of molecularly targeted agents (less than the maximum tolerated dose) • Safety profiles described by pediatric PITs of molecularly targeted agents were usually similar to the adult population 	<ul style="list-style-type: none"> • Challenges to matching adult and pediatric trials were discussed • Included PITs conducted outside of the United States 	<ul style="list-style-type: none"> • Eligibility criteria for the pediatric and adult trials weren't compared which could have impacted the analysis 	High	Low
Shah et al. (1998) / Phase I Therapy Trials in Children with Cancer	To examine the response and toxicity rates of therapies evaluated in PITs to identify trends in response and toxicity over time	56 PITs enrolling 1,606 patients between 1978 and 1996	Meta-analysis of previously reported PIT results	<ul style="list-style-type: none"> • PITs are a safe mechanism to determine the maximum tolerated dose, toxicity profile, and pharmacokinetics of new agents 	<ul style="list-style-type: none"> • Challenges to performing the statistical comparison between PITs were thoughtfully addressed 	<ul style="list-style-type: none"> • Phase I studies involving monoclonal antibodies were excluded from analysis • Few keywords were used in the literature search 	Medium	Medium

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Author / Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
<div><ul style="list-style-type: none">• 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• Delineation between stable response versus partial response is unclear• Only toxic death rates were included in analysis, not overall toxicity rates</div>								

Note: Rigor and Relevance to purpose of the review were evaluated as 'High', 'Medium', or 'Low' (Whittemore & Knafl, 2005)

Table 3

Findings and Evaluation of Adult Articles

Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
Berdel et al. (1988) / 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 PITs and 8 patients treated with low efficacy 1–2 medication regimens off-study	<ul style="list-style-type: none"> Quantitative, cohort pilot study Linear Analog Self-Assessment and Karnofsky Performance Score used to assess QOL at four timepoints 	<ul style="list-style-type: none"> No significant negative QOL influence in PIT group Slight positive influence of PIT 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 	<ul style="list-style-type: none"> Groups were compared to ensure similarity with respect to patient age, sex, spread of disease, and previous treatments Instruments had well-established reliability and validity 	<ul style="list-style-type: none"> Study was performed at a single site in Germany Pilot study with small sample 	Medium	Medium
Campbell et al. (1999) / 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 PITs, and to determine the acceptability of the QOL instrument	15 adult cancer patients participating in a PIT during 4-week recruitment period in 1997	<ul style="list-style-type: none"> Quantitative study One individual, semi-structured interview using the Schedule for the Evaluation of Individual QOL - Direct Weighting (SEIQoL-DW) 	<ul style="list-style-type: none"> 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 PIT participants 	<ul style="list-style-type: none"> Thorough analysis of best measures of QOL SEIQoL-DW allows the patient to determine areas to be measured and provides profile of QOL values and status 	<ul style="list-style-type: none"> Study was performed at a single site in Scotland Small sample size Instrument intended to measure changes in one person's QOL over time, has limited use in comparison of QOL between different groups of patients 	Medium	Medium
Carlson et al. (2005) / 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 PIT of the novel therapeutic reovirus	16 adult cancer patients interviewed prior to being accepted into the phase I trial	<ul style="list-style-type: none"> Mixed methods study One individual, semi-structured interview of health expectations where standardized QOL, distress, and spirituality instruments were completed 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Standardized instruments had well-established reliability and validity 	<ul style="list-style-type: none"> Study was performed at a single site in Canada Small sample size Recruitment details not provided Insufficient methodological detail to validate or evaluate qualitative interview and data analysis procedures (Creswell, 2013) 	Low	Medium

Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
Cohen et al. (2007) / Phase I Participants' Views of Quality of Life and Trial Participation Burdens	To assess participants' perception of experience on PITs including associated QOL	First 100 adult patients referred to a specified PIT; and 16 patients enrolled in the PIT	<ul style="list-style-type: none"> Qualitative study completed by referred patients Hermeneutic phenomenological interview with enrolled patients 	<ul style="list-style-type: none"> Participants established their current QOL by comparison with prior cancer treatments Indirect and procedural burdens of PIT participation had a significant impact on participants' current QOL 	<ul style="list-style-type: none"> Qualitative survey was previously used 88.9% (n=18) interview participation rate 	<ul style="list-style-type: none"> Validity of survey not addressed in article or in referenced secondary article; development of survey only briefly described (Creswell, 2013) Study performed at a single site, using one PIT that was procedurally onerous Insufficient methodological detail to evaluate phenomenological interview or data analysis (Creswell, 2013) 	Medium	High
Cox (1999) / Researching 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	<ul style="list-style-type: none"> Mixed methods, longitudinal study Semi-structured in-depth interviews and instruments completed at four timepoints 	<ul style="list-style-type: none"> Trial offer meant: hope, uncertainty, and being honored 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 	<ul style="list-style-type: none"> Data collected pre-, during, and post-trial, as well as at follow-up Patients recruited from a variety of trials QOL Instruments had well-established reliability and validity 71.4% (n=77) participation rate 	<ul style="list-style-type: none"> Study was performed at one regional site in the United Kingdom Data collected impacted by low retention, and biased towards individuals willing and able to talk about their trial experiences Insufficient methodological detail to validate or evaluate qualitative data analysis procedures (Creswell, 2013) 	Medium	High
Cox (2000) / Enhancing Cancer Clinical Trial Management: Recommendations 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	<ul style="list-style-type: none"> Mixed methods, longitudinal study Semi-structured in-depth interviews and instruments completed at four timepoints 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Data collected pre-, during, and post-trial, as well as at follow-up Patients recruited from a variety of trials QOL Instruments had well-established reliability and validity 71.4% (n=77) participation rate 	<ul style="list-style-type: none"> Study was performed at one regional site in the United Kingdom Data collected impacted by low retention, and biased towards individuals willing and able to talk about their trial experiences Insufficient methodological detail to validate or evaluate qualitative data analysis procedures (Creswell, 2013) 	Medium	Medium

Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
Cox (2002) / 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	<ul style="list-style-type: none"> Mixed methods, longitudinal study Semi-structured in-depth interviews and instruments completed at four timepoints 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Data collected pre-, during, and post-trial, as well as at follow-up Patients recruited from a variety of trials QOL instruments had well-established reliability and validity 71.4% (n=77) participation rate 	<ul style="list-style-type: none"> Study was performed at one regional site in the United Kingdom Data collected impacted by low retention, and biased towards individuals willing and able to talk about their trial experiences Insufficient methodological detail to validate or evaluate qualitative data analysis procedures (Cresswell, 2013) 	Medium	High
Cox (2003) / 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	<ul style="list-style-type: none"> Mixed methods, longitudinal study Semi-structured in-depth interviews and instruments completed at four timepoints 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Data collected pre-, during, and post-trial, as well as at follow-up Patients recruited from a variety of trials QOL Instruments had well-established reliability and validity 71.4% (n=77) participation rate 	<ul style="list-style-type: none"> Study was performed at one regional site in the United Kingdom Data collected impacted by low retention, and biased towards individuals willing and able to talk about their trial experiences Insufficient methodological detail to validate or evaluate qualitative data analysis procedures (Cresswell, 2013) 	Medium	Medium
Cox et al. (1996) / 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	<ul style="list-style-type: none"> Mixed methods, longitudinal study Semi-structured in-depth interviews and instruments completed at three timepoints 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Data collected pre-, during, and post-trial from a variety of trials QOL Instrument had well-established reliability and validity 	<ul style="list-style-type: none"> Study was performed at one site in the United Kingdom Small sample size Data collected impacted by low retention, and biased towards individuals willing and able to talk about their trial experiences Insufficient methodological detail to validate or evaluate qualitative data analysis procedures (Cresswell, 2013) 	Medium	High
Cox et al. (2005) / A Randomised Controlled Trial of Nurse-Managed	To present the quantitative findings from a nurse-led strategy	117 patients (n=59 intervention group, n=58 control group) enrolled in any PIT at	<ul style="list-style-type: none"> Randomized, pre-post mixed methods intervention study 	<ul style="list-style-type: none"> No difference between groups in scores for anxiety 	<ul style="list-style-type: none"> Study was performed at two sites in the United Kingdom 	<ul style="list-style-type: none"> Data collected impacted by low retention, and biased towards individuals willing and 	Medium	Low

Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
Trial Conclusion Following Early Phase Cancer Trial Participation	for improving the management of the conclusion of patients' participation in a PIT	two medical centers within a 36-month recruitment period from 2001–2004	<ul style="list-style-type: none"> • Nurse intervention included PIT exit interview, leaflet, and follow-up call • Quantitative instruments completed at two timepoints with in-depth interview at second timepoint 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 91% (n=129) participation rate • Reliability and validity of QOL instruments considered 	<ul style="list-style-type: none"> • able to talk about their trial experiences • High attrition rate • decreased study power • Instrument developed for study did not have established reliability or validity; development and origins not discussed 		
Daugherty et al. (2005) / Trusting God and Medicine: Spirituality in Advanced Cancer Patients	To examine the role of spirituality in terminally ill cancer patients who volunteer for PITs	162 cancer patients enrolled in a PIT from 1997–1999 and 156 advanced cancer patients not participating in a PIT from 1993–1996	<ul style="list-style-type: none"> • Quantitative, cohort study • Spirituality, QOL, and decision-making instruments were completed at one timepoint by PIT group; Control group participants and data were selected from a pre-existing data set 	<ul style="list-style-type: none"> • PIT group had slightly higher levels of spirituality than the control group • In PIT group, spirituality was positively associated with QOL • Spirituality was not associated with PIT patients' awareness of their prognosis or decision-making preferences 	<ul style="list-style-type: none"> • 95% (n not provided) participation rate, representing 75% of available cancer patients • Reliability and validity of instruments considered • Significant differences between group demographics were controlled for statistically 	<ul style="list-style-type: none"> • Study was performed at a single site in the United States • Control group participants and data were selected from a pre-existing data set, limiting data available 	High	Medium
Finlay et al. (2009) / Do Phase I 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 PITs over a period of two years	<ul style="list-style-type: none"> • Quantitative, cohort study • Instruments completed at one timepoint 	<ul style="list-style-type: none"> • Compared with other patients who had cancer, patients who were participating in PITs were less likely to want home care services, although they experienced a greater symptom burden • Groups differed significantly with respect to race 	<ul style="list-style-type: none"> • 88% (n=418) participation rate • Groups were compared to ensure similar demographics, and differences in performance score were controlled for statistically • QOL Instruments had well-established reliability and validity 	<ul style="list-style-type: none"> • Study was performed at 7 clinics of a large medical center in the United States • Development, reliability, and validity of home care services instrument weren't discussed 	Medium	Medium
George et al. (2016) / Sleep Quality and Its Association With Fatigue, Symptom Burden, and Mood in Patients With Advanced Cancer in	To describe sleep quality and its relation with fatigue, symptom burden, and mood in patients recruited from an	256 patients recruited from a phase clinical I trial clinic during the 16-month recruitment period	<ul style="list-style-type: none"> • Quantitative, cross-sectional study • Instruments completed at one timepoint 	<ul style="list-style-type: none"> • Poor sleep quality was a significant problem in the current study and was associated with greater fatigue, symptom burden, and mood disturbance. 	<ul style="list-style-type: none"> • Instruments used had well-established reliability and validity • Large sample size 	<ul style="list-style-type: none"> • Study was performed at one large medical center in the United States • Inclusion of all patients being seen in an early phase clinic (including n=138 (54%) considering participating in a trial, 	High	Medium

Title	Purpose	Sample and Setting	Design and Method	Findings Related to P/T Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
a Clinic for Early-Phase Oncology Clinical Trials	early-phase clinic for targeted therapy			<ul style="list-style-type: none">Sleep quality should be routinely assessed in patients with advanced cancer who are participating in early-phase clinical trials.		investigating further therapeutic options, or receiving off-protocol therapy) limited the applicability of the findings to this review		
Godskesen et al. (2013) / Phase I 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 P/T participation, and issues associated with the information-consent process	14 patients enrolled in one of three ongoing P/Ts during the 11-month recruitment period from 2011–2012	<ul style="list-style-type: none">Qualitative, cross-sectional studyOne individual, semi-structured interview	<ul style="list-style-type: none">Patients expressed unrealistic expectations of therapeutic benefit and inadequate understanding of P/T's purposePatients valued the close and unique medical and psychological attention they received by participating.Participation made patients feel unique and notable.	<ul style="list-style-type: none">Study was performed at two university hospitals in SwedenSufficient detail provided to validate and evaluate data analysis methods (Creswell, 2013)	<ul style="list-style-type: none">Data collected impacted by low retention, and biased towards individuals willing and able to talk about their P/T experiencesLow participation rate 22.9% (n=61)	Medium	High
Helft et al. (2003) / 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 P/T within the recruitment period	<ul style="list-style-type: none">Quantitative studyOne individual, structured interview conducted within 7 days of the start of the P/T using both quantitative and semi-quantitative instruments	<ul style="list-style-type: none">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.	<ul style="list-style-type: none">95% participation rateFunctional Assessment of Cancer Therapy—General instrument had well-established reliability and validity	<ul style="list-style-type: none">Development, reliability, and validity of questions used to assess coping and understanding of prognosis weren't discussedStudy was performed at one large medical center in the United States	Low	Low
Hui et al. (2010) / Timing of Palliative Care Referral and Symptom Burden in Phase I 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	<ul style="list-style-type: none">Quantitative, retrospective cohort studySecondary analysis of data extracted from chart, including QOL instruments completed on referral to palliative care services	<ul style="list-style-type: none">Patients referred by phase I oncologists had a better performance status but similar symptom burden compared to control groupPatients phase I involvement did not delay palliative care referral, but it did increase the likelihood of receiving	<ul style="list-style-type: none">Two groups were stratified by age, sex and cancer diagnosis in a 1:2 ratioInstruments used had well-established reliability and validity	<ul style="list-style-type: none">Study was performed at one large medical center in the United StatesDifferences between groups may have been contaminated by previous consultations with phase I oncologistsData collected retrospectively, limiting data available	Medium	Low

Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
chemotherapy in the last 30 days of life								
Hutchison (1998) / Phase I Trials in Cancer Patients: Participants' Perceptions	To determine how cancer patients perceive PITs in reference to trial participation and information received	28 adult patients receiving therapy on an oncology PIT during the 3-month recruitment period	<ul style="list-style-type: none"> Quantitative study One structured interview using a questionnaire with closed questions 	<ul style="list-style-type: none"> Patients participated in PITs because they offered hope, yet expectations were still realistic Benefits related to participating in PITs including amount and quality of nursing / medical care as compared to standard treatment 	<ul style="list-style-type: none"> Questionnaire was pilot-tested prior to its use; content validity and reliability were assessed Patients recruited from different PITs • 90.3% (n=31) participation rate 	<ul style="list-style-type: none"> Study was performed at one site in Europe Patients assessed as being too vulnerable were excluded, potentially introducing selection bias 	High	Medium
Jansen et al. (2016) / 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	<ul style="list-style-type: none"> Quantitative study One structured interview using a questionnaire with closed questions 	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> 73% (n=233) participation rate Study was performed at two large cancer centers in the United States Instruments used either had established reliability and validity 	<ul style="list-style-type: none"> Recruitment details not provided Phase of clinical trial was not delineated in results, limiting the applicability of findings to this review 	High	Low
Kessler et al. (2014) / Distress Among Caregivers of Phase I Trial Participants: A Cross-Sectional Study	To assess the distress and emotion regulation of caregivers of PIT participants to inform the design of future interventions	88 caregivers of patients enrolled in a PIT during the recruitment period	<ul style="list-style-type: none"> Quantitative cross-sectional pilot study Self-administered instruments completed at one timepoint between Course 1 Day 1 and Day 15 of PIT 	<ul style="list-style-type: none"> Caregivers exhibited greater distress than population norms. Emotion regulation was also moderately impaired. Caregivers identified positive aspects of caregiving despite exhibiting moderate distress. 	<ul style="list-style-type: none"> Instruments used had well-established reliability and validity 80% (n=110) participation rate 	<ul style="list-style-type: none"> Study was performed at one site in the United States 	High	Medium
Kvale et al. (2010) / The Experience of Older Patients With Cancer in Phase I Clinical Trials: A Qualitative Case Series	To explore the experiences of older patients with cancer in PITs	4 white older adults receiving treatment on a phase I oncology clinical trial	<ul style="list-style-type: none"> Qualitative, hermeneutic phenomenology study One in-depth semi-structured interview 	<ul style="list-style-type: none"> Social comparison influences decisions to enroll in PITs, shapes perceptions of supportive care needs, and encourages use of hope Social comparison can inhibit 	<ul style="list-style-type: none"> Interview guide included Phenomenological method provided rich data Sufficient detail provided to validate and evaluate data analysis methods (Creswell, 2013) 	<ul style="list-style-type: none"> Study was performed at one site in the United States Small sample size Patients considered too vulnerable were excluded, potentially introducing sample bias Leading / closed interview questions, 	Medium	Medium

Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
<p>contrary to phenomenology (Creswell, 2013)</p> <p>articulation of pain, suffering and symptom burden</p>								
Langenberg et al. (2016) / 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 PITs and to investigate their well-being after a patient's death	58 Partners of deceased cancer patients who participated in a PIT from 2007–2009	<ul style="list-style-type: none"> Quantitative study Instruments completed at one timepoint by hand, using standardized instruments to assess well-being and one novel instrument developed for study 	<ul style="list-style-type: none"> Although partners reported negative consequences on patients' quality of life, most did not regret patients' participation in the PITs. Depression, psychological distress, and complicated grief were important problems for partners after the patient's death. 	<ul style="list-style-type: none"> Standardized instruments had well-established reliability and validity 78.4% participation rate (n=74) 	<ul style="list-style-type: none"> Study was performed at one site in the Netherlands Reliability, validity, and development of novel instrument were not discussed 	Medium	Medium
Mack (1998) / 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 PITs	20 adult patients who consented to participate in an oncology PIT	<ul style="list-style-type: none"> Qualitative, longitudinal hermeneutic phenomenology study Two in-depth unstructured interviews 	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Adhered well to phenomenological methods Study was performed at three sites in the western United States Second interview added depth, identified changes over time 95.2% (n=21) participation rate Sufficient detail provided to validate and evaluate data analysis methods (Creswell, 2013) 	<ul style="list-style-type: none"> Data collected impacted by low retention, and biased towards individuals willing and able to talk about their PIT experiences Second interview was conducted at an unclear timepoint - several weeks to months after first interview 	High	High
Melink et al. (1992) / 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 PIT and 10 patients found ineligible to be treated in a PIT from 1983–1985	<ul style="list-style-type: none"> Quantitative, longitudinal pilot study Linear Analog Self-Assessment of QOL, performance status, and survival time assessed at two timepoints 	<ul style="list-style-type: none"> Cancer patients receiving treatment in a PIT had no significant changes in QOL or performance status after one course in a PIT Patients not eligible for a PIT experienced a significant decline in overall QOL and performance status one month later 	<ul style="list-style-type: none"> Instruments used had well-established reliability and validity 	<ul style="list-style-type: none"> Study was performed at one site in the United States Data collected biased by retention, 70% (n=64) evaluation rate on phase I arm and 35% (n=28) on control arm Marked differences between groups limited analysis 	High	Medium

Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
Meyers et al. (2004) / 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	<ul style="list-style-type: none"> Quantitative intervention pilot study QOL assessed with instrument at five timepoints Monitored referral to hospice and chemotherapy cycles administered 	<ul style="list-style-type: none"> PITs 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 	<ul style="list-style-type: none"> Instruments used had well-established reliability and validity Two groups were well matched in sex and age distribution Patients were followed until death 	<ul style="list-style-type: none"> Study was performed at one site in the United States Patients were assigned to groups based on geographical location of their home, potentially creating selection bias 	High	Medium
Moore (2001) / A Need to Try Everything: Patient Participation in Phase I Trials	To describe patients' perceptions of participating in PITs	15 patients enrolled in any PIT within the 4-month recruitment period	<ul style="list-style-type: none"> Qualitative, longitudinal study In-depth semi-structured interview and open-stem questionnaires completed at two timepoints 	<ul style="list-style-type: none"> 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 PIT is meaningful by providing a supportive structure and enabling hope 	<ul style="list-style-type: none"> Data collection tools were pilot tested prior to use in this study 83.3% (n=28) participation rate 	<ul style="list-style-type: none"> Study was conducted at one site in the United Kingdom Development and origins of questionnaire not discussed and questions not provided Data collected impacted by low retention, and biased towards individuals willing and able to talk about their PIT experiences Insufficient methodological detail to validate or evaluate interview or data analysis (Creswell, 2013) 	Medium	High
Rouanne et al. (2013) / 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 PIT with molecularly targeted agents	63 patients enrolled in any PIT within the 4-month recruitment period in 2011	<ul style="list-style-type: none"> Quantitative, longitudinal study Initial consultation Questionnaires completed at two timepoints 	<ul style="list-style-type: none"> Patients enrolled in molecularly targeted agent PITs 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 	<ul style="list-style-type: none"> Instruments used had well-established reliability and validity 85% (n=74) participation rate 	<ul style="list-style-type: none"> Study was conducted at one site in France Data collected impacted by decreased retention, and biased towards individuals completing questionnaires at both timepoints 	High	Medium
Sietz (1993) / Survival Work: The Experience of the Patient and the	To describe the experiences of patients and their spouses	Purposive sample of 24 patients enrolled in an experimental trial	<ul style="list-style-type: none"> Qualitative, longitudinal, grounded theory study 	<ul style="list-style-type: none"> Primary psychosocial process of participants was survival work: the 	<ul style="list-style-type: none"> Opening questions provided, along with probing techniques 	<ul style="list-style-type: none"> All patients enrolled were participating in the same experimental therapy trial of 	High	Medium

Title	Purpose	Sample and Setting	Design and Method	Findings Related to PIT Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
Spouse Involved in Experimental Treatment for Cancer	undergoing experimental therapy for advanced cancer	during recruitment period	<ul style="list-style-type: none"> Unstructured interviews at four timepoints 	<ul style="list-style-type: none"> work of choosing life over death. Three phases of survival work were identified: (1) engaging, (2) monitoring, and (3) carrying on. 	<ul style="list-style-type: none"> Sufficient detail to validate and evaluate methods and findings (Creswell, 2013) 	chemoembolization (not a PIT) <ul style="list-style-type: none"> Participation and retention rates not discussed 		
Sun et al. (2014) / 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 PIT.	14 patients who consented to participate in a PIT during the recruitment period	<ul style="list-style-type: none"> Pre-post quantitative intervention pilot study Intervention included baseline assessment, care conference, and two tailored patient educational sessions Quantitative instruments completed at three timepoints 	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> 70% participation rate Instruments used had well-established reliability and validity 	<ul style="list-style-type: none"> Small sample size Data collected impacted by low retention, and biased towards individuals willing and able to complete the study Study was performed at one sites in the United States 	Medium	Low
Wilson et al. (2005) / 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 PITs	117 patients (n=59 intervention, n=58 control group) enrolled in any PIT at two medical centers within a 36-month recruitment period from 2001–2004	<ul style="list-style-type: none"> Randomized, pre-post mixed methods intervention study Nurse intervention included PIT exit interview, leaflet, and follow-up call Quantitative instruments completed at two timepoints with in-depth interview at second timepoint 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Study was performed at two sites in the United Kingdom 91% (n=129) participation rate Reliability and validity of QOL instruments considered Sufficient detail provided to validate and evaluate methods and findings (Creswell, 2013) 	<ul style="list-style-type: none"> Data collected impacted by low retention, and biased towards individuals willing and able to talk about their trial experiences Instrument developed for study did not have established reliability or validity; development and origins not discussed Unclear who was involved with data analysis and whether the process was collaborative (Creswell, 2013) 	Medium	Medium
Wooten et al. (2011) / A Qualitative Assessment of the Experience of Participating in a	To explore the experiences of patients enrolled in a cancer-related clinical treatment	14 patients who completed any cancer clinical trial within the past six months; 71.4% (n=10) were	<ul style="list-style-type: none"> Qualitative, pilot study Participants took part in one of three focus groups 	<ul style="list-style-type: none"> Clinical trial participation is a positive experience, although there are practical and emotional burdens. 	<ul style="list-style-type: none"> Sufficient detail to validate and evaluate methods and findings (Creswell, 2013) 	<ul style="list-style-type: none"> Study was conducted at one site in Australia Discussion guide not provided Patients assessed as being too vulnerable were 	Medium	High

Title	Purpose	Sample and Setting	Design and Method	Findings Related to P/T Experience	Primary Strengths	Primary Weaknesses	Rigor	Relevance
Cancer-Related Clinical Trial	trial using a focus-group methodology	patients enrolled in P/Ts	<ul style="list-style-type: none"> Three participants did not attend a focus group (two were interviewed and one wrote feedback) 	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Sample questions provided from questionnaires 	<ul style="list-style-type: none"> excluded, potentially introducing selection bias 46.7% (n=30) participation rate, Small sample size included patients in any phase of a clinical trial 		
Yoder et al. (1997) / Expectations and Experiences of Patients With Cancer Participating in Phase I Clinical Trials	To describe the expectations and experiences of patients enrolling in P/Ts	37 patients enrolled in any P/T during the recruitment period	<ul style="list-style-type: none"> Quantitative, longitudinal pilot study Interviews conducted with structured questionnaires pre- and post-P/T participation 	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Sample questions provided from questionnaires 	<ul style="list-style-type: none"> Study was conducted at one site in the United States Development of questionnaires only briefly described, with minimal discussion of reliability and validity Data analysis methods not described Participation and retention rates not discussed 	Low	Medium

Note: Rigor and Relevance to purpose of the review were evaluated as 'High', 'Medium', or 'Low' (Whittemore & Knafl, 2005)

Table 4

Summary of Results of Article Evaluations

Table 4A: Pediatric Articles					
		Evaluation of Rigor			
		Low	Medium	High	Totals
Evaluation of Relevance	Low	0	0	9	9
	Medium	2	3	6	11
	High	0	1	0	1
	Totals	2	4	15	21

Table 4B: Adult Articles					
		Evaluation of Rigor			
		Low	Medium	High	Totals
Evaluation of Relevance	Low	1	3	1	5
	Medium	2	8	8	18
	High	0	7	1	8
	Totals	3	18	10	31

Table 5

Comparison of Findings from the Pediatric and Adult Literature

	PEDIATRIC LITERATURE	ADULT LITERATURE
Illness-Related Distress	<ul style="list-style-type: none"> • 38–46% of pediatric PIT participants experienced a grade 3 or 4 toxicity, and 12–24% experienced a dose-limiting toxicity (1 medium and 3 high rigor articles). • Majority of children were enrolled in a PIT for less than 2 months and were removed due to cancer progression (1 medium and 2 high rigor articles). • One medium rigor article found that parents and children reported a high degree of uncertainty and unknowns associated with PIT decision-making. 	<ul style="list-style-type: none"> • Being in a PIT may influence adult participants' experience of their symptoms (2 medium rigor articles). • PIT treatment burdens included frequent hospital visits, additional medical procedures, therapy toxicities, logistical problems, and financial cost (1 high and 5 medium rigor articles). • PIT treatment burdens negatively impacted QOL and became more significant after PIT enrollment (1 medium and 1 high rigor article). • Adult participants' sense of uncertainty may be greater during a PIT due to therapy unknowns, but the structure of the PIT may also decrease uncertainty (1 high and 5 medium rigor articles).
Defensive Coping	<ul style="list-style-type: none"> • No specific evidence related to pediatric PIT participants use of defensive coping strategies. 	<ul style="list-style-type: none"> • Adult PIT participants used evasive coping by avoiding transitioning to end-of-life care or by over-relying on providers (1 high and 2 medium rigor articles).
Courageous Coping	<ul style="list-style-type: none"> • Maintaining control, normalcy, and QOL were important to parents and children considering participating in a PIT (1 medium and 1 high rigor article). 	<ul style="list-style-type: none"> • PIT participation was overall a positive experience that supported optimism and courageous coping in adults (1 high and 6 medium rigor articles).
Interaction of Defensive and Courageous Coping Factors	<ul style="list-style-type: none"> • Pediatric PIT participants and their families thought and acted like the PIT therapy would improve, or even cure, their cancer (5 high rigor articles). • Mixed evidence on how PIT participation impacts or relates to the coping strategies of children with cancer near end-of-life (2 high rigor articles). 	<ul style="list-style-type: none"> • Adult PIT participants expressed an expectation that the PIT therapy would improve, or even cure, their cancer, however it is unclear how significant a problem unrealistic optimism was for adult PIT participants (1 low, 1 medium, and 1 high rigor article). • Both defensive and courageous coping strategies were used by adult PIT participants at trial conclusion (6 medium rigor articles). • Unclear whether adults' PIT participation represented 'survival work' and hence detracted from 'death work' (1 high and 2 medium rigor articles).
Social Integration	<ul style="list-style-type: none"> • No specific evidence on how PIT participation impacted or was affected by social integration. 	<ul style="list-style-type: none"> • Therapeutic alliance formed with health care providers provided adult PIT participants with a sense of working together to achieve a common goal (2 medium rigor articles). • Societal expectations to be brave and fight to overcome cancer could influence adults' PIT decision-making (2 medium rigor articles).
Family Environment	<ul style="list-style-type: none"> • A desire to protect their parents may influence children's assent to participate in a PIT (1 medium and 1 high rigor article). 	<ul style="list-style-type: none"> • Inclusion of family members when developing the PIT plan of care enhanced communication (1 low and 1 medium rigor article).
Derived Meaning	<ul style="list-style-type: none"> • PIT participation supported hope for a cure that, in turn, enhanced well-being (1 medium and 1 high rigor article). 	<ul style="list-style-type: none"> • PIT participation supported hope that improved well-being (1 high and 6 medium rigor articles). • PIT participation provided meaning by: trying a novel therapy, helping oneself, helping others, and contributing to research advances and that, in general, adult PIT participants did not regret participating in a PIT (1 high and 4 medium rigor articles). • Premature removal from a PIT led to a loss of at least some hope for the cancer improving (3 medium rigor articles).
Well-Being	<ul style="list-style-type: none"> • QOL was an important contributing factor to PIT decision-making (1 medium and 7 high rigor articles). 	<ul style="list-style-type: none"> • No significant changes in QOL were found over the first course of a PIT (2 medium and 2 high rigor articles).