Informational Meetings for Planning and Coordinating Treatment (IMPACT)

NCT04330833

Document date: October 27, 2026

Informational Meetings for Planning And Coordinating Treatment (IMPACT)

IUSCC-0705

Multiple Principal Investigators:

Susan M. Perkins, PhD, Principal Investigator Professor of Biostatistics & Health Data Science, Indiana University, Indianapolis, IN

Verna L. Ferguson, PhD, RN, FPCN, FAAN Principal Investigator
Professor, Saint Louis University, St. Louis, MO

Karen Moody, MD, MS, Principal Investigator
Director of Pediatric Supportive Oncology, The University of Texas MD Anderson Cancer Center

Support Provided by:
National Institutes of Health/National Cancer Institute (NIH/NCI)

1.0 Introduction to IMPACT (Informational Meetings for Planning And Coordinating Treatment

In the United States, the majority of children (>60%) who die from cancer experience significant pain and emotional suffering at end of life (EOL) [1]. In addition, the pain and suffering of these children is directly related to emotional distress in their parents [2]. These children are not enrolled in hospice [3] [4] and experience excessive rates of futile, high-intensity, medical interventions (e.g., intubation, ICU admission) at EOL [5]. This finding contrasts the fact that most parents would prefer a home death for their child [6]. There is strong evidence in adults with cancer, that hospice enrollment results in less pain and emotional suffering, fewer high-intensity medical interventions, and reduced caregiver emotional distress [7-9]. Also in adults, there is evidence that early EOL discussions facilitate longer hospice enrollment (>3 days) which is associated with better ratings of EOL care and greater likelihood that care is congruent with patient preferences [10]. In parents of children with cancer, early EOL discussions fosters hope and emotional support and reduce uncertainty [11], however no evidence-based interventions have been studied to foster early hospice enrollment or to reduce pain and emotional suffering in children with cancer.

IMPACT is a multisite cluster-randomized clinical trial that trains Care Team dyads to use a communication-based intervention about palliative care/end of life (PC/EOL) with the parents of poor-prognosis (<25% survival rate) pediatric cancer patients' to test effects on child end-of-life outcomes (i.e., hospice enrollment, high-intensity medical interventions, pain and suffering) and parental outcomes (i.e., emotional distress, uncertainty, hope, and healthcare satisfaction). The Care Team dyad consists of one physician intervener (MD or DO) and one RN/APP intervener (Registered Nurse or Advanced Practice Provider).

2.0 Preliminary Data and Rationale for Current Study Based on the ORBIT Model

Our prior work supports this Phase III efficacy RCT to evaluate COMPLETE (Communication Plan: Early through End of Life) [12]:

Study 1, Bereaved Parents' Perspectives (ORBIT 1A) (Oncology Nursing Foundation). In a qualitative study, we interviewed 28 bereaved parents of a child with brain cancer about memories of their providers' conversations about hospice care. Parents reported receiving hospice information near the child's death (96%), insensitive communication regarding EOL care (50%), and desire for earlier EOL discussions (~50%) [13]. These findings support early timing of COMPLETE and trained providers who empathically discuss EOL care.

Study 2, Phase 1 Expert panel for training and intervention development (ORBIT 1B) (NIH R21 NR011071-02). We developed the COMPLETE intervention to address parent-identified needs from Study 1 during a two-day workshop, with national experts (i.e., Pam Hinds; Richard Frankel). Then, to train Care Team dyads to deliver COMPLETE, we created 3 pediatric cases for bereaved parents to role-play with Care Team dyads and received feedback. Care Team dyads reported training was sufficient for them to deliver COMPLETE and it enhanced their EOL communication skills [14].

Study 2, Phase 2 COMPLETE I Prospective, 2-site, single-group pilot (ORBIT 2A) (NIH R21 NR011071-02). We evaluated acceptability, feasibility, and preliminary effects of COMPLETE with 13 parents of 11 children with high-grade malignant brain tumors. Enrollment rate was 92%. COMPLETE was feasible/acceptable and parents reported very high satisfaction with healthcare. COMPLETE I was associated with positive parental changes (Cohen's d post-intervention, p-value for overall time effect): significantly increased hope (d=0.7, p=<.0001); significantly decreased uncertainty (d=2.4, p=0.04), a trend towards decreased emotional distress (d =1.9, p=0.06), and significantly diminished pain (d=2.1, p<0.02) and procedural anxiety (d=3.4, p=<.0001) in their

children [15]. In post-intervention interviews, parents reported many positive benefits, including having: realistic hope and goals for their child, meaningful dialogue with their child's oncology providers, and future EOL options prior to a health crisis [16]. Sessions were integrated into regularly scheduled appointments, thus, 100% of sessions were attended.

Study 3, COMPLETE II Phase 1 Training and intervention refinement (ORBIT 1B/2A). Based on COMPLETE I results and consultation with VitalTalk expert Bob Arnold, we incorporated state-of-the-science EOL communication skills into COMPLETE intervention training [17]. Training refinements included: 1) 3 days training for Care Team dyads to improve collaboration and delivery; 2) trained actors (vs. bereaved parents) to role-play patients; 3) booster communication skills training to support Care Team dyad's use of empathic statements and family goals and values assessment; 4) inter-professional collaboration training; and, 5) off-site retreat center training to ensure focused time for interprofessional team-building and learning. Revised training resulted in improved use of empathic statements (11% vs. 100%; p<.002), and improved clinician self-assessed preparedness for these discussions vs. baseline (25% vs. 100%; p=.0003).

Study 3, COMPLETE II Phase 2 Feasibility, acceptability and effect sizes of intervention (ORBIT 2A/2B). (Walther Cancer Foundation) The revised COMPLETE intervention and training was implemented with 3 Care Team dyads who delivered COMPLETE II to a sample of 6 parents of children with poor prognosis cancer. Compared to COMPLETE I pilot, our evaluation of audio-recorded COMPLETE delivery demonstrated increased use of empathic statements, intervention fidelity, and inter-professional collaboration by Care Team dyads. Among children in COMPLETE I & II, 83% enrolled in hospice (median 30 days) vs. the national average of 40% and only 17% received high-intensity medical interventions at EOL care vs. the national average of 60%. Although non-significant due to small sample size parent and child clinical outcomes trended in the expected directions with increased parental hope, decreased parental uncertainty and decreased pain in the children. Healthcare satisfaction remained high throughout.

Study 4, Attention Control (ORBIT 1A/1B). MPI Ferguson served on the Children's Oncology Group (COG) and NCI funded (U10CA180886, PI Adamson) Systematic Review Study Panel to evaluate published patient/parent educational-delivery methods and parent-education needs during pediatric oncology care. At the 2015 COG sponsored State of the Science Symposium: Patient and Family Education in Pediatric Oncology in Dallas, TX, the panel presented evidence for 10 teaching strategies for education of parents of newly diagnosed children with cancer [18]. The Program A (Attention Control) protocol is based on these teaching recommendations and content in the NCI parent handbook.

Study 5, Infrastructure for COMPLETE intervention training (ORBIT 1B). (IU Health Values Grant) Haase collaborated with physicians from IU School of Medicine to build critical infrastructure to train MDs and RNs across the IUPUI health science campus to use VitalTalk PC/EOL communication skills. In total, we trained >100 RNs and MDs employed by IU Health over 2 years with high-training satisfaction. Based on our success, we received increased requests and institutional financial support to provide training across 5 hospitals in the IUPUI health science campus and we have a cadre of professional actors to serve as simulated patients/family members. In addition, study collaborators Haase, Moody, Fettig, and Newton completed the "VitalTalk Train-the-Trainers" curriculum in Aspen, CO.

3.0 Background and Rationale

3.1 Scientific Premise

Most children (>60%) who die from cancer are not enrolled in hospice at end-of-life (EOL)[3, 4] even though parents prefer a home death for their child [6, 19, 20]. These children unnecessarily

suffer from significant pain and emotional suffering related to high-intensity medical interventions at EOL [1, 21, 22]. High-intensity medical interventions include: emergency room visits, hospital or ICU admission, intubation and/or cardiac resuscitation within 30 days of death; lack of or <3 days hospice enrollment at EOL, IV chemotherapy within last 14 days of life, or death in acute care setting. All are markers of poor-quality care at EOL as defined by the National Quality Forum [23]. This dismal child EOL situation exists despite ample evidence that adult hospice enrollment provides the best care at EOL by reducing pain and emotional distress. It is also associated with fewer high-intensity medical interventions, greater emotional support for patients, and better caregiver bereavement outcomes [7, 24]. In addition, several studies demonstrate that early and ongoing goals-of-care conversations with adults facilitate earlier hospice enrollment and longer time in hospice provides greater benefits than brief time [25]. Despite evidence favoring hospice in adults, there are no effective intervention studies to improve hospice enrollment and decrease suffering in children with cancer at EOL. IMPACT is the first randomized control trial (RCT) aimed to improve hospice enrollment, reduce child physical and emotional suffering and parent distress at EOL. IMPACT provides a series of timely discussions of prognosis, values, goals of care, and advance-care planning between parents of children with poor prognosis cancer and their primary oncology Care Team dyads during routine clinical care.

3.2 NIH-relevant Problem

The NQF, Institute of Medicine (IOM) and the American Cancer Society reported at the "Comprehensive Cancer Care for Children" conference an imperative need to improve and expand early integration of pediatric PC; prioritize EOL communication that supports family shared-decision making and goal-concordant treatment; improve access to hospice; and train healthcare providers to initiate discussions of goals of care earlier in the cancer trajectory [26]. Similar recommendations to integrate early goals-of-care conversations and hospice care for children with cancer are set forth by the National Hospice and Palliative Care Organization [27] and the American Academy of Pediatrics [28]. The National Institute of Nursing Research identified palliative care (PC) and EOL care as research priorities for the 21st century with a focus on improving Care Team dyad communication with families. These organizations also indicate that Care team dyads have an ethical responsibility to inform parents of all treatment options, cure-directed and PC, at diagnosis and to initiate timely advance-care planning discussions, such as assessing location preferences for a child's EOL care [28]. This study addresses an important public health concern and aligns with the urgent national priority to improve palliative care (PC) and EOL care for children with cancer.

Hospice provides the best EOL care. Hospice care is designed to give supportive care for persons in the final stages of terminal illness and focus on comfort and QOL rather than cure. The goal is to enable patients to be comfortable and free of pain so that they can live each day as fully as possible. Hospice enrollment is an important quality indicator of EOL care in adults and is associated with better QOL at EOL [29]. These effects are enhanced with hospice enrollment >14 days [30]. In a large study comparing EOL experiences of adult patients with and without hospice, bereaved family members reported those enrolled in hospice had fewer unmet needs regarding pain management and emotional support. They were treated with greater respect and gave better ratings of care [7]. The benefits of hospice include better symptom management, reduced caregiver distress, and greater likelihood that patients' wishes will be honored [24].

The Medicaid hospice benefit allows for cure-directed and comfort-directed care simultaneously; thus, parents do not have to give up treatments (e.g., chemotherapy) for their

child in order to get hospice services [31]. Several US and international reports found the majority of parents would prefer a home death for their child [6, 19, 20]. Parents who use home-based PC report it to be a positive experience and they are able to spend more time with their dying child, have easier sibling care, and can grieve at their own pace at the time of death [32]. In a retrospective survey of bereaved parents, children who received home-based PC or hospice care were more likely to have more fun and meaningful activities, such as attending school and taking trips compared with children receiving usual care [33]. When a child's death occurs in home hospice care, parents report greater satisfaction with healthcare and improved bereavement outcomes [1, 19, 34]. IMPACT aims to facilitate hospice enrollment through repeated discussions of benefits and burdens associated with each goal-of-care option.

Children experience pain and suffering at EOL. There is strong evidence that children with cancer suffer from pain and uncontrolled symptoms at EOL and their parents consequently suffer as well [2, 35]. Studies of bereaved parents found children die from cancer in moderate to severe distress from pain, anxiety, and other symptoms [1, 36]. A prospective study confirmed this finding with child self-reports at EOL, wherein approximately 50% reported poor or fair QOL; 58% reported poor physical function; and 60% suffered distress from >10 symptoms [35]. Also, greater symptom burden and more inpatient days predict worse QOL near EOL [37]. The high-intensity medical interventions common in children with cancer at EOL are: mechanical ventilation and death in an acute care setting and these interventions are associated with poor QOL at EOL [22, 25]. Providers also rate EOL care better when high-intensity medical interventions are avoided and when children have less pain [38]. An RCT of electronic patient-reported feedback aimed to reduce symptom burden in children with advanced cancer improved QOL scores; however, these changes were not statistically significant [39]. IMPACT is the only other clinical trial that aims to reduce child pain and suffering at EOL.

Children's EOL care is not consistent with parents' preferences. Since home hospice is frequently the preferred EOL care location by children, parents, and clinicians [28], [40], there appears to be a disconnect between parent preferences for treatment and the actual care children receive at EOL as most die in an acute care setting. In a cross-sectional survey of providers and parents regarding the goals of care for children with advanced cancer, not surprisingly, there was poor alignment between parents and providers regarding prognosis and goals of treatment [41]. Observational studies in adults and children provide evidence that QOL at EOL is improved for patients when care is goal-concordant and comfort-focused [11, 38]. It is clear that providers and parents want to avoid high-intensity medical interventions at EOL. However, providers often do not have appropriate PC/EOL communication skills to guide families towards realistic comfort-focused interventions, as a result provider often postpone EOL discussions until very late. In fact physicians are aware of terminal prognosis on average 3 months earlier than parents [1, 42]. IMPACT aims to reduce the use of high-intensity medical interventions at EOL through early and ongoing discussions of goals of treatment to improve realistic goals-of-care alignment between parents and providers.

Timely goals-of-care discussions are lacking in pediatric oncology. Bereaved parents report unmet PC/EOL information needs, dissatisfaction with how providers communicate prognosis, and inadequate time allotted to have these conversations [43, 44]. In a study of bereaved parents of children with brain cancer, 14% reported having no EOL discussions, 50% thought information was conveyed in an insensitive manner, and 96% first received EOL information during their child's last week of life [13]. Even when providers do engage in

prognostic discussions with parents, critical elements to inform medical decision-making such as identifying goals of care and family values, are often lacking. Current pediatric oncology practice simply does not routinely incorporate the early, on-going, and in-depth discussions needed to achieve goal-concordant care [45, 46]. Yet, we know that parents and children want open and honest communication with their providers regarding prognosis and PC [47], [43],[48], [49]. Reasons why goals-of-care conversations do not routinely occur include physician and RN/APP provider misconceptions, distress, and overall lack of training. Prognostic uncertainty has also been cited as a barrier to these conversations, however, most of the time physicians can ascertain when a cure is realistic or not [50]. Many providers think honest disclosure of poor prognosis will take away patients' hope and cause them to feel depressed and referral to hospice will decrease the patient's survival. Evidence suggests the opposite is true; honest prognostic disclosure improves parental hope, and hospice involvement can actually extend survival [51, 52]. Providers' personal experiences of distress related to these difficult conversations can also prevent them from happening [50]. Pediatric oncology nurses report fear and poor self-efficacy related to these conversations as well as limited opportunities for training to improve their skills [53, 54]. Seventy percent of pediatric oncologists report feeling very anxious about EOL conversations [55]. Pediatric oncology training does not appropriately prepare providers to have these conversations. In a national survey of pediatric oncology program directors, 79% reported that more education and training in goal-setting with patients is needed [55, 56].

Skilled goals-of-care conversations can improve hospice enrollment. Many studies in adult cancer patients show that conversations about prognosis and advance-care planning are associated with less aggressive treatment near death, earlier hospice enrollment, and improved QOL at EOL [8, 11, 25, 57]. These conversations help to align goals of care with realistic prognosis which leads to goal-concordant care at EOL. Goal-concordant care is a central component of high-quality EOL care and is defined as treatments that support patient-identified realistic goals and respects patient-identified treatment limits [58]. Goal-concordant care is associated with better QOL at EOL and better bereavement outcomes in surviving family members [45]. Recent RCTs to improve goal-concordant care at EOL using new strategies for communication training of providers had promising findings [59-61]. Collectively, these RCTs found that compared with usual care, patients participating in goals-of-care conversations with trained providers were significantly more likely to enroll on hospice, less likely to visit the emergency department or to be admitted to the hospital at EOL, and were more satisfied with EOL care. Effective training for PC/EOL skills includes using standardized patient actors, multiple-day workshops, video or audio-recordings of providers, and feedback to providers. These methods result in increased physician use of empathic statements; effective use of silence and reflective listening; and use of clear prognostic statements [61-64]. In addition, we know this training of physicians in EOL discussions improves their confidence, and sense of personal accomplishment [65]. COMPLETE uses evidence-based communication training and tools to adequately prepare pediatric oncology physician and RN/APP providers to engage in goals-of-care discussions with parents. In retrospective pediatric studies, hospitalized children with cancer who received PC consultation (versus no consultation), including goals-of-care conversations, had fewer high-intensity interventions at EOL, more documented do-not-resuscitate (DNR) orders, and improved pain management [66]. Furthermore, earlier goals-of-care conversations (>30 days prior to death), resulted in significantly greater odds of the child dying in home hospice versus an intensive care setting [67]. Currently 1/3 of children's hospitals do not have access to PC specialists, therefore pediatric oncologists must deliver primary PC, including goals-of-care

discussions. IMPACT is the first study to train pediatric oncology Care Team dyads to conduct early and ongoing goals-of-care discussions with parents that balance honesty with empathy.

Parents experience significant distress directly related to their child's EOL experience. Bereaved parents report more ongoing distress if their child had unrelieved pain and a difficult moment of death [2]. Bereaved parents' suffering and poorer outcomes are also associated with lower ratings of the quality of care, and feeling less prepared for their child's death [68]. Parents whose children die at home with appropriate home care experience better psychological and social adjustment and less traumatic distress than parents whose children received EOL care in the hospital [34, 69]. Emotional distress experienced by some bereaved parents is related to receiving non-empathetic forms of provider communication [13]. Specifically, avoidance of prognostic disclosure by providers to parents of critically ill children is associated with parental distrust with providers, anger, and general feelings of betrayal [44]. Eliminating all suffering of parents with children with cancer is unrealistic; however, honest EOL communication, skillfully delivered would provide additional emotional support and help alleviate some aspects of emotional distress. Parents report that clear and honest EOL conversations promote peace of mind and reinforces their highly-valued roles as expert care providers and primary decision makers for their child's care [51, 70],[44], [71]. To decrease distress, IMPACT gives parents multiple opportunities to ask clarifying questions, process emotions, and receive emotional support from their child's medical team.

When parents receive honest prognostic information, they report more hope and less uncertainty [72],[73]**.** Parental uncertainty often occurs due to receiving too little, too much, or unclear information; confusion regarding treatment options; and unpredictability of cancer sequelae, including death [74],[75]. Parents report that not having information is more upsetting than knowing prognosis, even when prognosis is poor, because the uncertainty is so unsettling [44]. Bereaved parents report feeling unprepared for their child's death due to a lack of timely and clear prognostic information [13]. In contrast, when frank prognostic disclosure occurs, parents have improved hope and relief of uncertainty and shared-decision making is facilitated [74]. When parents understand terminal prognosis earlier, they are more likely to enroll their children in hospice with a goal of comfort care and satisfaction with healthcare is higher [1]. Parents of children with a terminal cancer prognosis often still focus on cure; however, if they were guided by healthcare providers to understand that cure is unrealistic, they could broaden their focus of hope to include improving QOL, being pain-free at EOL, and having a peaceful death [76, 77],[46]. Hope is a recognized universal coping strategy of parents of children with cancer and is characterized as having multidimensional elements (e.g., positive outlook, feeling of wellbeing, expectation of realistic goal attainment). With the exception of our two pilot studies, which showed improved parental hope and reduced uncertainty, there are no prospective studies of interventions to address uncertainty and hope in parents of children with cancer [78].

Therapeutic alliance is strengthened by high-quality EOL discussions and positively impacts care-giver outcomes [79]**.** Therapeutic alliance is characterized as shared decision-making goals, mutual understanding, caring, trust, respect, acknowledgement of patients' personhood, and provider honesty and competency [80]. In adult oncology patients, therapeutic alliance is inversely associated with psychological symptom burden and high-intensity interventions at EOL. It is also positively associated with patient's feelings of support, existential well-being, and emotional acceptance of terminal illness [80]. Parents of children newly diagnosed with cancer report that high-quality information about prognosis bolsters trust in their physician [81]. There are no prospective studies of interventions to foster parent/provider

therapeutic alliance in pediatric oncology [78]. COMPLETE Care Team dyad PC/EOL communication training and intervention strategies (e.g., hope and non-abandonment messaging and visual aids) strengthen the Care Team dyad /parent relationship to increase therapeutic alliance.

3.3 Objectives and Outcomes

3.3.1 Primary Aim

Aim 1: Determine the efficacy of COMPLETE versus usual care to foster hospice enrollment.
Hypothesis 1: Compared to usual care, children on COMPLETE arm will enroll earlier in hospice.

3.3.2 Secondary Aims

Aim 2: Determine the efficacy of COMPLETE on child outcomes: pain and emotional suffering; and use of high intensity medical interventions at EOL.
Hypothesis 2: Compared to usual care, children exposed to COMPLETE will have reduced pain and emotional suffering throughout their trajectory and at EOL, and less use of high-intensity medical interventions at EOL.
Aim 3: Determine the efficacy of COMPLETE on parent outcomes: emotional distress, uncertainty and hope, and satisfaction with healthcare.
Hypothesis 3: Compared to usual care, parents exposed to COMPLETE will have less emotional distress and uncertainty, more hope and greater healthcare satisfaction throughout their child's trajectory, including EOL.

3.3.3 Exploratory Aim

Aim 4: Examine the extent to which the effects of COMPLETE on child and parent outcomes are mediated through therapeutic alliance and goals-of-care alignment
Research Question: What percent of variance observed in outcomes are explained by therapeutic alliance and goals-of-care alignment?

4.0 Eligibility

4.1 Inclusion Criteria and Rationale

Children meeting all criteria are eligible:

1) age 1 month to less than 18 years. Children who were enrolled on study before the age of 18 will continue to be eligible even if they reach 18 years or older while on study.
2)

- **newly diagnosed**, defined as being within 16 weeks (112 days) from the time of diagnosis of cancer not including the day of diagnosis [Newly diagnosed timing is based on national recommendations for introducing PC/EOL discussions with parents of children with poor prognosis cancer at diagnosis[82]];

  OR

- **relapsed cancer**, defined as within 16 weeks (112 days) of first-time relapse/evidence of progression of disease as noted by scan or biopsy after previous diagnosis of cancer.

3) Diagnosis of poor prognosis cancer defined as *approximately* <25% estimated overall survival, or at the discretion of attending with documentation of appropriate rationale for determination of

poor prognosis [PC/EOL interventions are most relevant to parents of children with poor prognoses]

AND/OR

4) Cancer falls into the following diagnosis categories, ***including but not limited to***:

Central nervous system tumor:
- Atypical teratoid rhabdoid tumor
- Glioblastoma multiforme
- Diffuse intrinsic pontine glioma
- Embryonal tumors with multilayered rosettes
- Other high-grade glioma
- Gliomatosis cerebri

Non-neural solid tumor:
- Metastatic hepatoblastoma (depending on location)
- Metastatic osteosarcoma
- Metastatic Ewing's sarcoma
- Metastatic rhabdomyosarcoma
- Metastatic desmoplastic small round cell tumor (DSRCT)
- Other metastatic sarcoma/carcinoma – at discretion of attending
- Metastatic unknown primary, rare pathology – ***at discretion of attending***.

Any questions or uncertainty about patient eligibility related to diagnosis will be discussed with MPIs.

5) Assent obtained from children ≥7 years old for their own and their parent/guardian's participation, although this age may differ across performance sites as a result of variations in state law and/or local institutional policy. Children will be asked to complete measures; they are not required to participate in sessions but can attend if parent agrees (COG IRB guideline; COG, 2010).

Parents/guardians meeting all the following criteria are eligible:

1) the decision maker(s) for their child [intervention expected to facilitate decisions by parents/legal guardians];
2) ≥18 years of age [likely to be mature enough to make difficult decisions];
3) biological parent(s), stepparent, or legal guardian (e.g., adoptive parent) [generalizability];
4) child meets inclusion criteria;
5) informed of child's cancer diagnosis [need to be informed of diagnosis prior to informed consent]; and
6) able to read, speak, and understand English [beyond scope of this first efficacy study to deliver and monitor intervention in other languages].
7) Must be willing to be audio recorded during all study sessions.

4.2 Exclusion Criteria

The child and parents will be excluded if:

1) parent has neurological and/or cognitive impairments likely to interfere with study participation.
2) the child ≥7 years old does not provide assent.
3) parent refuses to be audio recorded (if there is a 2nd parent who agrees to be recorded, that parent and the child would still be eligible)

5.0 Research Design, Methods, Procedures

Study Design. This is a multi-site, 2-group, cluster-randomized controlled trial, with clusters randomized by pediatric oncology practices. Cluster randomization is to prevent contamination across study conditions within Care Team dyad collaborative practices. As shown in Figure 3, the 2 groups are Attention Control (Program A) and COMPLETE intervention (Program B). Parent and child outcomes are assessed at baseline, post-intervention and approximately every 1-4 months post-intervention, depending on clinical status and treatment protocol, until EOL/EOS.

Participant Enrollment and Randomization

Figure 3. Study Schema

Cluster randomize Care Team Dyads	
Program A: Attention Control	Program B: COMPLETE Intervention
Parent(s)/Child recruit, enroll, consent/assent post diagnosis or first relapse	Parent(s)/Child recruit, enroll, consent/assent post diagnosis or first relapse
T1: Baseline data prior to Session 1	T1: Baseline data prior to Session 1
Session 1: After T1 baseline data collection.	Session 1: After T1 baseline data collection.
Session 2: approx. 1-4 mos. after Session 1	Session 2: approx. 1-4 mos. after Session 1
Session 3: approx. 1-4 mos. after Session 2	Session 3: approx. 1-4 mos. after Session 2
T2: Post-intervention data approx. 1-3 weeks after Session 3	T2: Post-intervention data approx. 1-3 weeks after Session 3
T_F: Follow-up data approx. every 1-4 mos. after T2	TF: Follow-up data approx. every 1-4 mos. after T2
T_{EOS}: post-death or end-of-study	T_{EOS}: post-death or end-of-study

T=time point; F=follow-up; EOS=end of study; mos.=months

5.1 Parent and Child Recruitment and Consent/Assent

At all sites, Care Team dyads will identify eligible participants from their practices and the site project manager (PM) will confirm eligibility. The Care Team dyads will then assess parent(s) interest (and that of the child, if age appropriate) and subsequently one of the study team members will obtain written informed consent from parent(s) and signed assent from child participants ≥7 years old. Although both parents are not required to participate, both parents are considered subjects if they both consent to participate. If one parent consents and another parent does not wish to consent to participate in the study but does wish to be present during

the intervention sessions, then a form providing permission to be audio-recorded will still be required, as all sessions are audio-recorded.

5.2 Setting

As in our other NIH-funded, multi-site RCTs, we selected sites based on a key personal interview, survey data, and responsiveness to requests. We considered the number and diversity of study-eligible children over the past 2 years; commitment of at least 2 pediatric oncology physicians and 2-4 RN/APPs willing to participate regardless of randomized group assignment; qualifications and commitment of Site-PI; availability of evaluators; administrative commitment for Care Team dyad intervener training and flexibility to deliver the intervention.

All participating sites are academically affiliated, have pediatric oncology programs seeing on average 45 patients yearly, and draw from large catchment areas. All sites are Children's Oncology Group (COG) members using standardized therapeutic protocols. Similar to our pilot studies, most activities will occur during regularly scheduled outpatient visits. Medical and nursing hospital executives from all sites provided written commitments to support and facilitate conduct of our study. All sites verified dedicated private space for intervention delivery and ability to care for unsupervised children when intervention sessions are delivered without the child's presence.

5.3 Randomization

Across the sites, the neuro-oncology and non-neuro solid tumor pediatric oncology sub-specialty practices will be randomized to Program A (Attention Control) or Program B (COMPLETE) using covariate constrained randomization [83] based on:
1) previous PC/EOL communication skills training,
2) number of patients seen annually per Care Team dyad, and
3) each team's disease subspecialty (CNS vs. non-CNS solid tumor).

All possible allocations of Care Team dyad will be calculated, then the list will be limited to those that meet pre-specified criteria for balance. The actual allocation will then be chosen randomly from this acceptable list.

6.0 Study Procedures

6.1 Program A (Attention Control) and Program B (COMPLETE)

Commonalities across Program A and B include:
1) The Care Team dyad is the primary oncology team;
2) intervention delivered by protocol-trained Program A or Program B interveners;
3) intervention delivery integrated into routine clinical encounters;
4) clinician-led intervention discussion based on parent's preferences for information;
5) same number and length of intervention and evaluation sessions;
6) same intervention timeframes -three sessions delivered post-diagnosis, or after first time relapse/evidence of progressive disease and aligned with child's treatment evaluations;
7) same outcome measures and time points;
8) all intervention and evaluation sessions audio-recorded to facilitate collection of behavioral outcome data and to monitor protocol fidelity, and
9) families receive a $20 gift card at each time point for completing measures.

6.2 Program A - Attention Control (also referred to as Enhanced Usual Care Control) Description

Program A, attention control parent education, is designed to enhance data-collection sites' current education practices for parents of newly diagnosed children. All parent sessions will be audio-recorded. Audio recordings from the IMPACT study sessions may be transcribed and de-identified for use in a future retrospective study examining elements of the attention control session.

A subset of recordings will be systematically reviewed for quality assurance monitoring throughout the study. Program A includes: 1) the 2016 Children's Oncology Group (COG) Expert Consensus Panel evidence-based recommendations for delivery of education to parents of newly diagnosed pediatric oncology patients; and 2) the National Cancer Institute (NCI) on-line parent resource handbook titled: "The Child with Cancer: A Parent's Guide." Program A content is based on the NCI Parent Handbook and the COG recommendations.

Figure 1. Table of Contents: *Children with Cancer, A Guide for Parents*

Introduction 1

DIAGNOSIS
Types of Childhood Cancer 2
Diagnosing and Staging Cancer 4
Talking With Your Child 8

TREATMENT
Hospitals That Specialize in Treating Children With Cancer 14
Clinical Trials 23
Cancer Treatments and Side Effects 30
Common Health Problems 45

SUPPORT
Finding Ways to Cope and Stay Strong 52
Helping Your Child to Cope 55
Helping Brothers and Sisters 60
Getting Organized 63

LIFE AFTER
Survivorship and Follow-up Care 66
If Treatments Aren't Working 72
Looking Forward 75

RESOURCES
Practices That Help Children: Integrative Medicine Approaches 76
Medical Tests and Procedures 79

Parents will receive an in-person or remote session (with or without child present at parental discretion) approximately every 1-4 months depending on the child's clinical course and/or treatment protocol, for a total of 3 sessions. At each session, parents choose 2-3 topics to review with the RN/APP intervener. COG recommended NCI topic areas included for parents to choose from are shown in Figure 1: a) diagnosis b) treatment; and c) support.

Program A delivery strategies based on the 2016 COG Expert Consensus Panel recommendations include: (a) assessing parents' readiness to learn; (b) sharing information based on parents' identified priority learning needs; and (c) providing multimedia information via verbal and written formats; (d) providing appropriate parent education internet resources [e.g. NCI link to the full parent handbook]; (e) providing ample time for parents' to ask questions and process shared information; and (f) providing opportunities to repetitively receive information. Copies of printed topics selected from the NCI parent resource will be shared with parents during Program A sessions. The NCI parent resource handbook is publicly accessible and free via the NCI website.

6.3 Program B (COMPLETE) Intervention Description

Program B is a PC/EOL communication intervention delivered over three approximately 1-hour sessions with parents (and child at parental discretion) enrolled in the study. Parents and children have varying degrees of comfort with discussions of cancer treatment and prognosis. Current standard of practice is to allow parents to have ultimate decision regarding whether their child will remain present for these discussions. In our study, we will follow this standard practice.

Program B is delivered by inter-professionally trained Care Team dyads, who will deliver the intervention to the parents of patients from their practice who have enrolled on the study. Research has shown that incorporation of the primary oncology team is necessary to improve goal-concordant care. We have therefore chosen to use the primary oncology Care Team dyads to deliver the intervention to their patients' parents.

The first COMPLETE session will occur during the first and routine discussion with parents regarding the child's cancer treatment plan. Sessions 2 and 3 will coincide with the next two treatment response evaluation discussions (approximately 1-4 months post Session 1 depending on child's clinical course and/or treatment protocol). Sessions will be audio-recorded to facilitate collection of behavioral outcome data and to monitor protocol fidelity. Audio recordings from the IMPACT study sessions may be transcribed and de-identified for use in a future retrospective study examining elements of the intervention.

Table 1. *REMAPS / COMPLETE Intervention*

	Strategy	Key Elements
R	RAPPORT / REVIEW / REFRAME	• Ask family how they are doing currently • Ask-Tell-Ask: Diagnosis • Ask-Tell-Ask: Treatment • Ask-Tell-Ask: Prognosis (using percentages) • Review Slides 1 and 2 with family
E	EXPECT EMOTION	• Provide realistic hope messages • Provide non-abandonment, "we" messages • Use VitalTalk NURSE Statements (Naming, Understanding, Respecting, Supporting, Exploring)
M	MAPPING / MEANING	• Ask what matters most to the child/family (values) • Ask about the child/family's hopes, worries, fears, concerns • Reflective Listening
A	ALIGN GOALS	• Review Slide 3: Experiences of Other Families • Introduce concept of goals of care • Establish specific goals of care for child and family (where are we on Slide 3?) • Demonstrate sensitivity to the fact that families have dual goals of care (i.e. cure & comfort)
P	PLAN	• Discuss treatment options consistent with child's prognosis and family's goals of care • Determine a plan for moving forward based on goals of care, values & hopes • Discuss recommendations for treatment (i.e. cancer directed therapy, antibiotics, transfusions, etc) • Introduce, explain, and discuss parental preferences for breathing machines and CPR/DNR
S	SYNOPSIS / SUMMARY	• Ask child/family if they have any questions • Express gratitude to child/family • Reassure presence and support of clinical team • Give slides to family for future reference • Plan next visit

COMPLETE is a series of 3 PC/EOL discussions with the purpose of improving parental comprehension of the options for goals of treatment, along with the benefits and burdens of each option. This discussion is facilitated by training Care Team dyad interveners to balance honesty with empathy while following the "REMAPS" guide (Table 1) in their discussions with parents. The "REMAPS" guide contains all elements of COMPLETE that are included in the quality assurance monitoring checklist. REMAPS stands for: R-rapport, review, reframe; E-expect emotion; M-mapping and meaning; A-align goals; P-Plan, and S-Summarize, Synopsis. Each of these REMAPS elements can be tailored for each family based on the child's disease status and the parent(s)' preferences. In addition, three visual figures are incorporated in these discussions to help with comprehension. These include: Figure 2. Fostering Therapeutic Alliance, Figure 3. Building Rapport, and Fig 4. Experiences of Other Families.

Because intervention delivery is integrated into routine clinical encounters, the venue/format of the intervention will generally mirror that of the clinical encounter. In other words, if the clinical encounter occurs via videoconference, the intervention will most likely also be conducted via teleconference. If treatment evaluation appointments occur in-person at the clinic or hospital, then the intervention session will most likely occur in-person as well.

Figure 2. Fostering Therapeutic Alliance

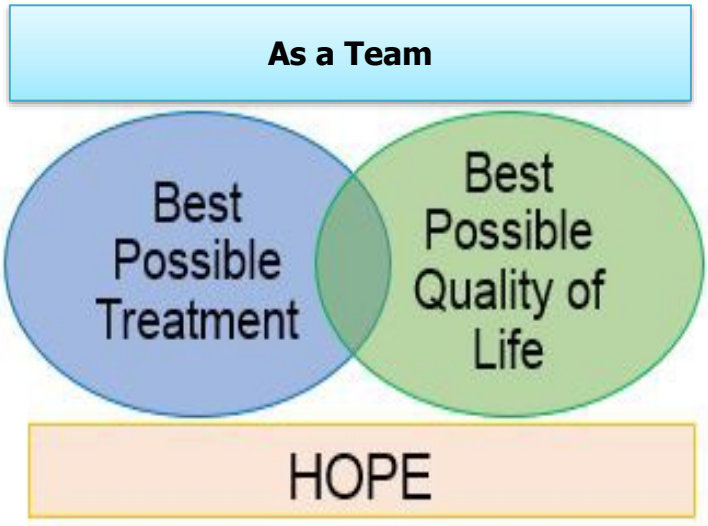


Figure 3. Building Rapport

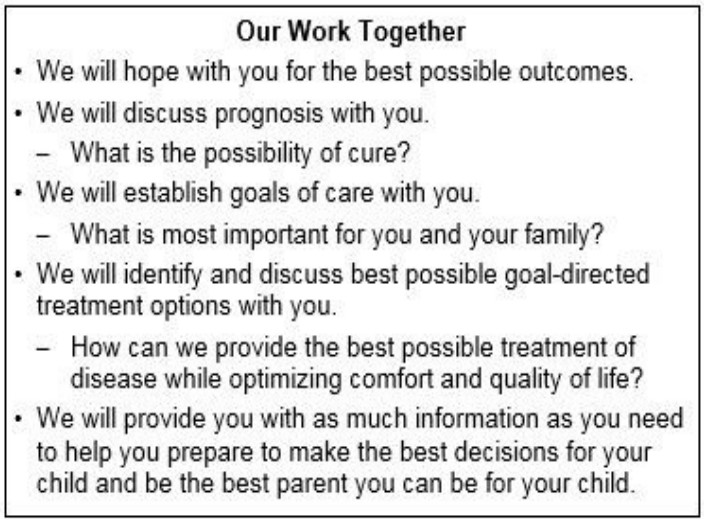
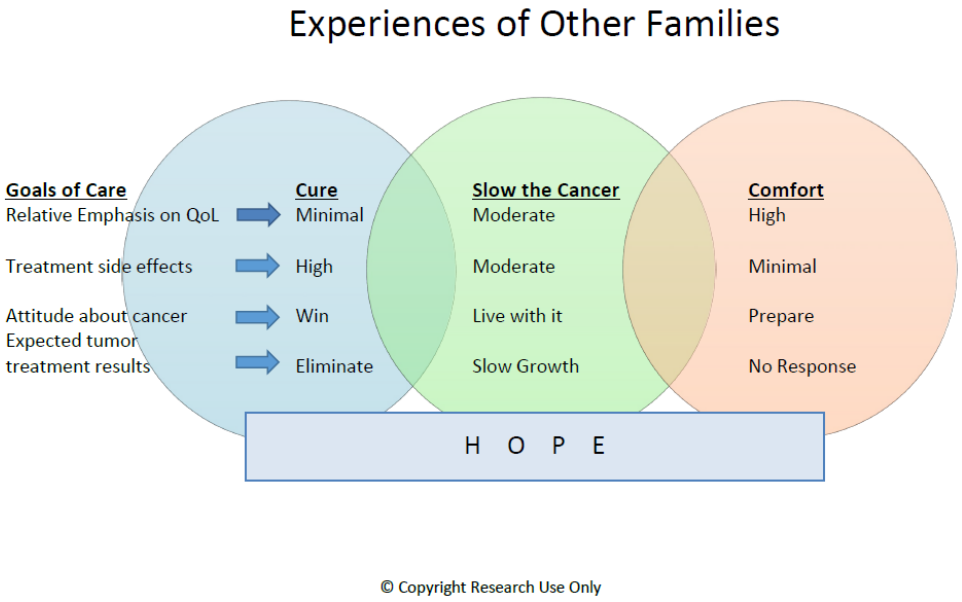


Figure 4. Experiences of Other Families



Materials/Data Collection. Prior to Session 1, a blinded Evaluator (CRA) will meet with the parent(s) either in-person, via telephone, or secure HIPAA-compliant video teleconference platform (e.g., Zoom Health, Webex) to complete baseline (T1) measures (evaluation session) using REDCap. All subsequent

measures will be administered by a trained evaluator masked to study condition. Time 2 (T2) measures (evaluation session) will be completed approximately 1-3 weeks post Session 3. Follow up measures (TF) will be obtained approximately every 1-4 months post Session 3 until end-of-life or end-of-study (TEOS), whichever occurs first. Given the nature of the child's condition, parent participants who miss one or more windows to complete follow-up measures will not be excluded from the study. Although reasonable efforts will be made to contact participants to complete data, participants are expected to participate as they are able and willing up to study endpoints.

After TEOS, chart review data will be collected by a research team member regarding: (1) number days the child was on hospice, (2) number and types of high-intensity EOL interventions (i.e., DNR code status; location of death; number of emergency room visits within last 30 days; number of hospitalizations within last 30 days, receipt of intravenous chemotherapy in the last 14 days of life).

For completion of the parent and child measures, a trained and blinded evaluator will be present either in person or via phone/videoconference throughout the data collection session. The evaluator will remain available in real time as participants complete the surveys to answer questions and to facilitate the completion of measures in REDCap. Whenever possible, measures will be completed in the clinic or hospital, in a quiet/private setting. If parents are not coming to clinic within the necessary timeframe, measures will be completed remotely via the web, with the evaluator on the phone/videoconference. The evaluator will notify the Site PM after each set of measures is completed. Evaluation sessions will be audio-recorded to monitor evaluation/data collection protocol fidelity.

All measures will be completed by participants in REDCap using a computer, smart phone, or tablet. Should paper measures be necessary for any reason (e.g., no internet access), they will be secured in a locked cabinet dedicated to our study, in a locked office at the site. The data will be entered from the paper forms into REDCap by a study team member at that site as soon as possible after the evaluation session.

Medical information will be obtained from chart reviews, relevant to diagnosis, relapse (if applicable), and treatments. Study team members will enter these data via REDCap.

Any private, identifiable health information that is collected will be protected according to procedures outlined in subsequent sections describing data safety and monitoring.

Note: A blinded Evaluator (CRA) will be used at all sites with the exception of Riley Hospital for Children because that was the pilot intervention site.

6.4 Potential Risks

Risks to child/parent participants are considered minimal and include:
1) breach of confidentiality;
2) increased fatigue for the child or parent as a result of participating in study sessions or completing measures;
3) psychological discomfort for the parent and/or child during sessions with interveners and when responding to evaluation questions; and,
4) cultural distress regarding communication about cancer diagnosis and death.

6.5 Informed Consent and Assent

Care Team dyad interveners from both study arms will identify eligible parents of patients under the physician's primary oncologic care according to eligibility criteria and contact the site project manager (PM) or PI to ensure eligibility. Once eligibility has been confirmed, a study team member will obtain written informed consent from parent(s) and written assent from children ≥ 7 years old following the requirements for human participants by the Institutional Review Board.

Informed consent/child assent procedures will preserve participants' right to refuse participation and guarantees that refusal to participate will not affect their usual medical care. Informed consent sections for parents include a discussion of the following topics:
1) a summary of why the study is being done and why it is considered research,
2) the study procedures, including the anticipated length of time that they will participate,
3) the potential risks, benefits, costs, and compensation should they chose to participate,
4) confidentiality,
5) parent's rights as a participant, including stopping study participation at any time, and
6) who to contact should any questions arise throughout their time on study.
Child assent (for children ≥7 years old) will be obtained via discussion of an assent document similar to that of the parent consent form. Children will be presented with this information in a manner which is in alignment with their developmental/cognitive abilities. Children will be encouraged to ask questions throughout the assent process. Should a child ≥7 years old decide not to assent to their and/or their parent's participation, the family will not be eligible for the study.
Those who choose to proceed with signing consent will be provided with a copy to retain for their records.
Children who reach the age of majority while on study will be re-consented.

Researchers intend to use audio recordings from the IMPACT study sessions in a future retrospective study, where research on the recordings will be conducted under a separate IRB-approved protocol. To accomplish this, clinicians will first be informed of this potential research and provide written consent as documentation of consent in order for the recordings to be used in the future research. If the clinicians do not provide consent, those recordings will not be used in future research.

Potential Benefits of the Proposed Research to Research Participants and Others
While taking part in this study, parent and child participants in Program A will have the benefit of the opportunity to have one-on-one time with a trained RN/APP to ask questions and learn about topics not usually discussed, but that many parents want more information about. They also will have opportunities to clarify information about caring for their child that is often difficult to grasp in what is usually one pre-discharge session.

Parents and children in Program B may benefit by having a clearer understanding of the possibility of changing goals of care. Since overall, we anticipate the intervention will increase goal-concordant care and improve the EOL experiences of children and their parents participating in Program B, the expected benefits mitigate the small risks of psychological discomfort and participant fatigue as well as the very remote risk of a breach in confidentiality. All study personnel will be trained to manage and support parents' emotional responses.

6.6 Importance of Knowledge to be Gained

The knowledge gained from the proposed research will provide essential information on the appropriate timing and delivery methods of PC/EOL conversations to maximize important clinical outcomes such as hospice enrollment, child pain and emotional distress, and parental distress in the very poor prognosis pediatric cancer population and their families. The risks in this study are minor (temporary psychological discomfort and fatigue) compared with the potential to improve a child's quality of life at the end of their life and decrease parental distress.

7.0 Measures/Data Collection Instruments (See Appendix)

7.1 Eligibility Verification Form

This form includes baseline information on diagnosis, prognosis, and other criteria. This form will be used to verify and document participant eligibility.

7.2 Demographic Form

This investigator-developed form collects basic contact and demographic information, including race, ethnicity, income, and education.

7.3 Chart Extraction Form

This investigator-developed form includes items that detail clinical information and treatments the child is receiving at the time of the interventions and within 30 days from end-of-study or EOL.

Sample items for both deceased and alive children include the prognosis, whether palliative care consultation was received, treatment regimen within the last 30 days, code status, and whether or not they are on hospice.

For deceased children only, additional items include 9 high intensity EOL interventions (identified by the National Quality Forum) and location of death.

After chart extraction, two blinded team members will independently determine whether treatment was cure directed, to slow the cancer, or to provide comfort. The last question on this form is used in conjunction with the Goals-of-care Questionnaire in determining whether care at EOS/EOL is aligned with goals.

7.4 Human Connection Scale [HCS] (Therapeutic Alliance)

This 16-item validated reliable questionnaire measures the therapeutic alliance between advanced cancer patients and their child's healthcare providers (i.e., physician form and RN/APP form) using a 4-point response option that varies with question content. Higher scores indicate greater therapeutic alliance [80].

7.5 Goals-of-care Questionnaire

The adapted form [58] is completed by the Care Team dyad and Parent(s). It is 1 item with 3 options: "Your current goal of care for your patient (for clinician)/your child (for parent) is:

- Cure-directed (i.e. medical/surgical treatment aimed at curing the cancer);
- Slowing the Cancer (i.e., medical /surgical treatment not expected to cure patient, but to palliate patient by slowing the cancer); or,

- Providing Comfort (i.e. treatment directed at providing comfort above all else)

7.6 Parent Experience of Child Illness-Short Form [PECI-SF] (Emotional Resources and Emotional Distress)

This 25-item scale measures parent adjustment to caring for a seriously ill child. Subscales assess parents' emotional resources, emotional distress (guilt and worry, and unresolved sorrow and anger), and caregiver uncertainty. Response options range from 1 (never) to 4 (always). The PECI has strong psychometric properties, and evidence of construct validity with established parent adjustment measures [84, 85].

7.7 Herth Hope Index [HHI] (Hope).

This 12-item scale measuring hope (realistic) has response options of 1 (strongly disagree to 4 (strongly agree). Higher scores indicate greater hope. This psychometrically sound scale demonstrated criterion-related validity through high correlations with the Herth Hope Scale ($r > .92$) [86].

7.8 Pediatric Healthcare Satisfaction Hematology/Oncology Module [Peds QL HCS] (Satisfaction with Healthcare).

This 24-item scale measures parent satisfaction with care received from their child's oncology healthcare providers. Subscales assess parental satisfaction with:
1) delivery of care;
2) information received on child's diagnosis and treatments;
3) inclusion of family;
4) technical skills in managing their child's symptoms; and
5) attention to their child's emotional needs.

Responses range from 0 (very dissatisfied) to 4 (very satisfied). The scale demonstrated strong internal consistency with parents of children with cancer [87, 88].

7.9 The Pediatric Quality of Life Inventory – General [PedsQL] 4.0 (Child Quality of Life).

The PedsQL 4.0 emotional functioning subscale has 5 items which ask about emotional symptoms over the previous 7 days. There are 3 child–reported versions: young child (5-7 years), child (8-12 years) and teen (13-18 years), and 5 parent-proxy reported versions: infant (1mo-1 year), toddler (2-4 years), young child (5-7 years), child (8-12 years) and teen (13-18). Response options range from 0 (never) to 4 (always). Both scales have strong psychometric properties and evidence of construct validity in this population. All scales are converted to a 0-100 score for comparability across ages. If a child cannot or does not wish to complete a measure, the parent-proxy measure will be used [89, 90].

7.10 The Pediatric Quality of Life Inventory- Cancer Module [PedsQL] 3.0 (Child Quality of Life).

The 24-item PedsQL encompasses 8 subscales to assess parental perception of their child's problems with: 2 items for pain and hurt; 5 items for nausea; 3 items for procedural pain; 3 items for treatment anxiety; 3 items for worry; 4 items for cognitive problems; 3 items for body image; and 3 items for communication. The PedsQL includes items specific for ages 2-4 (toddler), 5-7 (young child), 8-12 (child), and 13-18 (adolescent). The scale for toddlers does not include cognitive problems. Each item is rated on a 5-point scale ranging from 0 (never) to 4 (almost always). If a child cannot or does not wish to complete a measure, the parent-proxy measure will be used [89, 90].

8.11 The Pediatric Quality of Life Inventory- Infant Scales

The Infant Scale contains 5 subscales to assess parental perception of their infant's physical, emotional, social and cognitive functioning and physical symptoms. The scale includes items specific for infants ages 1-12 months and 13-24 months. Each item is rated on a 5-point scale ranging from 0 (never) to 4 (almost always).

8.0 Study Calendar/Timeline

Table 2. Study Calendar/Timeline

Study Timeline	Year 1				Year 2				Year 3				Year 4				Year 5				Year 6			
	8/13/19-7/31/20				8/1/20-7/31/21				8/21-7/22				8/22-7/23				8/23-7/24				8/24-7/25			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Study Start-up and Training Activities: hire personnel, finalize protocol, randomize teams at sites, contract sites, register in Clinicaltrials.gov, obtain regulatory approval, conduct Program A (Attention Control group) and Program B (Intervention group) training, and refine REDCap data entry system	X	X	X	X	X	X																		
Recruitment/Enrollment of new patients and overall % accrual		X	X	X	X	X	X	25%	X	X	X	50%	X	X	X	X	X	X	X	100%				
Prepare submit progress and final reports to NIH, IU & IRB				X				X				X				X				X				X
Deliver intervention/control: Intervention delivery (Programs A and B)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Data Collection: T1 (baseline) and T2 (post Session 3) data collection/entry, and quality assurance/data safety management		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Follow-up Data Collection: TF and TEOS data collection/entry, and quality assurance/data safety management				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Data Analysis																	X	X	X	X	X	X	X	X
Dissemination: Presentations, manuscripts, and report results in ClinicalTrials.gov								X				X				X			X	X	X	X	X	X

9.0 Adverse Events and Reporting Guidelines

9.1 Definitions of Adverse Event.

Adverse Event (AE): As defined by the NIH, an adverse event is defined as any untoward medical occurrence that may present itself during treatment, and which may or may not have a causal relationship with the treatment.

Serious adverse event (SAE): An adverse event that results in any of the following outcomes: death, a life-threatening adverse event, in-patient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Unexpected adverse event: An adverse event, of which the specificity or severity is not listed in the study protocol, or informed consent document.

Attribution: Attribution is the determination of whether an adverse event is related to a medical treatment or procedure. The categories of attribution are:

Definite: The adverse event is clearly related to the study drug/procedure/treatment.
Probable: The adverse event is likely related to the study drug/procedure/treatment.
Possible: The adverse event may be related to the study drug/procedure/treatment.

Unlikely: The adverse event is doubtfully related to the study drug/procedure/treatment.
Unrelated: The adverse event is clearly NOT related to the study drug/procedure/treatment.

Classification and grading: Classification and grading of adverse events will utilize the National Cancer Institute Common Terminology Criteria for Adverse events (CTCAE) version 5.0 to determine the severity of the reaction for adverse event reporting. A copy of the current CTCAE version 5 is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Reporting of Adverse Events

Adverse events that may possibly be related to the intervention and occur during Program A or Program B sessions will be monitored by the RN/APP or the Care Team dyad delivering the sessions and those occurring during data collection will be monitored by evaluators. Cancer-related death is not an SAE in this study.

Adverse events that may occur and could be related or possibly related to this study include only:
a) psychological discomfort that causes inability to perform normal daily activities, or
b) psychological discomfort that is life-threatening to participant or to those around them.

Both a) and b) type of adverse events described above require immediate notification to the primary oncologist and site PI for referral for mental health services. If a participant is experiencing a type b adverse event, referral to appropriate mental health services should be made emergently.

Adverse events as identified above which meet the following criteria will require **prompt reporting to the IU IRB**: An event that is assessed by the local principal investigator (PI) as
1) unexpected,
2) related or possibly related to participation, AND
3) suggests that the research places subject(s) or others at greater risk of harm than was previously known.

Participating Site Reporting Responsibilities

Reporting to Indiana University

Any serious adverse event that could possibly be related to the study intervention must be reported to Indiana University (IU) by a participating site within **1 business day** of notification or discovery of the incident, using the *SAE/Protocol Deviations Form* in REDCap. All SAEs must be reported to IU by the PI of the participating site if the event is possibly, probably, or definitely related to the study intervention. In addition to completion of this form, a letter must be sent to IU which identifies the event, is signed by the local principal investigator or treating physician, includes the applicable study number and title, and contains the following:

- Site assessment of the event attribution to study intervention
- Site assessment of event expectedness (expected vs. unexpected)
- Assessment of whether or not the research places subjects at a greater risk of harm than was previously known or recognized,
- Assessment of the event's effect on the risk to benefit ratio,
- Statement as to whether the informed consent statement should reflect changes in the potential risks involved

- Statement as to whether the event has been reported previously, and if so, whether the frequency is considered unusually high

Send to: Indiana University – Purdue University Indianapolis
ATTN: Susan M. Perkins, PhD
E-mail: sperkin1@iu.edu

The IU project manager, or designee, will distribute the reports to all participating sites.

In addition, any major protocol deviation which could impact participant safety and/or integrity of study data, or subject's willingness to enroll in study, will require site PIs to complete a SAE/Protocol Deviations Form in REDCap and to notify MPIs/IU PM within 2 working days, as MPI/IU PM must submit to IU IRB within 5 working days.

Adverse events that may possibly be related to the intervention and occur during Program A or Program B sessions will be monitored by the RN/APP or the Care Team dyad delivering the sessions and AEs occurring during data collection will be monitored by evaluators. Any concerns will be reported to the site-PI or their designee within 24 hours. Participants will have a local phone number to call if problems occur. If a participant calls and reports an adverse event related to study procedures, it will be brought to the attention of the site-PI or their designee within 24 hours. AEs not classified as serious will be reported to MPIs and the IU PM via phone call or email and a written AE report will be submitted to MPIs/IU PM within 7 days.

Indiana University Reporting Responsibilities

All study-related AEs (minor and serious) will be reported to the IU IRB annually (continuing review) by Indiana University. AEs will continue to be reported until participant is listed as off study. In addition, the IU PM will ensure all site PIs are updated with AE and SAE information at the monthly PI/PM meetings. MPIs will also ensure that adverse consequences due to the study are included in all progress reports and competitive and non-competitive renewal applications to the NCI.

In addition, the IU School of Medicine Simon Cancer Center Data Safety Monitoring Committee will review AEs quarterly to assess risk-benefit ratio of study and make recommendations to IRB and MPIs as needed. If risk benefit ratio deemed NOT in favor of benefit, the study will be permanently closed to accrual. (See DSMP for details

In addition to the responsibilities above, the lead site will also be responsible for reporting study-related adverse events to the funder.

9.2 Protections Against Risk

Fatigue. Interveners and evaluators will be trained to observe for increasing participant fatigue. If the intervener or evaluator observes fatigue in children or parents during sessions, they will encourage the participants to take a break. They will also ask parents to indicate if the child's or their own fatigue is at a level where the activity should be stopped. Program A and Program B Sessions, and evaluations will be stopped if the intervener or evaluator assesses a level of fatigue in the child or parent that

precludes their ability to participate or complete the measures. Children and parents will be informed they can stop the session at any time and/or stop their involvement in the study at any time.

Psychological Discomfort. Interveners and evaluators will receive specific training in identifying and responding to psychological discomfort related to sessions and completion of measures. Parents and children will be informed that they can stop the session at any time and/or stop their involvement in the study if they become too uncomfortable. Should significant psychological discomfort (defined under Adverse Events) be identified, a protocol will be in place to notify the site PI, who will notify one of the study MPIs and the IU PM to be reported to the Single IRB at IU. The participant's primary attending oncologist and RN/APP (the Care Teamdyad) will be notified of the concern in order to make a decision regarding referral to a mental health specialist. The site PI or PM will follow up with the MPI and IU PM within 24 hours on the outcome of decisions made. If a child gives any indication that the level of psychological distress is at a dangerous level to self or others, the child's parent and attending oncologist will be immediately consulted to arrange an appropriate mental health evaluation. In the event that a parent is judged to be a danger to self or others, the child's primary care oncologist will be consulted to arrange an appropriate mental health evaluation. Again, parents and children will be informed they can stop the session at any time and/or stop their involvement in the study at any time

Cultural distress. Our study team members will be directed to consider and use current recommended culturally sensitive communication practices during all participant encounters. During training, we will provide a review of recommended culturally competent patient-provider communication practices in the care of cancer patients. We will also provide booster training discussions related to enrollment of diverse populations. Concepts that will be reviewed during the training of study team members that will have direct contact with patients and families (e.g. interveners, project managers, evaluators) include:
1) Cultural-focused concepts and provider communication considerations (e.g., self- awareness of one's current cultural knowledge/competence and attitudes; influence of intervener's own culture and heritage; cultural assessment of patients/family members' beliefs and values and health care preferences);
2) NIH recommendations related to the importance of conveying 'cultural respect' and clear language during all communication with patients and family members;
3) Recommended communication strategies to consider prior to engaging in communication with culturally diverse participants (e.g., consideration of the impact of culture on the patient-provider encounter and/or the provider's culture specific knowledge, such as traditional cultural practices);
4) Seeking existing cultural support resources from one's own institution for protocol related activities (e.g., introducing the study to eligible participants from diverse cultures).

Vulnerable Subjects. This study carries no more than minimal risk to subjects. Rationale for the inclusion of children in this study is that we have developed an intervention that aims to address a significant problem that affects children 1 month to <18 years of age with poor prognosis cancer, namely poor quality of life (particularly near end-of-life), due to aggressive medical treatments that are NOT aligned with patients' goals and values (and a concomitant lack of focus on comfort and symptom control). We hypothesize that this lack of alignment is due to lack of early and sustained PC/EOL communication between providers and parents (the decision makers). Parents will receive the communication intervention. However, children may participate in the intervention sessions with Care Team dyads at the parent's discretion. We will ask children ≥7 to for assent prior to their parent's enrollment in the study.

Children must provide assent to participate in the study per requirements for human participants by the sIRB. In addition, children do not have to participate in the intervention if they do not want to, as the intervention is directed at the parent(s). Children who choose to participate and become distressed during the intervention and children that do not wish to participate will be provided a safe, supervised setting, to play. All sites also verified availability of dedicated space and the ability to care for unsupervised children when intervention sessions are being delivered without the child present. Children will be asked to complete measures (PedsQL), however, if they do not feel up to it, their parent will complete the validated parent-proxy measures for the PedsQL.

10.0 Data Safety Monitoring Plan for Low-Risk Trials

This trial will comply with the current requirements of the Data and Safety Monitoring Plan (DSMP) of the IUSCC.

In accordance with the DSMP of the IUSCC, investigators will conduct continuous review of data and patient safety. *Quarterly* review meetings are required and will include the: principal investigator, clinical research specialist, and/or research nurse data manager and/or study coordinator, and other members as per the principal investigator's discretion. In addition, **conference calls** with investigators and staff at participating sites will be scheduled **at least monthly** (and more often as needed) to discuss study progress. If there are no patients on treatment or in follow-up, email communication will be used in lieu of a teleconference, or in the circumstance where a scheduling conflict does not permit phone attendance. *Quarterly* meeting summaries will include and document review of data and patient safety by including: the number of patients, eligibility of patients enrolled at each site, study-related serious adverse events (SAEs) or unanticipated problems (UPs) (both IU and those reported from other institutions), and protocol deviations. Meeting minutes will be submitted and reviewed by the DSMC.

- **Study Auditing and Monitoring:** All trials are subject to auditing and/or monitoring per the currently approved DSMC Charter.

- **Reporting Guidelines:** The DSMC has streamlined the reporting process by utilizing reports from OnCore®. This has allowed the direct view of reports within the Clinical Trial Management System (CTMS); thus discontinuing paper reports. SAE reports are entered into OnCore® and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review.

- **Reporting Death:** Death will be captured in REDCap and reported per local IRB reporting guidelines.

- **Study Accrual Oversight:** Accrual data will be entered into the IU Simon Cancer Center OnCore® system. The Protocol Progress Committee (PPC) reviews study accrual twice per year while the PPC coordinator reviews accrual quarterly.

- **Continuing Review**: All Continuing Reviews (CR) will be reviewed annually or as dictated by the Institutional Review Board. IU is responsible for submitting the Continue Review.

- **Protocol Deviations:** Investigators are required to submit protocol deviations to the DSMC via the OnCore® database.

- **Early Study Closure**: At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the DSMC. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

10.1 Monitoring the Safety of Participants

MPIs will be responsible for ensuring that the proposed trial is conducted, recorded, and reported in accordance with the study protocol, Good Clinical Practice (GCP), sIRB, and NIH policy and procedures. Specifically, trial quality assurance as it relates to participant safety will occur in 2 areas: 1) procedures for the protection of human subjects (consent process, and data confidentiality), and 2) participant safety (study-related adverse events, determination for significant benefit or risk, attention to new literature that indicates an unexpected change to risk profile of study). Monitoring in these areas will occur by the Executive team/MPI's to ensure appropriate confidentiality procedures and consent process are being followed. IUSM SCC DSMC and MPI's will notify the sIRB of any necessary modifications to the protocol based on risk assessment and AEs. No protocol modification will be instituted without sIRB approval.

10.2 Temporary or Permanent Suspension Plan. Plans for assuring that any action resulting in a temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI grant program director responsible for the grant. If the risk-benefit ratio requires re-evaluation at any time during the course of the study, MPI's will suspend accrual at all sites until appropriate adjustments have been made in consultation with IUSM SCC DSMC and the sIRB. If the IUSM SCC DSMC at any point deems risk-to-benefit ratio NOT in favor of benefit, the study will be permanently closed to accrual. MPI Verna Ferguson will report any temporary or permanent suspension of study to NCI within 24 hours.

10.3 Plans for Monitoring Trial Performance, Assuring Protocol Fidelity, and Data Integrity. The Executive Team, Data Management Team, and Quality Assurance (QA) Teams for Program A, Program B, and Evaluation have comprehensive QA and protocol fidelity monitoring processes to ensure:

- Strict adherence to protocol procedure (all study data are collected consistently, thoroughly, and according to study protocol; highest level of intervention fidelity; interveners deliver the intervention with the same completeness, consistency, and accuracy, etc.)
- Proper documentation in an organized, logical, and coherent manner to allow for proper data analysis and add credibility to the findings of the research.
- That the quality of care rendered to the study participants is consistent with the standards established within the study protocol.
- Excellent team communication (MPIs have regularly scheduled meetings with PI/PMs, interveners, evaluators, QA team etc.)

Tables 3 and 4 summarize intervention fidelity strategies and intervention receipt. Strategies are based on our prior studies and NIH Behavior Change Consortium recommendations.

Table 3. Fidelity strategies for treatment delivery:

Goal	IMPACT Strategies
Control for provider differences.	• Audio-recorded sessions to allow QA team to provide feedback to interveners. • External and self QA with goal of minimum of 80% fidelity according to checklist. • Regular intervener meetings to discuss intervention delivery. • Statistical design to account for intra-class correlation. • Post-study analysis of participant measures, therapeutic alliance, and satisfaction with healthcare

Minimize "drift" in provider intervention delivery	• External QA monitoring of 25% of audio-recorded intervention sessions chosen at random. • Self QA will recur if intervener has had a > 2 months lag in intervention delivery. • Separate scheduled conference calls for both intervention teams and evaluation teams to both elicit concerns and provide corrective feedback.
Differentiation of treatments	• Manualized operating procedures for Program A (Attention Control group) and Program B (Intervention group) protocols. • Audio-recorded sessions for self and external QA monitoring using standardized fidelity checklists for intervention and standardized usual care control conditions' core element inclusion and exclusion of proscribed practices.
Ensure adherence to intervention fidelity.	• See QA strategies listed above. • Feedback to interveners regarding fidelity to intervention during sessions using documented QA monitoring feedback based on the Self-Evaluation/Intervention Fidelity QA Checklist and in-person mentoring if intervener struggling with a specific part of intervention. • Commitments obtained from site leadership to protect intervener time and provide private space for treatment delivery.

Table 4. Fidelity strategies for receipt of treatment [91]:

Goal	Intervention Fidelity Strategies
Ensure session attendance	Sessions scheduled during routine outpatient visits or during inpatient stays coincident with initial treatment plan discussions, and treatment response evaluations
Ensure participant comprehension	Interveners actively encourage parent participation and assess parental comprehension (Ask-tell-Ask, open-ended questions, active listening, use of silence).
Minimize barriers to intervention receipt	Within specified guidelines the intervention is tailored to meet participant preferences and needs. Interveners will have extensive training on de-escalating emotions, negotiating conflict and empathic communication/delivery of bad news.

10.4 Data and Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMC) of the Indiana University Simon Cancer Center (IUSCC) is responsible for patient safety and privacy protection, compliance with required reporting, and study integrity for all trials conducted at IU. Members are subject matter experts from multiple disciplines including medical oncology, pediatrics, biostatistics, behavioral oncology, radiation oncology, urology, surgery, gynecologic oncology, data and project management and research administration who are appointed by the DSMC Chair. The DSMC will provide independent oversight of the clinical trial so that study integrity is assured. The DSMC will meet per the currently approved DSMP, led by the DSMC Chair and Coordinator, and will review all adverse events, monitoring and auditing reports, unanticipated problems and study non-compliance events that require expedited reporting. Meeting minutes will be maintained by IU. Specifically the DSMC has the following responsibilities:

- Assessment of the adequacy of trial-specific Data Monitoring and Safety Plan (DSMP) of studies that are not subject to external monitoring, including investigator initiated studies, and establish risk based monitoring determination.
- Review safety data for investigator initiated trials including study-related adverse events, unanticipated problems and study non-compliance events requiring expedited reporting.
- Conduct routine study monitoring and auditing in compliance with the IUSCC data quality control review process.

Case Report Forms and Data Submission: This study will utilize electronic Case Report Form completion in RedCAP database. Access to data through REDCAP is restricted by user accounts and assigned roles. Once logged into the REDCAP system with a user ID and password, REDCAP defines roles for each user which limits access to appropriate data.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines.

11.0 Study Withdrawal/Discontinuation

Parent participants that convey a desire to withdraw from the study will be withdrawn immediately. Also, parent participants that display significant emotional distress during the delivery of the protocol will be withdrawn immediately. Any withdrawal will be documented in REDCap and the IRB and primary physician will be notified.

Parent participants may express a desire to stay on study but would like to discontinue completing the study survey measures at each follow-up timepoint. Completing all follow-up timepoint study measures is not a requirement for study participation. Therefore, these participants can continue to be on study and followed through chart review until EOL/EOS, even if follow up study survey measure completion ceases.

12.0 Statistical Considerations

Sample Size Justification. We have selected a sample size for enrollment of 83 families per group (166 families total) for this study. Detailed power calculations for the primary outcome and key secondary outcomes below show this is sufficient to achieve greater than or equal to 80% power for each outcome. Since we will enroll one child per family and expect both parents to participate about 25% of the time, this will mean we will enroll 166 children (of which approximately 80 will die during the follow-up period) and 208 parents from 166 families total. With 25% attrition, we expect 126 children (of which approximately 60 will die during the follow-up period) and 156 parents from 126 families to complete the study. This will result in ample power for the primary outcome, and sufficient power for secondary outcomes.

We based our power calculations on standard methods for independent data and then inflated for the non-independence. Analysis will employ sophisticated methods to deal with the non-independence. Our primary outcome is days on hospice for those children that die during the study. This is typically a median of < 3 days 1 and in Study 2 the median was 30 days. We conservatively propose a clinically relevant increase in median days on hospice of 14.18 Based on simulations in SAS V9.4, and assuming an exponential distribution for days on hospice, with 11 deaths observed per group (22 total) we would have 83% power to detect this effect size with a two-sided Wilcoxon Rank Sum test (alpha=0.05). Accounting for clustering by practice (ICC up to 0.1 and 6 deaths per practice) 33 deaths would need to be observed. Based on effect sizes for key secondary continuous outcomes from Study 2 ($d \geq 0.7$ for child pain and emotional suffering; and parental hope, uncertainty, and emotional distress), 126 children and 126 parents total would afford ≥80% power across a range of ICCs for practice and parent (13 parents per practice – see Table 5) based on a two-sided two sample t-test (alpha=0.05), equivalent to an average effect over repeated measures, and also adjusting for baseline using an ANCOVA model with a baseline to post-intervention correlation of 0.5. For the secondary outcome of

high intensity treatment, 19 deaths per group (38 total) would be needed to detect a decrease from 60% 8 to 17% (Study 2) with 80% power using a chi-square test with alpha=0.05 or 57 deaths total accounting for clustering ((ICC up to 0.1 and 6 deaths per practice). Based on our eligibility criteria, and assuming approximately 75% will be deceased at 5 years (from an exponential distribution), we expect there to be at least 40 deaths per group (80 total) if we enroll 83 families per group in the study assuming 15 families per group enroll by the end of Year 1, 40 by the end of Year 2, and 28 by the end of Year 3. Accounting for up to 25% attrition, we would expect 126 children and 156 parents (25% of families with both parents participating) to complete the study and to observe 60 deaths on-study. Thus we will have sufficient power for both the primary and key secondary outcomes if we enroll 83 families per group across 13 practices.

Table 5: Total N needed for various ICCs assuming 13 parents per practice (power 80%, two-sided alpha = 0.05)

Parent→	**0.10**	**0.20**	**0.30**	**0.40**	**0.50**
practice↓					
.05	84	86	88	90	92
.10	116	118	122	124	126

Analysis Plan. We will modify our pilot study's REDCap database for this trial. REDCap is ideal for consistent data collection into a single database across multiple sites and so the data can be easily accessed for quality control monitoring and statistical analysis. Analyses will be performed in SAS V9.4. Prior to hypothesis testing, we will calculate Cronbach's alphas to assess internal consistency and reliability on all multiple-item scales. We will compare the COMPLETE group to the standardized attention control group with respect to demographic and baseline outcome variables using two-sample t-tests, chi-square tests, or Fisher's Exact tests as appropriate. We will adjust for multiple comparisons using Holm's method for all subscale-based secondary outcomes (e.g. PECI). Some longitudinal data will be missing secondary to child death during study. We will fit pattern mixture models for all outcome analyses described below using PROC MI and MIANALYZE[92] as this approach can handle missing data that are not missing at random. All outcome models will control for T1 outcomes (if applicable), sex of child and caregiver, nurse credentials (RN vs APP), first-time relapsed (y/n), and any demographic variables that are not balanced across conditions. Interactions of child or caregiver sex with treatment (COMPLETE vs Control) will be examined for differential effects by sex to examine sex as a biological variable. Similarly, we will also examine interactions of the first-time relapsed variable with treatment. All analyses will be intention-to-treat. Our primary analysis for the Aim 1 Hypothesis will be to compare days in hospice for children that die during the study between COMPLETE vs Control using Wilcoxon Rank Sum Test for clustered data [93]. For the secondary hypotheses in Aims 2 and 3:
1) use of high-intensity medical interventions at EOL will be tested with a generalized linear mixed model that accounts for subjects clustering within Care Team dyads via a random effect;
2) other secondary outcomes in Aim 2 and Aim 3 are continuous (parent emotional distress and satisfaction with health care; child emotional wellbeing and symptom burden) and will be modeled with linear mixed models.

Fixed effects will include treatment, baseline outcome, time (as a repeated measure), and the interaction of treatment with time.). Random effects will include practice (nested within intervention) and family (nested within practice). Family random effects will allow for inclusion of data from both parents where applicable. A covariance structure that allows for repeated measures across time will also be specified and sensitivity analyses will be done to assess the structure (e.g. exchangeable, AR1).

With these models, we can examine both effects at specific time points and trends over time. The models also allow for outcomes to be collected at different times for different subjects.

For Aim 4, though this study is not powered to test mediation, the indirect effects of the intervention through changes in the proposed mediators (therapeutic alliance and goals-of-care alignment) on primary and secondary outcomes will be estimated using the percentile bootstrap method in MPLUS [94] after fitting the appropriate mediation models: 1) generalized linear mixed models for days on hospice (gamma link) and high intensity treatment (logit link), and 2) linear mixed models for other secondary outcomes. Results will inform a future mechanism-based study.

13.0 Data Management

Data Integrity will be ensured as follows: The data management system will ensure child/parent participant data confidentiality. The data manager and/or IU PM will assist the PI in training the site PMs and research assistants/evaluators on use of the data entry system. Measures will be completed in the clinic or hospital, in a quiet/private setting. At times, when parents are not coming to clinic within the necessary timeframe, measures will be completed remotely via the web, with the evaluator on the phone or videoconference. The evaluator will immediately notify the site PM after each set of measures is completed. Evaluation sessions will be audio-recorded to monitor evaluation/data collection protocol fidelity.

Generally, all measures will be completed by parent participants (and child participants, when applicable) using direct entry on tablet, computer, or smart phone into REDCap, a HIPAA compliant web-based data management system, in real-time with the Evaluator present (in person or by phone/teleconference). If the session occurs in person, the evaluator will be trained to be positioned where he/she cannot view the computer screen during completion of measures by participants to assure a sense of privacy while monitoring the data collection.

Should paper measures be necessary, they will be kept in a locked file cabinet dedicated to the study in a locked office of the site PI or PM. The data from the paper form should be entered into REDCap by study personnel at that site as soon as possible after the evaluation session. Digital audio recordings of study sessions will be uploaded to a secure, HIPAA-compliant password-protected, web-based application. After uploading the recording, it will be immediately erased from the recording device. Each study team member will be given a unique user authorization ID and password to log into the data management system. Access to data will be restricted based on role-specific user privileges. Computers and tablets used to enter data will be accessed through passwords and kept in locked spaces.
Data monitoring will occur in three stages:
1) field editing for missing data by evaluators;
2) review for completeness/accuracy by Data Management Team; and
3) QA Evaluation Team review of the audio-taped evaluations to ensure correct procedures for evaluation are followed.

Data will be converted to a format (e.g., SAS / MPlus) suitable for statistical analysis. Rudimentary analyses by the Statistician and Data Management team will be conducted to ensure that the data have been properly merged and to identify any unexpected trends. Periodic reports will be generated to identify outliers, missing data, and other problems of data quality and to document study progress. All data will be reviewed and processed through several verification and edit-checking programs.

14.0 Privacy/Confidentiality Issues

Demographic and other survey data will be entered into a REDCap database. Access to data through REDCap is restricted by user accounts. Once logged in to the REDCap system with a user ID and password, REDCap limits access to data depending on user role. Audio recordings of study sessions will be uploaded to a secure, password protected data storage platform. Computers and tablets used to enter data will be accessed through passwords and kept in locked spaces.

For evaluation sessions occurring in person, the evaluator will be trained to be positioned where he/she cannot view the computer screen during completion of measures by participants to assure a sense of privacy while monitoring the data collection.

Email correspondence will not contain any subject identifiers; only a subject assigned ID number will be used.

The grant duration is five years. Data collection will occur over approximately 3.5 years. Data will be stored according to rules and regulations or indefinitely because of potential dissemination of the results and future secondary analysis.

16.0 MULTICENTER GUIDELINES

Study Documents

IU will make IRB approved documents available to participating sites once approved.

Each participating site must submit regulatory documents to IU; the IU lead project manager will be responsible for keeping and managing all documents either electronically or in a binder. These documents may include (all documents submitted by participating sites to their local IRBs, delegation of authority log, protocol training log, protocol signature page, documentation of training in Human Subjects Protection including Good Clinical Practice, curriculum vitae for Site PI and Co-Is or biosketch, and copies of medical licenses) IU will provide each participating site with a comprehensive list of the required documents prior to study start-up, throughout the duration of the study and upon study close-out. It is the responsibility of the participating site to maintain copies of all documentation sent to IU.

Study Initiation

Before activating the clinical trial at each participating site, the IU lead project manager, or designee, will ensure that:

- IU **Institutional Review Board (IRB) approval** has been obtained.
- Research staff at the participating sites have been trained in data entry into *REDCap.*
- A **start-up meeting** with each participating site has taken place via telephone conference. The start-up meeting will cover protocol details (including eligibility criteria, intervention, etc.), responsibilities of the participating investigators, and reporting procedures.

Patient Enrollment

After eligibility is confirmed by the participating site staff, a completed eligibility checklist, and the signed consent will be uploaded/entered into REDCap. The IU lead project manager, or designee, will be notified when a patient is enrolled and will then register the patient in OnCore®. The site PM will verify subject eligibility for each site at the following time points: subject first enrolled, if a study team has staff changes, or if an amendment affecting eligibility has been implemented.

Data Monitoring

All multicenter investigator-initiated trials are subject to data monitoring by the IUSCC Compliance Office, or designee. External sites will be notified of upcoming monitoring visits and will be expected to provide the IUSCC Compliance Office, or designee, with de-identified source documents for remote monitoring of patients and a detailed monitoring report will be provided to the participating site. The IU project manager or designee will also forward any monitoring and/or auditing reports to the DSMC.

When a patient enrolled on this trial, or the trial itself, is selected for local monitoring or auditing, the participating site will forward the results to the IU lead project manager, or designee. In addition, if a participating site patient is selected for local auditing by the IUSCC DSMC, the site will be responsible for sending IUSCC de-identified source documents.

Record Retention

All documentation of adverse events, records of, and all IRB correspondence will be stored in accordance with all applicable federal guidelines.

Following closure of the study, each participating site will maintain a copy of all site study records in a safe and secure location. IU will inform the investigator at each participating site at such time that the records may be destroyed.

PROTOCOL SIGNATURE PAGE

Informational Meetings for Planning and Coordinating Treatment (IMPACT)

VERSION DATE:

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's (Lead PI's) overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Indiana University Simon Cancer Center and keep a record for your files.

_____ _____

Signature of Investigator Date

_____

Investigator Name (printed)

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

_____ ❑ Not Submitting to IRB

Expected IRB Submission Date

15.0 References

1. Wolfe, J., et al., *Symptoms and suffering at the end of life in children with cancer.* N Engl J Med, 2000. **342**(5): p. 326-33.
2. Kreicbergs, U., et al., *Care-related distress: a nationwide study of parents who lost their child to cancer.* J Clin Oncol, 2005. **23**(36): p. 9162-71.
3. Hakanson, C., et al., *Place of death of children with complex chronic conditions: cross-national study of 11 countries.* Eur J Pediatr, 2017. **176**(3): p. 327-335.
4. Feudtner, C., et al., *Shifting place of death among children with complex chronic conditions in the United States, 1989-2003.* JAMA, 2007. **297**(24): p. 2725-32.
5. Schindera, C., et al., *Predictors of symptoms and site of death in pediatric palliative patients with cancer at end of life.* Am J Hosp Palliat Care, 2014. **31**(5): p. 548-52.
6. Bluebond-Langner, M., et al., *Preferred place of death for children and young people with life-limiting and life-threatening conditions: a systematic review of the literature and recommendations for future inquiry and policy.* Palliat Med, 2013. **27**(8): p. 705-13.
7. Teno, J.M., et al., *Family perspectives on end-of-life care at the last place of care.* JAMA, 2004. **291**(1): p. 88-93.
8. Wright, A.A., et al., *Place of death: correlations with quality of life of patients with cancer and predictors of bereaved caregivers' mental health.* J Clin Oncol, 2010. **28**(29): p. 4457-64.
9. Ferrell, B.R., et al., *Improving the quality of cancer care: implications for palliative care.* J Palliat Med, 2014. **17**(4): p. 393-9.
10. Wright, A.A., et al., *Family Perspectives on Aggressive Cancer Care Near the End of LifeFamily Perspectives on Aggressive Cancer Care Near the End of LifeFamily Perspectives on Aggressive Cancer Care Near the End of Life.* JAMA, 2016. **315**(3): p. 284-292.
11. Mack, J.W., et al., *End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences.* J Clin Oncol, 2010. **28**(7): p. 1203-8.
12. Czajkowski, S.M., et al., *From ideas to efficacy: The ORBIT model for developing behavioral treatments for chronic diseases.* Health Psychol, 2015. **34**(10): p. 971-82.
13. Hendricks-Ferguson, V.L., *Parental perspectives of initial end-of-life care communication.* Int J Palliat Nurs, 2007. **13**(11): p. 522-31.
14. Hendricks-Ferguson, V., kane JR, Pradhan KR, et al., *Evaluation of Physician and Nurse Dyad Training Procedures to Deliver a Palliative and End-of-Life Communication Intervention to Parents of Children with a Brain Tumor.* Journal of Pediatric Oncology Nursing, 2015.
15. Hendricks-Ferguson, V.L., et al., *Stories and Music for Adolescent/Young Adult Resilience During Transplant Partnerships: Strategies to Support Academic-Clinical Nurse Collaborations in Behavioral Intervention Studies.* Clin Nurse Spec, 2017. **31**(4): p. 195-200.
16. Hendricks-Ferguson, V.L. and J.E. Haase, *Parent Perspectives of Receiving Early Information About Palliative and End-of-Life Care Options From Their Child's Pediatric Providers.* Cancer Nurs, 2018.
17. Back, A.L., et al., *Teaching communication skills to medical oncology fellows.* J Clin Oncol, 2003. **21**(12): p. 2433-6.
18. Rodgers, C., et al. *Effective delivery of patient and family education in pediatric oncology: A systematic review.* . in *Children's Oncology Group: Patient/Family Education in Pediatric Oncology: State of the Science Symposium*. 2015. Dallas, TX.
19. Dussel, V., et al., *Looking beyond where children die: determinants and effects of planning a child's location of death.* J Pain Symptom Manage, 2009. **37**(1): p. 33-43.

20. Hechler, T., et al., *Parents' perspective on symptoms, quality of life, characteristics of death and end-of-life decisions for children dying from cancer.* Klin Padiatr, 2008. **220**(3): p. 166-74.
21. Feudtner, C., *Collaborative communication in pediatric palliative care: a foundation for problem-solving and decision-making.* Pediatr Clin North Am, 2007. **54**(5): p. 583-607, ix.
22. Johnston, E.E., et al., *Disparities in the Intensity of End-of-Life Care for Children With Cancer.* Pediatrics, 2017. **140**(4).
23. Forum, N.Q., *A National Framework and Preferred Practices for Palliative and Hospice Care Quality: A Consensus Report*, NQF, Editor. 2006, National Quality Forum: https://www.qualityforum.org/Publications/2006/12/A_National_Framework and Preferred Practices for Palliative and Hospice Care Quality.aspx.
24. Ferrell, B. and M. Grant, *Different models of palliative care have emerged during the growth of palliative care. Introduction.* Semin Oncol Nurs, 2014. **30**(4): p. 201-2.
25. Wright, A.A., et al., *Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment.* Jama-Journal of the American Medical Association, 2008. **300**(14): p. 1665-1673.
26. *Institute of Medicine*. in *Comprehensive Cancer Care for Children and Their Families: Summary of a Joint Workshop by the Institute of Medicine and the American Cancer Society*. 2015. Washington (DC).
27. NHPCO, *National Hospice and Palliative Care Organization Call to Action: Improving Palliative Care*. 2002: Alexandria, VA.
28. American, A.o.P., *American Academy of Pediatrics. Committee on Bioethics and Committee on Hospital Care. Palliative care for children.* Pediatrics, 2000. **106**(2 Pt 1): p. 351-7.
29. Earle, C.C., et al., *Identifying potential indicators of the quality of end-of-life cancer care from administrative data.* J Clin Oncol, 2003. **21**(6): p. 1133-8.
30. S., K.A., et al., *Hospice enrollment saves money for Medicare and improves care quality across a number of different lengths-of-stay.* Health Affairs, 2013. **32**(3): p. 552-561.
31. Miller, E.G. and C. Feudner, *Health Reform Law Allows Children in Hospice to be Treated for their Disease. .* American Academy of Pediatrics News, 2013. **34** (14).
32. Collins, J.J., M.M. Stevens, and P. Cousens, *Home care for the dying child. A parent's perception.* Aust Fam Physician, 1998. **27**(7): p. 610-4.
33. Friedrichsdorf, S.J., et al., *Improved quality of life at end of life related to home-based palliative care in children with cancer.* J Palliat Med, 2015. **18**(2): p. 143-50.
34. Mulhern, R.K., M.E. Lauer, and R.G. Hoffmann, *Death of a child at home or in the hospital: subsequent psychological adjustment of the family.* Pediatrics, 1983. **71**(5): p. 743-7.
35. Rosenberg, A.R., et al., *Quality of Life in Children With Advanced Cancer: A Report From the PediQUEST Study.* J Pain Symptom Manage, 2016. **52**(2): p. 243-53.
36. Wolfe, J., et al., *Easing of suffering in children with cancer at the end of life: is care changing?* J Clin Oncol, 2008. **26**(10): p. 1717-23.
37. Tomlinson, D., et al., *Parent reports of quality of life for pediatric patients with cancer with no realistic chance of cure.* J Clin Oncol, 2011. **29**(6): p. 639-45.
38. Mack, J.W., et al., *Parent and physician perspectives on quality of care at the end of life in children with cancer.* J Clin Oncol, 2005. **23**(36): p. 9155-61.
39. Wolfe, J., et al., *Improving the care of children with advanced cancer by using an electronic patient-reported feedback intervention: results from the PediQUEST randomized controlled trial.* J Clin Oncol, 2014. **32**(11): p. 1119-26.
40. Goldman, A., S. Beardsmore, and J. Hunt, *Palliative care for children with cancer--home, hospital, or hospice?* Arch Dis Child, 1990. **65**(6): p. 641-3.

41. Rosenberg, A.R., et al., *Differences in parent-provider concordance regarding prognosis and goals of care among children with advanced cancer.* J Clin Oncol, 2014. **32**(27): p. 3005-11.
42. Wolfe, J., et al., *Understanding of prognosis among parents of children who died of cancer: impact on treatment goals and integration of palliative care.* JAMA, 2000. **284(19):2469-75**(19): p. 2469-2475.
43. Mack, J.W. and J. Wolfe, *Early integration of pediatric palliative care: for some children, palliative care starts at diagnosis.* Curr Opin Pediatr, 2006. **18**(1): p. 10-4.
44. Mack, J.W. and S. Joffe, *Communicating About Prognosis: Ethical Responsibilities of Pediatricians and Parents.* Pediatrics, 2014. **133**: p. S24-S30.
45. Sanders, J.J., J.R. Curtis, and J.A. Tulsky, *Achieving Goal-Concordant Care: A Conceptual Model and Approach to Measuring Serious Illness Communication and Its Impact.* J Palliat Med, 2018. **21**(S2): p. S17-S27.
46. Kamihara, J., et al., *Parental hope for children with advanced cancer.* Pediatrics, 2015. **135**(5): p. 868-74.
47. Lannen P, et al., *Absorbing information about a child's incurable cancer. .* Oncology, 201-. **78**: p. 259-266.
48. Jalmsell L, et al., *Children with cancer share their views: tell the truth but leave room for hope. .* Acta Paediatr, 2016. **105**: p. 1094-1099.
49. Mack, J.W., et al., *Communication about prognosis between parents and physicians of children with cancer: parent preferences and the impact of prognostic information.* J Clin Oncol 2006. **24**(3): p. 5265-5270.
50. Mack, J.W. and T.J. Smith, *Reasons why physicians do not have discussions about poor prognosis, why it matters, and what can be improved.* J Clin Oncol, 2012. **30**(22): p. 2715-7.
51. Mack, J.W., et al., *Hope and prognostic disclosure.* J Clin Oncol, 2007. **25**(35): p. 5636-42.
52. Connor, S.R., et al., *Comparing hospice and nonhospice patient survival among patients who die within a three-year window.* J Pain Symptom Manage, 2007. **33**(3): p. 238-46.
53. Hendricks-Ferguson, V.L., et al., *Novice Nurses' Experiences With Palliative and End-of-Life Communication.* J Pediatr Oncol Nurs, 2015. **32**(4): p. 240-52.
54. Montgomery, K.E., K.J. Sawin, and V. Hendricks-Ferguson, *Communication During Palliative Care and End of Life: Perceptions of Experienced Pediatric Oncology Nurses.* Cancer Nurs, 2016.
55. Hilden, J.M., et al., *Attitudes and practices among pediatric oncologists regarding end-of-life care: results of the 1998 American Society of Clinical Oncology survey.* J Clin Oncol, 2001. **19**(1): p. 205-12.
56. Roth, M., et al., *An assessment of the current state of palliative care education in pediatric hematology/oncology fellowship training.* Pediatr Blood Cancer, 2009. **53**(4): p. 647-51.
57. Rocque, G.B., et al., *Implementation and Impact of Patient Lay Navigator-Led Advance Care Planning Conversations.* J Pain Symptom Manage, 2017. **53**(4): p. 682-692.
58. Turnbull, A.E. and C.S. Hartog, *Goal-concordant care in the ICU: a conceptual framework for future research.* Intensive Care Med, 2017. **43**(12): p. 1847-1849.
59. Detering, K.M., et al., *The impact of advance care planning on end of life care in elderly patients: randomised controlled trial.* BMJ, 2010. **340**: p. c1345.
60. Patel, M.I., et al., *Delivering End-of-Life Cancer Care: Perspectives of Providers.* Am J Hosp Palliat Care, 2018. **35**(3): p. 497-504.
61. Curtis, J.R., et al., *Effect of a Patient and Clinician Communication-Priming Intervention on Patient-Reported Goals-of-Care Discussions Between Patients With Serious Illness and Clinicians: A Randomized Clinical Trial.* JAMA Intern Med, 2018. **178**(7): p. 930-940.
62. Back, A.L., et al., *Efficacy of communication skills training for giving bad news and discussing transitions to palliative care.* Arch Intern Med, 2007. **167**(5): p. 453-60.

63. Bays, A.M., et al., *Interprofessional communication skills training for serious illness: evaluation of a small-group, simulated patient intervention.* J Palliat Med, 2014. **17**(2): p. 159-66.
64. Bernacki, R.E., S.D. Block, and F. American College of Physicians High Value Care Task, *Communication about serious illness care goals: a review and synthesis of best practices.* JAMA Intern Med, 2014. **174**(12): p. 1994-2003.
65. Clayton, J.M., et al.*). Evaluation of a novel individualized communication-skills training intervention to improve doctors' confidence and skills in end-of-life communication.* Palliat Med, 2013. **27**(3): p. 236-243.
66. Osenga, K., et al., *A Comparison of Circumstances at the End of Life in a Hospital Setting for Children With Palliative Care Involvement Versus Those Without.* J Pain Symptom Manage, 2016. **52**(5): p. 673-680.
67. Kaye, E.C., et al., *Illness and end-of-life experiences of children with cancer who receive palliative care.* Pediatr Blood Cancer, 2018. **65**(4).
68. McCarthy, M.C., et al., *Prevalence and predictors of parental grief and depression after the death of a child from cancer.* J Palliat Med, 2010. **13**(11): p. 1321-6.
69. Goodenough, B., et al., *Bereavement outcomes for parents who lose a child to cancer: are place of death and sex of parent associated with differences in psychological functioning?* Psychooncology, 2004. **13**(11): p. 779-91.
70. Levetown, M. and B. American Academy of Pediatrics Committee on, *Communicating with children and families: from everyday interactions to skill in conveying distressing information.* Pediatrics, 2008. **121**(5): p. e1441-60.
71. Hinds, P.S., et al., *An international feasibility study of parental decision making in pediatric oncology.* Oncol Nurs Forum, 2000. **27**(8): p. 1233-43.
72. Clayton, J.M., et al., *Fostering coping and nurturing hope when discussing the future with terminally ill cancer patients and their caregivers.* Cancer, 2005. **103**(9): p. 1965-75.
73. Mack, J.W., et al., *Communication about prognosis between parents and physicians of children with cancer: parent preferences and the impact of prognostic information.* J Clin Oncol, 2006. **24**(33): p. 5265-70.
74. Nyborn, J.A., et al., *"Don't Try to Cover the Sky with Your Hands": Parents' Experiences with Prognosis Communication About Their Children with Advanced Cancer.* J Palliat Med, 2016. **19**(6): p. 626-31.
75. Markward, M.J., K. Benner, and R. Freese, *Perspectives of parents on making decisions about the care and treatment of a child with cancer: a review of literature.* Fam Syst Health, 2013. **31**(4): p. 406-13.
76. Clayton, J.M., et al., *Sustaining hope when communicating with terminally ill patients and their families: a systematic review.* Psychooncology, 2008. **17**(7): p. 641-59.
77. Himelstein, B.P., et al., *Pediatric palliative care.* N Engl J Med, 2004. **350**(17): p. 1752-62.
78. Sisk, B.A., et al., *Communication in pediatric oncology: State of the field and research agenda.* Pediatr Blood Cancer, 2018. **65**(1).
79. Trevino, K.M., et al., *The lasting impact of the therapeutic alliance: Patient-oncologist alliance as a predictor of caregiver bereavement adjustment.* Cancer, 2015. **121**(19): p. 3534-42.
80. Mack, J.W., et al., *Measuring therapeutic alliance between oncologists and patients with advanced cancer: the Human Connection Scale.* Cancer, 2009. **115**(14): p. 3302-11.
81. Marron, J.M., et al., *Intended and unintended consequences: Ethics, communication, and prognostic disclosure in pediatric oncology.* Cancer, 2018. **124**(6): p. 1232-1241.
82. C., K.E., S. Friebert, and J.N. Baker, *Early Integration of Palliative Care for Children with High-Risk Cancer and Their Families.* Pediatric Blood and Cancer. **63**(4): p. 593-597.

83. Chaudhary, M.A. and M.L. H., *A SAS Macro for Constrained randomization of group-randomized designs.* Comput Methods Programs Biomed, 2006. **83**(3): p. 205-210.
84. Bonner, M.J., et al., *Development and validation of the parent experience of child illness.* J Pediatr Psychol, 2006. **31**(3): p. 310-21.
85. Bonner, M.J., et al., *Brief report: psychosocial functioning of fathers as primary caregivers of pediatric oncology patients.* J Pediatr Psychol, 2007. **32**(7): p. 851-6.
86. Herth, K., *Abbreviated instrument to measure hope: development and psychometric evaluation.* J Adv Nurs, 1992. **17**(10): p. 1251-9.
87. Varni, J.W., *Development of the pediatric hematology/oncology parent satisfaction survey.* Children's Health Care, 2000. **29**(4): p. 243-255.
88. Varni, J.W., et al., *Evaluation of the built environment at a children's convalescent hospital: development of the Pediatric Quality of Life Inventory parent and staff satisfaction measures for pediatric health care facilities.* Developmental and Behavioral Pediatrics, 2004. **25**(1): p. 10-20.
89. Varni, J.W., et al., *The Pediatric Cancer Quality of Life Inventory (PCQL). I. Instrument development, descriptive statistics, and cross-informant variance.* J Behav Med, 1998. **21**(2): p. 179-204.
90. Varni, J.W., M. Seid, and C.A. Rode, *The PedsQL: measurement model for the pediatric quality of life inventory.* Med Care, 1999. **37**(2): p. 126-39.
91. Robb, S.L., et al., *Ensuring treatment fidelity in a multi-site behavioral intervention study: implementing NIH Behavior Change Consortium recommendations in the SMART trial.* Psychooncology, 2011. **20**(11): p. 1193-201.
92. B., R., O'Kelly M., and T. R., *Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models.* Pharm Stat, 2013. **12**(6): p. 337-347.
93. Datta, S. and G.A. Satten, *Rank-Sum Tests for Clustered Data.* Journal of the American Statistical Association, 2005. **100**(471): p. 908-901.
94. S., F.M., T.A. B., and M.D. P., *Explanation of Two Anomalous Results in Statistical Mediation Analysis. .* Multivariate Behav Res 2012. **47**(1): p. 61-87.