Abbreviated Title: EMI Children/YA with Cancer

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Title: Feasibility and Preliminary Efficacy of an Enhanced Mindfulness Intervention for Children and Young Adults with High Grade or High-Risk Cancer and Their Caregivers: A Pilot Randomized Controlled Trial

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PRÉCIS

Background

- Children and young adults diagnosed with a high-grade or high-risk cancer (e.g., diffuse intrinsic pontine glioma, glioblastoma multiforme, relapsed-refractory leukemia, refractory metastatic sarcomas) face a poor prognosis given limited curative options.
- Recent research has indicated that this population of patients and their parents experience elevated stress and poorer health-related quality of life (HRQL) relative to normative samples.
- Recently published psychosocial standards of care in pediatric oncology *strongly recommend* that children diagnosed with cancer and their caregivers receive early and continued assessment of their wellbeing and have access to interventions to optimize functioning and HRQL. In addition, there is increasing recognition of the importance of palliative interventions *early* in the disease trajectory.
- Despite this recommendation, minimal research has examined supportive care interventions for this population early in the disease trajectory.
- Mindfulness-based interventions (MBIs) have empirical support for their feasibility and efficacy in alleviating emotional distress and physical symptoms in children and adults with chronic health conditions, including terminally-ill patients and their caregivers.

Objectives

- To assess the feasibility of an enhanced mindfulness intervention (EMI) in children and young adults (ages 5-24 years) with a high-grade or high-risk cancer with poor prognosis and one of their primary caregivers.

Eligibility

- Children and young adults ages 5-24 years and a parent or adult primary caregiver
- Diagnosis of a high-grade or high-risk cancer with poor prognosis
- English speaking
- Must have access to a mobile device or computer with internet.
- Potential participants will be excluded if there is evidence of pre-morbid severe cognitive or psychiatric disability in parent or child that would impair their capacity for participation, or if there is evidence of clinical disease progression at the time of referral to this study, such that it would prevent the child from engaging in the intervention.

Design

- This is a pilot randomized controlled trial that will compare feasibility and preliminary efficacy of an 8-week EMI group (n=10 dyads) compared to a psychoeducation control group (n=10 dyads).
- All participants will complete measures of feasibility (primary outcome) and exploratory outcomes at baseline and following the 8-week intervention. Exploratory measures will include emotional (e.g., depression, anxiety) and physical (e.g., pain, fatigue) wellbeing, as well as baseline mindfulness/self-compassion.
- The 8-week EMI will consist of one initial in-person session with the child and parent, a series of at-home assignments, and two “booster” sessions. The psychoeducation group will be given educational material about coping with cancer.
- The psychoeducation group will be offered the opportunity to participate in the EMI 8 weeks post-baseline.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To assess the feasibility and acceptability of an enhanced mindfulness intervention in children (ages 5-17) and young adults (ages 18-24) with a high-grade or high risk cancer and one of their primary caregivers. Feasibility and acceptability will be evaluated based on the following:

A. Proportion of eligible dyads who enroll during a two-year period
B. Treatment specific retention among all randomized participants, with a target retention rate of 70% over the 8 week EMI/control period
C. Compliance with at-home practices, with a proposed target rate of 4 out of 7 days per week on average over the 8 week EMI period
D. Parent and patient reports of satisfaction on the feasibility questionnaire; for youth ages 8+ and caregivers, average item scores >3.0 will be deemed to reflect adequate feasibility

1.1.2 Exploratory Objectives

1.1.2.1 To assess changes pre- to post-intervention in child anxiety, depression, positive and negative affect, stress, pain behavior, fatigue, mindfulness, and health-related quality of life compared to children in the psychoeducational control group.

1.1.2.2 To assess changes pre- to post-intervention in caregiver anxiety, depression, stress, fatigue, sleep disturbance, psychological flexibility, mindfulness, and self-compassion compared to parents in the psychoeducational control group.

1.2 BACKGROUND AND RATIONALE

A cancer diagnosis in childhood can have an adverse impact on the wellbeing of pediatric patients and their parents. Decades worth of research suggests that children diagnosed with cancer and their parents experience elevated levels of distress and lower quality of life compared to normative samples [1], although only a minority of individuals experience clinically significant anxiety or depression [2]. Post-traumatic stress symptoms (PTSS), a precursor to post-traumatic stress disorder, have been widely reported by pediatric patients and caregivers [3,4] and can persist over time when not addressed [5]. Children with brain tumors stand out relative to pediatric patients with other types of cancer due to their negative social competence as well as poorer long-term quality of life, and may require more intensive support and interventions that are different in scope, timing, and content than those that may be beneficial for patients with other diagnoses [6,7].

Recent research has specifically examined the needs of children with cancer who do not have a high likelihood of cure. For example, a longitudinal study suggests that children with high-grade brain tumors exhibit worse physical functioning, increased anxiety, and lower health-related quality of life (HRQL) compared to normative samples [8]. Further, parents of children with high-grade brain tumors report high levels of emotional distress [8], which is significantly associated with reductions in their child's HRQL [8,9]. Despite these difficult circumstances, minimal research has specifically addressed the psychosocial sequelae of these children and their parents or offered palliative interventions—defined as efforts to reduce suffering across physical, psychological, social, and spiritual domains—early in the disease trajectory.

Recent psychosocial standards of care in pediatric oncology *strongly recommend* that children diagnosed with cancer and their parents receive access to interventions to mitigate stress and

preserve their wellbeing 1. To date, there are no known psychological interventions designed for children with a high-grade/high-risk cancer or their parents that address quality of life and stress *early in the disease trajectory*. The literature in this population has overwhelmingly focused on end-of-life care, which is at odds with the recent consensus that palliative care be established well before progression of disease 10,11. Indeed, a recent review cited strong support from the American Society for Clinical Oncology, the Institute of Medicine, and the American Academy of Pediatrics that we provide early integration of palliative care for children with *all high-risk cancers*, a standard that is unfortunately not being met.12

The general psychosocial literature in pediatric oncology (not specific to cancer type) has documented a range of supportive psychological protocols for childhood cancer patients 1,13. Cognitive-behavioral therapy (CBT) is a commonly cited modality, which includes pragmatic skills training (e.g., communication skills) and the development of problem-focused coping skills (e.g., identifying and restructuring distorted or "unhelpful" thoughts) for pediatric cancer patients 13-16. In addition, CBT has been paired with interventions grounded in family systems theory that aim to enhance coping, problem solving, and communication among parents and siblings of pediatric cancer patients 15-18. Although positive findings are reported in individual studies, a meta-analysis of psychological interventions in pediatric oncology revealed only a small effect of treatments on parental distress and adjustment and no effect on outcomes in children 19. This suggests that many existing psychosocial intervention models are not fully supporting the needs of pediatric cancer patients and their families.

1.2.1 Mindfulness-based interventions

Mindfulness is a secular meditative practice that aims to cultivate nonjudgmental awareness of the present moment. Mindfulness-based interventions (MBIs) entail a diverse set of practices that direct an individual's attention to internal (e.g., physical sensations, cognitions, emotions) and external (e.g., sights, sounds) stimuli. These practices can be tailored to alert the participant's attention to condition-specific stimuli (e.g., pain, fatigue) or can be generalized to nonspecific stimuli (e.g., nature, music). Among children and adolescents, mindfulness practices often go beyond simple mindful breathing and entail more active strategies in order to enhance engagement and adherence. MBIs have been trialed with a broad range of populations spanning the developmental trajectory (i.e., preschool through old age 20-22), including among patients with mental health (e.g., post-traumatic stress, anxiety) and physical health (e.g., chronic pain, cancer) conditions 23-28. There is a rapidly growing body of literature documenting the benefits of MBIs for symptoms of stress, worry/anxiety, and sadness/depression in clinical and nonclinical populations 26,29,30. In addition to psychological benefits, mindfulness practices exert physical health benefits. Indeed, research has demonstrated a positive effect of MBIs on inflammation, cardiac functioning (e.g., blood pressure, heart rate variability), and neuroendocrine functioning (e.g., release of stress hormones such as cortisol) across populations 31-33.

The benefits of MBIs are specifically documented in the oncology literature, and there is evidence to suggest they would be valuable for youth 34. Meta-analyses report robust effects of MBIs on symptoms of anxiety and depression in adult cancer patients on active treatment and survivors 30,35. Several studies report reductions in fatigue and pain in cancer patients following mindfulness practices 33,36-38. Notably, MBIs have been piloted with adult oncology patients with incurable disease and their caregivers with positive initial results: The research suggests strong feasibility in addition to lower levels of emotional reactivity, more psychological acceptance of difficult events, and reduced caregiving burden in terminally-ill oncology patients 24,39,40.

To date, two studies have examined MBIs in pediatric oncology, *specifically with adolescents and young adult patients*. Both studies utilized traditional Mindfulness-Based Stress Reduction (MBSR), a structured group-based protocol consisting of 90-minute sessions for 8 consecutive weeks with homework in between 41. One study included a sample of adolescent and young adult survivors of cancer, and demonstrated a significant positive effect of the intervention on emotional distress and HRQL, in addition to a reduction in negative attitudes toward self 42. The second study included a small sample of adolescents (n=7) either in remission or undergoing active treatment 43, and results indicated strong acceptance of the intervention model and unanimous benefit for handling stress. In this study, however, the researchers indicated barriers to recruitment and participation due to the time-heavy and intensive nature of the MBSR program, in addition to scheduling challenges inherent to a group-based program. These data suggest that MBIs may be suitable and potentially beneficial for youth with high-grade/high-risk cancers and/or their parents, but that a time-intensive protocol is likely prohibitive. Although a brief MBI has not been examined in pediatric oncology patients, brief protocols have been successful in several studies, including adult cancer patients and youth without cancer. These studies used protocols consisting of limited in-person contact with the research team and primarily relied on at-home practice (i.e., 10 to 20 minutes of daily exercises) or even single sessions, and have been associated with multiple positive psychological and physical outcomes 33,44,45.

Considerable research has examined the potential mechanisms through which mindfulness exerts its effects. Across populations, the aim of mindfulness is to increase attention to the present moment and expand openness to, and acceptance of, both desirable *and* challenging experiences. By engaging in this mindset during a single exercise, practitioners experience momentary enhancement of personal resources, such as increased cognitive flexibility, positive affect, and vagal tone 32,46-48. This is evidenced by patient responses on questionnaires in addition to neuroimaging and psychophysiological data 32,49,50. For example, regions of the brain such as the anterior cingulate cortex (ACC), which enables executive attention and inter/intrapersonal awareness, exhibited increased white matter integrity following a brief mindfulness intervention 51. In addition, short mindful breathing practices have been associated with relative improvements in left prefrontal activation – a region of the brain with self-regulation and behavioral flexibility 52. Empirical research has also demonstrated that, over time, a regular mindfulness practice can help an individual cultivate *durable personal resources* that persist outside of active practice. In other words, mindfulness does not eliminate feelings of stress, worry, or sadness; rather, it increases psychological resources such that individuals have more energy to cope with the emotions and stress that accompany a terminal cancer diagnosis and associated medical treatment. Given that so much of cancer care is depleting, the capacity to restore and cultivate personal resources among patients and caregivers through MBIs is noteworthy and has great potential to improve quality of life for these individuals.

1.2.2 Preliminary Data

As part of a larger study examining long-term outcomes of pediatric brain tumor patients post-radiation therapy, we have evaluated psychological sequelae and quality of life among children with high-grade and high-risk cancers and their parents. Our unpublished data suggest very elevated levels of stress among caregivers, in addition to clinically-elevated difficulties with family-based communication and coping. Moreover, HRQL data suggest that approximately 40% of children experience frequent worries and more than half of parents surveyed report that their child's illness interferes with their child's happiness to some degree. On measures of physical wellbeing, these children and adolescents report significant levels of fatigue compared to normative samples. Taken together, these data suggest elevated stress and difficulties coping

among parents, coupled with significant fatigue and illness-related impairment in quality of life among children with high-grade/high-risk cancers. These preliminary findings support the need for supportive psychological interventions in this population.

1.2.3 Summary and Future Directions

Interventions that mitigate suffering and enhance wellbeing in children with high-grade and high-risk cancers and their parents are sorely needed, given the absence of empirically-supported psychological interventions for this population. The proposed project will be the first known study to evaluate a supportive psychological intervention in this group of children and parents and is well-suited to the NIH Intramural Research Program. It will be the first in a series of planned studies. After establishing feasibility and preliminary efficacy, we plan to seek additional funding for a larger, sufficiently-powered, randomized controlled trial that allows for testing the statistical and clinical efficacy as well as potential mediators and patterns of change over longer time periods. Additional future directions include testing the EMI against or alongside traditional cognitive behavioral strategies in children with high-grade/high-risk cancers and parents, in addition to children and families facing other types of pediatric cancer and those undergoing transplant (due to cancer, primary immunodeficiency). Future research also would aim to evaluate the efficacy of this intervention when administered by supportive care staff (e.g., recreational therapy/child life) or nurses. The ultimate goal of this study is to translate this program into a clinical service that has benefits to patients across disease groups.

In short, the current protocol represents a first-of-its-kind study in an area very much in need of empirical attention. It reflects a relatively low cost, simple, and brief intervention that, if proven feasible and efficacious, could rapidly translate into clinical practice.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria for Patients

2.1.1.1 Patients diagnosed with a high-risk/high-grade cancer (e.g., high-grade brain tumors, relapsed/refractory acute lymphoblastic leukemia, acute myeloid leukemia, high-grade sarcoma) characterized by poor prognosis (e.g., estimated 5-year survival rate <30% based on scientific consensus in the literature, where available, or by expert physician report), as confirmed by medical record review.

2.1.1.2 Patients with active disease

2.1.1.3 Age $\geq$ 5 years and $\leq$ 24 years of age.

2.1.1.4 Must be able to speak and understand English.

2.1.1.5 Must have a parent or adult primary caregiver willing to participate in the study.

2.1.1.6 Ability of subject or parent/guardian to understand and the willingness to sign a written informed consent document.

2.1.1.7 Must have access to a computer/mobile device and the internet.

2.1.2 Exclusion Criteria for Patients

2.1.2.1 Patients will be excluded if there is evidence of pre-morbid severe cognitive or psychiatric disability that would impair their capacity for participation or completion of evaluations in the judgment of the investigators.

2.1.2.2 Evidence of disease progression at the time of referral to this study to the extent that it would impede participation or completion of evaluations as determined by the medical advisory investigator in conjuction with the study PI/adjunct PI.

2.1.2.3 Patients with treatment-related sequelae so severe that they would be unable to complete the study-related evaluations or intervention (e.g., treatment toxicity) as determined by the medical advisory investigator in conjuction with the study PI/adjunct PI.

2.1.3 Inclusion Criteria for Parent or Adult Primary Caregiver

2.1.3.1 Must be a parent or primary caregiver of a child (age 5 to 24 years of age) who has been diagnosed with a high-grade/high risk tumor that carries poor prognosis (as defined above); and must live in the same household as the patient for a majority of the time.

2.1.3.2 Must have a child willing to participate in the study

2.1.3.3 Must be able to speak and understand English.

2.1.3.4 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.3.5 Must have access to a computer/mobile device and the internet.

2.2 RECRUITMENT STRATEGIES

Patients and parents or adult primary caregivers will be referred by principal investigators or attending physicians in the Pediatric Oncology Branch at the NCI and other local centers (e.g., Johns Hopkins Hospital, CNMC, Sibley Memorial) who provide care for patients with high-grade or high-risk cancers with poor prognosis. NCI patients and caregivers who may be eligible for this study will be approached about the study by a medical team member, and provided with preliminary information about the EMI. If interested, they will be referred to the study team who will contact them to review the study and informed consent procedures. Patients who are referred by community providers will be approached about this study by a member of their clinical team. If interested, patients will be given the contact information for the researchers on the EMI protocol or authorize their clinical provider to send their contact information to the research team. The POB EMI research team will then contact the prospective participants to review the study procedures and screen for eligibility. A study flyer and email script are provided in the Recruitment Material Package. This protocol may also be abstracted into a plain language announcement posted on NIH websites.

2.3 SCREENING EVALUATION

2.3.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Review of existing medical records to include H&P, laboratory studies, etc. to confirm study eligibility. The medical/research team will document that the patient participant has received a diagnosis of high-grade or high-risk cancer with poor prognosis.
    - The medical advisory investigator (MAI) will be approached to discuss patient participant eligibility based on their medical status, including clinical disease progression, cognitive ability, and the timing for enrollment on this study.
- Email, written, in person or telephone communications with prospective subjects. During preliminary discussions with the parent/primary caregiver, the ability to understand the

requirements of the study and ability to understand English, and the availability of internet access and IT equipment will be evaluated.

Please see request for waiver of consent for pre-screening activities in Section **7.3.2**.

2.3.2 Screening activities performed after a consent for screening has been signed

No additional screening activities associated with this study.

2.4 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.5 INTERVENTION ASSIGNMENT AND RANDOMIZATION/STRATIFICATION PROCEDURES

2.5.1 Cohort

Number	Name	Description
1	Patients	Patients with a diagnosis of a high-grade or high-risk cancer with active disease and poor prognosis.
2	Parents	Parent or adult primary caregiver of patient participants.

2.5.2 Arms

Number	Name	Description
1	EMI Group	Participate in an in-person session followed by a series of at-home assignments, and two “booster” sessions.
2	Control Group	Participants will briefly meet with a member of the research team who will assess parent and child coping, and provide the child-caregiver dyad educational material about coping with cancer

2.5.3 Stratifications

Name	Distinct Options	Notes
Adolescents	Yes: 13-17 years old No: 5-12 years old	
Young Adults	Yes: 18-24 years old No: > 18 years old	

2.5.4 Randomization and Arm Assignment

Patients, cohort 1, will be randomized between arms 1 and 2 stratifying for age. Once randomization of the patient has occured their parent or primary caregiver, cohort 2, will be directly assigned to the arm in which their child was assigned.

2.6 BASELINE EVALUATION

Following parental consent and child assent, the parent/caregiver (see **Table 1**) and the participant (see **Table 2**) will complete a baseline assessment (Time 1) including questionnaires that assess their stress, emotional (e.g., depression, anxiety) and physical (e.g., pain, fatigue) wellbeing, in addition to baseline mindfulness/self-compassion. Disease parameters (e.g., cancer type and location, treatment history and radiation/chemotherapy doses, steroid use) will be abstracted from medical records. Participants will then be randomized to the enhanced mindfulness intervention (n=10 dyads) or a psychoeducation control group (n=10 dyads). The experimental design is depicted in **Figure 1**.

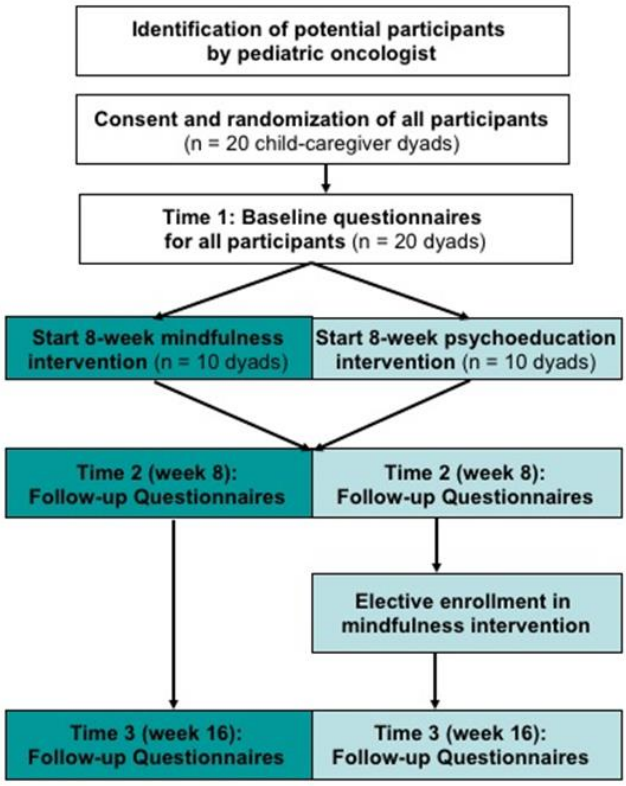

Figure 1 (See the Study Instrument 1 for descriptions of the measures).

2.6.1 Measures assessing caregiver (parent) functioning:

1. Demographic Questionnaire (5 minutes)

(see Study Instrument 1 for additional information regarding measures)

Table 1: Measures assessing parent functioning

Study Variable	Measure	Time Point	Time to Complete (approximate)
Self-compassion	The Self-Compassion Scale	All	10 minutes
Acceptance	Illness Cognition Questionnaire	All	< 5 minutes

Study Variable	Measure	Time Point	Time to Complete (approximate)
Mindfulness skills	Mindful Attention and Awareness Scale (MAAS)	All	5 minutes
Emotional well-being	PROMIS Emotional Distress: Anxiety and Depression, Short Forms 8a	All	5 minutes
Physical well-being	PROMIS Fatigue and Sleep Disturbance, Short Forms 6a	All	< 5 minutes each
Affect	Positive and Negative Affect Scale	All	5 minutes
Coping	Coping Inventory	All	<5 minutes
Feasibility	Feasibility Survey	Post-EMI	5 minutes
Total amount of time at each assessment			**~ 35 minutes**

2.6.2 Measures assessing Patient Functioning

(see Study Instrument 1 for additional information regarding measures)

Table 2: Measures assessing patient functioning

Study Variable	Measure	Time Point	Time to Complete (approximate)
HRQL	Impact of Pediatric Illness (IPI), self- and caregiver-report (ages 5+)	All	10 minutes
Mindfulness skills	Child and Adolescent Mindfulness Measure (CAMM), self-report (ages 8+)	All	5 minutes
Emotional wellbeing	PROMIS Emotional Distress: Anxiety and Depression, self-report (ages 8+) and caregiver report (ages 5+)	All	< 5 minutes
Physical wellbeing	PROMIS Pain Behavior, Short form 8a, self-report (ages 8+) and caregiver report (ages 5+)	All	< 5 minutes
Physical wellbeing	Neuro-Qol Fatigue, short form, self-report (ages 8+)	All	< 5 minutes
Physical wellbeing	PROMIS \Fatigue, short form 8a, caregiver report (ages 5+)	All	<5 minutes
Affect	Positive and Negative Affect Scale – Child Shortened version	All	<5 minutes

Feasibility	Feasibility Survey, self- and caregiver-report (ages 5+) • Patient participant ages 5-7 (interview with 3-point Likert scale) • Patient participant **ages 8+** (5 point Likert scale)	Post-EMI	5 minutes
Total amount of time at each assessment for child participants ages 8+			**~ 30-35 minutes**
Total amount of time at each assessment for child participants ages 5-7			**~ 10-15 minutes**
Total amount of time at each assessment for caregiver-proxy report			**~20-25 minutes**

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a pilot trial that principally aims to evaluate the feasibility of a novel EMI for children and young adults with high-grade/high-risk cancers and their caregivers. Secondarily, through the use of a pilot randomized-controlled design, this trial will examine the preliminary efficacy of the EMI (n=10 dyads [patient participant and parent/primary caregiver]) compared to a psychoeducation control (n=10 dyads). This study design was chosen because randomized pilots provide both feasibility and preliminary efficacy data, which are essential for justifying larger trials and/or evaluating limitations of the intervention.

At baseline, all participants will complete a series of measures assessing their functioning including emotional (e.g., depression, anxiety, stress) and physical (e.g., pain, fatigue) wellbeing, positive and negative affect, coping, and mindfulness/self-compassion.

Patient-parent/caregiver dyads will be randomized to one of two groups: the EMI group or the psychoeducation control group. The EMI group will participate in an in-person session followed by a series of at-home assignments, and two "booster" sessions. At the conclusion of the EMI, measures will be repeated (8 weeks post-baseline: Time 2), and again at 16-weeks post-baseline (Time 3). At the 8 week timepoint, the EMI group will also complete a measure of feasibility, which is a primary outcome for this study. Measures will be administered either with paper forms or electronically via iPads in clinic, or from participants' home computer. Caregiver forms will take approximately 30-35 minutes to complete. For children ≥ 8 years old and young adults, questionnaires will take approximately 30-35 minutes to complete. Children 5-7 years old will complete an abbreviated set of questionnaires (i.e., 10-15 minutes), given the limited availability and reliability of self-report measures in this age group.

Upon randomization to the psychoeducation group, patient participants and their parent/primary caregiver will briefly meet with a member of the research team who will assess parent and child coping, and provide the child-caregiver dyad educational material about coping with cancer (see Study Instrument 2). One of the psychologists will call or videochat with the family at 1 week and 3 weeks post-baseline to be consistent with the EMI group, although these phone contacts are not expected to take as long as in the EMI group. If more intensive services are needed, the patient will be taken off study and the research team will continue to provide more frequent mental health services as needed. At the conclusion of 8 weeks and completion of the measures (Time 2), the psychoeducation group will be offered the opportunity to participate in the EMI. If

participants in the psychoeducation group would like to participate in the EMI but travel to the NIH presents a hardship, the option will be made available to complete the EMI training via videochat and materials will be sent via postal mail.

The final set of questionnaires (i.e., Time 3) will be administered to parents and children in both the EMI and the psychoeducation group 16-weeks post-baseline. This time point will be used to evaluate the longer-term outcomes among patients and caregivers and to track functioning over time. It will also provide additional post-EMI data for any dyads from the control condition that electively enrolled in the EMI at Time 2. If a participant in either the EMI group or control group exhibits significant clinical disease progression after enrollment, such that they are no longer able to participate in the intervention and/or complete study-related questionnaires, they will be taken off study. If this were to occur, caregivers would be offered the option of remaining on study to complete the intervention. If patients are taken off-study before the 8-week time point due to disease progression and cannot be evaluated, they will not be included in the target *N* and can be replaced by a new participant.

3.2 IN-PERSON SESSION

3.2.1 Enhanced Mindfulness Intervention Group

The in-person session for the EMI group will be scheduled to coincide with an already scheduled clinic visit whenever possible. Dyads assigned to participate in the mindfulness intervention will be paired with two members of the clinical research team (i.e., two psychologists/psychology associates trained in mindfulness-based interventions, referred to as "mindfulness coaches"). Following completion of the baseline measures, the child participant will meet with one member of the research team for an initial training session, while the parent participant will have a concurrent training session with the second member of the research team.

The initial in-person session will last 75-90 minutes, and child and parent sessions will follow the same format. Specifically, the session will include a brief interview to build rapport and to further assess overall wellbeing, sources of stress (related and unrelated to cancer), and existing coping strategies (15-20 minutes). Subsequently, using developmentally-appropriate language and exercises, mindfulness will be introduced and practiced (30 minutes), followed by a discussion of personally-relevant values and goals (20 minutes) in which the mindfulness practice can be contextualized and individualized for each participant.

The parent and child participant will come together for the final 15 to 20 minutes of the training session. This time will afford an opportunity to teach parents about the mindfulness practices assigned to their children and allow dyads to participate in a joint mindfulness exercise.

Given the broad age range of this intervention, the interview style and exercises utilized for the in-person training sessions will be unique for each age group of young children, adolescents, and parents (separate semi-structured manuals will be used to guide in-person sessions for children ages 5-7, 8-12, 13-24 years old, and parents, while maintaining consistency in the format across age groups). For example, the mindfulness coach will rely on interactive exercises and playful language to ascertain information from younger children during the interview (e.g., use caricatures to represent feelings when talking about stress) and to introduce mindfulness (e.g., create a "mindfulness jar" to represent the concept of mindfulness). In contrast, with adolescents and parents, the sessions may be more heavily weighted toward traditional verbal discussion/instruction. Flexibility will be permitted to adapt explanations based on a participant's developmental stage and breaks will be offered when needed. Note: While mindfulness practices will be based on age/development, they will be standardized in length (i.e., approximately 15

minutes) and will utilize similar themes (e.g., mindful breathing, body awareness) across participants.

Following the in-person session, parents and children will be asked to practice mindfulness exercises at least 4 out of 7 days per week (see Section **3.3** for Home-Based Mindfulness Exercises). To facilitate at-home practice, each child and parent participant will receive a series of 4 exercises, lasting approximately 15 minutes each. Participants are given leeway to choose among these exercises throughout the duration of the intervention and the research team will track which exercises are practiced throughout the week. For parents, at-home practice will consist of .mp3 audio files with guided mindfulness practices. Youth participants will receive multiformat exercises (e.g., age-appropriate .mp3 audio files, art-based exercises, interactive games that can be done with the assistance of a caregiver or sibling). Several mindfulness practitioners and researchers have developed exercises that are for the mutual benefit of parents and children [53,54], which can be practiced together. Adaptations of these exercises will be provided to families of younger children (i.e., <8 years old), so as not to overburden a parent with independent practice *and* their child's practice separately. Children who are nonverbal (i.e., cannot express themselves verbally) due to their disease and/or treatment will have access to appropriate interventions that do not entail verbal skills.

Approximately one week and three weeks after the initial in-person training session, a brief (i.e., 30 minute) follow-up sessions will take place with the two-person research team. We anticipate that the majority of participants in this study will be staying at or nearby the NIH during this time period, or will be visiting the NIH frequently (e.g., receiving radiation treatment through other protocols at the NIH Intramural Research Program), which will make it possible to schedule follow-ups in person. For in-person follow-up, caregivers and children will each meet separately with their mindfulness coach, and then come together at the end of the follow-up for a joint meeting. If participants are not available for an in-person follow-up, sessions will take place via video chat (e.g., Skype, FaceTime) or telephone if video chat is unavailable. The literature suggests comparable efficacy between in person and teletherapy, which makes this a valid option [55]. The purpose of these follow-up sessions is to troubleshoot any challenges that arise (e.g., difficulty finding time to practice) and to engage in a clinician-guided practice. Depending on the age and functional limitations of the child, remote follow-up sessions will take place jointly with the parent/child or separately. Attendance in follow-up sessions will be systematically tracked and will be evaluated as part of the feasibility of this intervention.

Throughout the intervention, weekly text messages (or emails when text is not an option) will be sent to parent participants and youth with a personal cell phone, in which we will ask individuals to indicate the number of days practiced in the past week. The following script will be used as a guideline: "Hello. Just checking in to ask how many days you have practiced mindfulness over the past week (since INSERT DATE). Please reply by text (or email) with your response." The weekly interval will mitigate concerns regarding inaccurate recall [56,57], without overburdening families. Among younger children who do not have a personal cell phone, compliance data will be collected through parents, or children (>7 years old) will be loaned an iPod (with parental permission) from the study team through which compliance data can be obtained. All participants will also be provided with an optional tracking sheet, on which they can keep track of practice days and note the specific exercises completed (Study Instrument 3).

3.2.2 Psychoeducation Group *(Control group)*:

After completing baseline questionnaires, dyads randomized to the psychoeducation group will meet for a brief in-person session, which will include an interview to further assess overall wellbeing, sources of stress (related and unrelated to cancer), and existing coping strategies

(approximately 30 minutes). This is consistent with the EMI group. Subsequently, participants will receive a handout providing information on coping in the context of cancer. This will include specific information for pediatric patients and, separately, parents, which will be briefly reviewed with families (15 minutes). This sheet has been adapted using existing informational sheets available through the NIH and the American Cancer Society (Study Instrument 2).

Approximately one week and three weeks after the initial in-person session, a brief (10 minute) the trainer will attempt to check-in with participants in the psychoeducation group, typically by phone. The purpose is to assess ongoing coping and ensure there are not clinically-relevant concerns that warrant additional support. If significant clinical concerns arise, the research team will have a discussion with patients and caregivers about coming off study and receiving more consistent and personalized therapeutic support by a member of the Health Psychology Group or a therapist in their community. In the event of a community referral, the research team will work with the family to identify potential providers.

Within a year following the baseline session (i.e., Time 2), parents and children in the control group will be asked to complete a second set of questionnaires assessing their quality of life, emotional and physical wellbeing, and state of mindfulness (See **Table 1**) *if* there are no major changes to their health status (including psychiatric and physical wellbeing). In addition, all participants in the EMI group will be asked to complete a feasibility questionnaire assessing their impression of the intervention. At this point, individuals initially assigned to the control condition will be offered an opportunity to participate in the EMI.

3.3 Enhanced Mindfulness Intervention (Immediate Intervention Group)

After patients and their caregivers complete the in-person session (see *Experimental Design* in the Research Project Narrative for additional details), they will be provided with structured mindfulness exercises to practice at home. They will be asked to practice at least one mindfulness activity (out of 5 primary choices) at least 4 out of 7 days per week, with an ideal goal of daily practice. The home-based practices are tailored based on the participant's developmental stage, though each age group shares three common practices (i.e., Loving Kindness, Body Scan, and Mindful Breathing). Below is a brief description of the at-home practices that will be offered to participants, arranged by age group. Flexibility is permitted within the intervention protocol to adapt exercises or offer alternative practices for patients when needs arise (e.g., cognitive and/or verbal limitations, physical limitations). This will be addressed on a case-by-case basis with participants during the initial in-person session, at which point adaptations/alternatives will be provided. Patients and caregivers will be allowed to choose among the mindfulness exercises provided (the research team will track their choices via a tracking sheet). All materials needed to complete these exercises will be provided to participants.

3.3.1 Home-Based Mindfulness Practices for Caregivers

Home-based practices for caregivers will primarily consist of guided mindfulness meditations via audio recordings. This will include brief (i.e., 5-minute) and extended (i.e., 15-20-minute) formats. Audio files (.mp3 files) will be provided to caregivers immediately following or during the in-person session and can be downloaded to a smart phone, tablet, or computer. Mp3 players will be available for any participant who does not have access to a personal device through which these files can be accessed. Descriptions of these exercises are available in Study Instrument 4.

3.3.2 Home-Based Mindfulness Practices for Adolescents and Young Adults (13-24 years old)

Home-based practices for adolescents will be multi-format in nature. Exercises aim to increase awareness of emotional and physical experiences, and enhance attunement to environmental stimuli. Although each of these exercises can be completed independently, they can also be completed with the company of a caregiver. Descriptions of these exercises are in Study Instrument 5.

3.3.3 Home-Based Mindfulness Practices for Youth (8-12 years old)

Home-based practices for pre-adolescent youth will be multi-format in nature. Exercises aim to increase awareness of emotional and physical experiences, and enhance attunement to environmental stimuli. Exercises are completed independently or with a caregiver. Reinforcement (e.g., tangible items like stickers, praise, positive attention) can be paired with these exercises to increase engagement in this age group. Descriptions of these exercises can be found in Study Instrument 6.

3.3.4 Home-Based Mindfulness Practices for Children (5-7 years old)

Mindfulness practices for young children are interactive and engaging. These exercises are intentionally game-like and utilize reinforcers (e.g., tangible items, positive caregiver attention) to help sustain participation and patient enjoyment. Tangible reinforcers (e.g., stickers) will be provided in the mindfulness toolkit. All exercises should be completed with a caregiver and offer mutual benefit such that a caregiver would not have to complete a separate practice. Descriptions of these exercises are in Study Instrument 7.

3.4 COST AND COMPENSATION

3.4.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not generally be provided or paid for by the NIH Clinical Center.

3.4.2 Compensation

Participants (each child and each parent/caregiver) will receive compensation ($20) for completing each set of questionnaires to thank them for their time and effort spent participating in this study. The maximum compensation that any participant can receive is $60 (questionnaires at baseline, 8 weeks and 16 weeks). Funds will be distributed in accordance with the Clinical Center's Research Volunteer system, such that participants can have the money directly deposited to a bank account or have a check mailed to them.

In addition, each parent-child dyad will receive a mindfulness toolkit as part of this study, which will provide them with all the necessary supplies to practice the mindfulness exercises outside the clinic. Because we anticipate that some families will be away from their home environment while they participate in this project, it is essential that all equipment be provided to families. This will include pragmatic supplies to complete exercises (e.g., art supplies for art-based mindfulness exercises such as Mandalas, bubbles, copyrighted audio files, headphones) in addition to tools to enhance their experience (e.g., eye pillow, meditation mat). Collectively, these supplies will cost approximately $100 per dyad. These costs are covered by a grant through the St. Baldrick's Foundation, awarded to Dr. Allen in support of this study.

3.4.3 Reimbursement

This study does not offer reimbursement for, or payment of, travel, lodging or meals.

3.5 OFF STUDY CRITERIA

Subjects will be removed from the study for any of the following:

- Completed study follow-up period (16 weeks)
- Participant requests to be withdrawn from study
- Participant becomes too ill to continue participation
- Participant is in need of additional psychotherapeutic support due to significant mental health concerns (e.g., moderate to severe depression or anxiety)
- Inability to consent / loss of capacity
- Lost to follow-up
- Investigator discression
- Death

3.5.1 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to respond to 2 or more timepoint check ins and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up..

4 DATA COLLECTION AND EVALUATION

4.1 DATA COLLECTION

The PI/adjunct PI will be responsible for overseeing entry of data into an in-house password protected electronic system (Labmatrix) and ensuring data accuracy, consistency and timeliness. The principal investigator, adjunct principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **5.2.1**..

4.2 DATA SHARING PLANS

4.2.1 Human Data Sharing Plan

Identified or coded, linked data will be shared with approved outside collaborators under appropriate agreements; and de-identified data will be shared at the time of publication and or public presentation.

4.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

5 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

5.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

5.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

5.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

5.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

5.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

5.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are participating in the intervention period on the trial to discuss each dyad. All data will be collected in a timely manner and reviewed by the principal investigator or medical advisory investigator. Events meeting requirements for expedited reporting as described in section **5.2.1** will be submitted within the appropriate timelines.

The principal investigator and medical advisory investigator (when indicated) will review adverse event and study data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

6 STATISTICAL CONSIDERATIONS

6.1 STATISTICAL HYPOTHESIS

The current protocol is a pilot study, and therefore its primary aim does not include hypothesis testing. Components of feasibility (as described in section **6.1.1**) will be evaluated during the recruitment phase (i.e., proportion of eligible dyads who enroll) and following the 8-week EMI/psychoeducation period.

6.1.1 Primary Objective

The primary objective of this study is to assess the feasibility and acceptability of an enhanced mindfulness intervention in children and young adults (ages 5-24) with a high-grade or high-risk cancer and one of their primary caregivers. Feasibility and acceptability will be evaluated based on the following:

1. Proportion of eligible dyads who enroll during a two-year period
2. Treatment specific retention among all randomized participants, with a target retention rate of 70% over the 8 week EMI/control period
3. Compliance with at-home practices, with a proposed target rate of 4 out of 7 days per week on average over the 8 week EMI period
4. Parent and child reports of satisfaction on the feasibility questionnaire; for youth ages 8+ and caregivers, average item scores >3.0 will be deemed to reflect adequate feasibility

Of note, because the sample size of this study is very limited, even the results of the comparisons tested using statistical methods and identified within the primary objective will be considered descriptive and hypothesis generating.

6.2 Sample Size Determination

Sample size determination was not undertaken for this protocol because it is a small pilot intervention primarily aiming to test the feasibility of the proposed EMI. We specifically aimed to recruit 10 dyads per arm because this sample size would provide enough subjects to yield data appropriate for a pilot study. It is also anticipated that this sample can be recruited within a reasonable amount of time, over a 2 year period (1 to 2 dyads per month, on average). The proposed sample size will likely limit the ability to evaluate preliminary efficacy, which is an exploratory aim.

6.3 Populations for Analyses

For the primary outcome of feasibility, all randomized participants will be included. In addition, as described below in section **6.4.2**, we will track total number of eligible individuals approached about the intervention (prior to randomization/enrollment), which will allow us to evaluate the proportion of eligible dyads who enroll. To evaluate exploratory aims, a modified intent-to-treat dataset will be used and will include all participants who, at a minimum, complete the initial in-person training (across EMI and psychoeducation conditions) and questionnaires at Time 1 (baseline) and Time 2 (8 weeks).

6.4 Statistical Analyses

6.4.1 General Approach

For descriptive statistics, categorical data will be presented as percentages. Continuous data will be presented as means with standard deviations and ranges. For inferential statistics, statistical significance will be declared if α=0.05 and tests will be two-tailed; results will be interpreted in the context of a pilot study in which statistical testing is for descriptive purposes. For exploratory analyses, checks of assumptions will be conducted and corrective procedures will be applied accordingly (e.g., transformation of non-normal data or nonparametric tests will be substituted).

6.4.2 Analysis of the Primary Endpoints

Planned analysis: For the primary feasibility aim, descriptive and summary statistics will be used to report parent and child rates of intervention completion, as well as ratings of satisfaction with the intervention via responses on a feasibility questionnaire. A Z-test for binomial proportion with continuity correction will be used to examine whether the retention rate and at-home practice compliance rate are lower than the target (i.e., respectively, a target of 70% participants retained over 8 weeks and a practice rate of 4 out of 7 days per week on average over 8 weeks). Retention rate will be evaluated across the experimental and control groups, and separately for each. In addition, descriptive and summary statistics will be used to detail the total number of patients screened, determine rates and reasons for non-eligibility and patient refusal, the number and type of adverse events (if any), and the number of days practiced (obtained via text/email) by each participant. A series of t-tests (for continuous variables) and Chi-square tests (for non-continuous variables) will be used to examine potential differences between eligible patients who accept or decline study participation; between participants who meet (versus do not meet) the target practice rate (i.e., 4 out of 7 days completed); and for other medical, psychological, and contextual factors. Nonparametric models will be used if data do not meet assumption checks.

6.4.3 Sub-Group Analyses

As described in section **2.5.3**, randomization will be stratified by child age for youth ages 5-12, 13-17, and 18-24 years old. Caregivers will be directly assigned to the child's randomization group (i.e., EMI or psychoeducation control). From a feasibility perspective, stratification will allow us to evaluate enrollment/retention data per age group across conditions (reducing the bias associated with enrollment/retention in a single arm treatment study), which will be useful to inform larger RCTs in the future. Stratification across ages will also better allow us to assess exploratory efficacy aims (see **6.4.5**) among developmental cohorts.

Further, as described in **6.4.2**, we will evaluate demographic and medical/disease-related factors that are associated with components of feasibility.

6.4.4 Tabulation of individual Participant Data

Individual participant data will be listed by measure and time point.

6.4.5 Exploratory Analyses

Given the small sample, there may be limited power to detect changes on all exploratory outcome measures. Descriptive and summary statistics will be used to summarize secondary outcome measures between the EMI and control groups. Bivariate analyses (i.e., correlations, chi-square analysis as appropriate) will then be conducted to identify potential covariates for subsequent analyses. Dependent samples t-tests will assess changes pre- to post-intervention in child anxiety, depression, pain behavior, fatigue, mindfulness, and health-related quality of life among youth in the EMI group and also youth in the psychoeducational control group.

In addition, using dependent samples t-tests, we will explore changes pre- to post-intervention in caregiver anxiety, depression, stress, fatigue, sleep disturbance, psychological flexibility, mindfulness, and self-compassion among the intervention group and also parents in the psychoeducational control group. Given the small sample, these analyses will be considered hypothesis generating.

Linear regression models using the 8-week or 16-week assessment as the outcome will be considered in an effort to preliminarily estimate the effect size of the intervention, with

adjustment for potential confounders including scores at baseline. We will assess which demographic (e.g., age), medical, psychological, and environmental factors are related to preliminary efficacy of the intervention.

7 HUMAN SUBJECTS PROTECTIONS

7.1 RATIONALE FOR SUBJECT SELECTION

7.1.1 Participation of Children

The age range of patients eligible for this trial is at least 5 years of age and less than or equal to 24 years of age. Physicians, nurses, and multidisciplinary support teams of the POB, NCI and Clinical Center will provide patient care. The staff of the POB has expertise in the management of children with complex oncologic disorders, neurocognitive testing in children and complications of all types of oncologic conditions. Full pediatric support and subspecialty services are available at the NIH Clinical Center.

This study will be limited to English speaking subjects and their parent or primary caregive. The rationale for this is that the at-home intervention materials currently only available in English as well as many of the outcome measures have only been validated in English.

7.2 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

7.2.1 Risks for parents/caregivers

For parents or caregivers helping their child participate in this study, there is the risk of the time commitment involved in the initial one on one session, the time required to complete the questionnaires at 3 time points, check their study emails/texts, participate in the home-based practices for themselves, and to encourage their child and review the activities and progress with their child.

7.2.2 Risks for patient participants

Similarly, the major risk for participants is the time commitment of participation. The content and context of the program is specifically tailored for the targeted age group, and the interview style and exercises utilized for the in-person training sessions will be unique for each age group, young children, adolescents and young adults in an attempt to maintain interest, keep the participant engaged and involved in active participation.

7.3 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or cosent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with polices, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted

remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found here.

7.3.1 Consent Process for Minors

Consent will be obtained from parent(s)/guardians of minor children as described in Section **7.3**.

Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. The assent process will take place in conjunction with consent; therefore, in person and remote assent are permitted under the same circumstances as in person and remote consent. Verbal assent will be obtained as appropriate for children ages 5-11. The assent document will be used to guide this discussion. Should a child in this age group (5-11) choose to sign the assent document they will not be discouraged; however it is not required. Children under the age of 18, but who are age 12 or older will be asked to sign an age appropriate assent form. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

7.3.2 Request for Waiver of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in section **2.3** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will

be provided with additional pertinent information after participation as they will be informed whether are not they are eligible to sign a consent for additional screening.

7.3.3 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require that consent be obtained from the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. Given the length of time that has transpired for some of the subjects since their last visit for this study, we request waiver of informed consent for those individuals who have completed their participation in the research study and have met the off-study criteria defined in section **3.5**.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.
    a. Analysis of samples and data from this study involves no additional risks to subjects.
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. Retention of these samples or data does not affect the welfare of subjects.
(3) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.
(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
    a. We do not anticipate that any information generated by these studies would be pertinent in any way to the health and treatment of these research subjects. However, if such information is generated, and we are able to locate the research subject(s), we would provide the information to them. The subjects who are provided the data will not be contacted by anyone connected with the research without prior approval by the IRB.

8 REGULATORY AND OPERATIONAL CONSIDERIATIONS

8.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping

- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

8.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing, and inspection by local and regulatory authorities.

8.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

8.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by NCI CCR research staff will be secured, and password protected. At the end of the study, all study databases will be archived at the NCI CCR: NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

9 REFERENCES

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