PROTOCOL TITLE:

The Promoting Resilience in Stress Management (PRISM) Intervention: a multi-site randomized controlled trial for Adolescents and Young Adults with advanced cancer

SPONSOR: Dana-Farber Cancer Institute

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AYA		Adolescent and Young Adult
CRA		Clinical Research Associate
DFCI		Dana-Farber Cancer Institute
HRV		Heart Rate Variability
HRQOL		Health-Related Quality of Life
PRISM		Promoting Resilience in Stress Management
PRISM-AC		PRISM for Patients with Advanced Cancer
RCT		Randomized Controlled Trial
RPCA		Resilience in Pediatric Cancer Assessment
SCH		Seattle Children's Hospital

1. Objectives

1.1 Overview. Among patients with cancer and their families, early integration of palliative care may improve quality of life. This is particularly important for Adolescents and Young Adults (AYAs) because their distinct developmental challenges related to identity, relationships, and vocation may add to the burden of cancer.[1-5] Among AYAs with advanced cancer, most understand that they may die and report that discussing end-of-life preferences, goals, and fears would be helpful; however, only 53% engage in such conversations.[6-8] While national guidelines call for integrated palliative care in AYA oncology,[9-11] developmentally targeted, evidence-based interventions designed to meet psychosocial and communication needs are lacking.

A potential barrier to improving the experiences of AYAs with advanced cancer may be their limited opportunities to develop "resilience resources" such as stress-management, goal-setting, positive reframing, and meaning-making skills.[12] These resources may mitigate negative outcomes, facilitate engagement in goals of care discussions, and improve quality of life.[13-15] Furthermore, promoting these resources among AYAs may give them the tools to more successfully navigate the challenges of the cancer experience.

Our research program is built on the central hypothesis that promoting resilience resources will improve psychosocial well-being. Over a series of studies, we developed a conceptual framework of resilience in pediatric cancer,[12,16] affirmed associations between resilience resources and outcomes,[17] and developed a novel resilience resources intervention (Promoting Resilience in Stress Management, PRISM).[18] PRISM is a manualized, skills-based training program comprised of four 30-60 minute, in-person, one-on-one sessions plus a facilitated parent/caregiver/spouse/significant other family-meeting.

We recently completed a pilot Randomized Controlled Trial (RCT) to test the efficacy of PRISM among 100 AYAs, 6-months following their diagnosis of new (n=73) or recurrent (n=27) cancer (manuscript under review). Final results suggest PRISM is feasible, highly acceptable, and associated with increased patient-reported resilience as well as key clinically significant patient-centered outcomes such as quality of life and psychological distress. Subgroup analyses comparing patients with advanced cancer to those with new cancer suggested differentially stronger positive effects in the advanced cancer group, raising a hypothesis to be tested in dedicated trials. However, qualitative feedback from patients with advanced cancer suggested refinements targeting hopes, worries, and contextual meaning-making might strengthen PRISM's usefulness.

The overall objective of this project is to refine PRISM to meet the distinct needs of AYAs with Advanced Cancer. We will first adapt and iteratively test the existing PRISM based on established guidelines for intervention development.[19] Then, we will conduct a multi-site randomized controlled trial to test the efficacy of a new PRISM for Advanced Cancer (PRISM-AC). Exploratory outcomes will assess a biomedical variable associated with psychological distress called heart rate variability (HRV). We hypothesize that AYAs with advanced cancer who receive PRISM will report fewer mixed affective symptoms and show improved biomedical outcomes. Findings will inform the development of larger dissemination studies and standards of AYA end-of-life and palliative care. Ultimately, this research has the potential to reduce the burden of cancer in a highly vulnerable population.

1.2 Purpose of the Study Protocol

1.2.1 The protocol is intended to be used by all study staff as the approved procedures for conduct of the study.

1.2.2 Primary Aim: Evaluate the effect of PRISM-AC compared to usual care on Health-Related Quality of Life (HRQOL) among AYAs with advanced cancer or recurrent/progressive tumors.

1.2.2.1 Primary Outcome Measure: AYA-reported Pediatric Quality of Life Inventory 4.0 (PedsQL)[20,21] scores 3-months post-enrollment.

1.2.2.2 Primary Hypothesis: PRISM will be associated with higher patient-reported HRQOL compared to usual care.

1.2.3 Secondary Aims

1.2.3.1 Create PRISM-AC by refining the existing PRISM for patients with advanced cancer.

1.2.3.1.1 Deliverable: Refined manual of PRISM with targeted elements to meet the needs of patients with advanced cancer.

1.2.3.1.2 Anticipated Findings: PRISM-AC will target the same 4 resilience resources and have additional module and practice opportunities for meaning-making and advance care planning.

1.2.3.2 Assess the feasibility and acceptability of PRISM-AC.

1.2.3.2.1 Deliverable: feasibility will be defined as >70% enrollment and >70% completion of at least 4 sessions. Acceptability will be evaluated qualitatively.

1.2.3.2.2 Anticipated Findings: PRISM-AC will be feasible and acceptable.

1.2.3.3 Determine if PRISM-AC improves other key patient-reported outcomes

1.2.3.3.1 Outcome Measures: Anxiety and Depression (measured with Hospital Anxiety and Depression Scale, HADS)[22], symptom burden (Memorial Symptom Assessment Scale, MSAS)[23,24], hopeful patterns of thought (Hope Scale)[25], Cancer-Specific Quality of Life (PedsQL 3.0 Cancer Module)[21], and Resilience (Connor Davidson Resilience Scale, CDRISC-2) 3-months post-enrollment.

1.2.3.3.2 Hypotheses: PRISM recipients will report lower anxiety and depression, lower symptom distress, higher hope, and higher resilience compared to controls.

1.2.3.4 Evaluate the impact of PRISM-AC on parent distress.

1.2.3.4.1 Outcome Measures: parent anxiety (Generalized Anxiety Disorder Screener, GAD-7),[26] depression (PHQ-8),[27,28] and HRQOL (SF-36),[29] 3-months post-enrollment.

1.2.3.4.2 Hypothesis: Parents of PRISM-AYAs will report lower anxiety and depression, and better HRQOL compared to parents of AYAs in usual care.

1.2.3.4.3 Exploratory Outcome: Family Experience (selected items from Hospital Consumer Assessment of Healthcare Providers and Systems [HCAHPS] survey).[30]

1.2.3.5 Evaluate the impact of PRISM-AC on family "palliative care activation."

1.2.3.5.1 Outcome measures: (a) AYA- and parent- perceptions of AYA involvement in Decision-Making, measured with the Decision-Making Involvement Scale[31]; (b) medical record documented goals of care conversations; and, (c) medical record documented AYA utilization of formal palliative care and other psychosocial services, hospice, limitation of intervention orders, and other advance care plans.

1.2.3.5.2 Hypothesis: PRISM families will demonstrate higher levels of activation compared to usual care.

1.2.3.6 Explore longitudinal impact of PRISM-AC on above outcomes at 6-, 9-, and 12-months following enrollment.

1.2.4 Exploratory Aims

1.2.4.1 Prospectively describe associations between PRISM, patient reported anxiety and depression, and stress biomarkers.

1.2.4.1.1 Outcome measures: heart rate variability (HRV) as measured by the standard deviation of normal to normal beats (SDNN).

1.2.4.1.2 Hypothesis: PRISM recipients will demonstrate larger improvements in HRV compared to controls.

1.3 Rationale for the Selection of Outcome Measures

Palliative Care interventions aim to alleviate suffering and improve HRQOL.[32,33] Hence, we selected HRQOL as our primary outcome, with additional clinically relevant patient-centered outcomes including symptom burden and psychological symptoms as our secondary outcomes.

Patient outcomes are not the only ones of import in pediatric, adolescent, and young adult populations. Indeed, patient and parent outcomes are inextricably linked. Parent psychological distress is highly prevalent among children with advanced cancer, and it is associated with perceived child suffering and quality of family communication.[34] Hence, we elected to determine if a patient-centered intervention could also improve parent outcomes.

Regarding palliative care utilization, traditional measures focus on the circumstances of death (e.g., chemotherapy within the last 30 days, advance care planning documentation). These metrics are less relevant in pediatric and AYA populations.[35] AYA advanced cancer may last years.[36] Content and AYA participation in goals of care discussions evolve.[35,37] Low-intensity palliative chemotherapy may improve quality of life.[38] And, AYAs defer to their parents for medical decision-making, suggesting formal advance care planning documents incompletely represent AYA perspectives.[35] For these reasons, pediatric palliative care research has shifted towards outcomes of patient/family engagement and activation.[35] Activation is defined as the extension of self-efficacy into self-management. It implies knowledge and confidence to take action, actively change behaviors, and maintain changes over time.[39] It may be more representative of evolving pediatric and AYA palliative care involvement. Importantly, higher activation is associated with improved psychological wellbeing and HRQOL among adults with chronic illness,[40,41] and with medication-adherence and clinical outcomes in pediatric settings.[42-44] Hence, we selected global activation as a measure of palliative care utilization in this study.

Emerging data indicate anxiety and depression can impact cancer-related outcomes through immune-mediated processes, with sympathetic nervous system activation as a central mechanism.[45] HRV is a commonly used, noninvasive indicator of autonomic nervous system activity with published normative values.[46]

Finally, few palliative care studies include longitudinal outcomes assessments.[33,47] In order to explore the durable impacts of PRISM-AC, as well as capture cohort data to describe ongoing patient-reported and parent-reported outcomes, we will continue to survey patients and families quarterly for a year following their enrollment.

2.0 Background

2.1 Prior Literature and Previous Studies

2.1.1 *Background & Rationale*

Adolescents and Young Adults (AYAs) with cancer are at high risk of poor psychosocial outcomes, perhaps because cancer disrupts normal developmental experiences like establishment and identification of personal, social, and sexual identity, and pursuit of educational and vocational goals.[1-5] Unmet needs (e.g., inadequate psychosocial support and lack of information about disease management) may further contribute to poor outcomes, including poor health-related quality of life (HRQOL).[48-51]

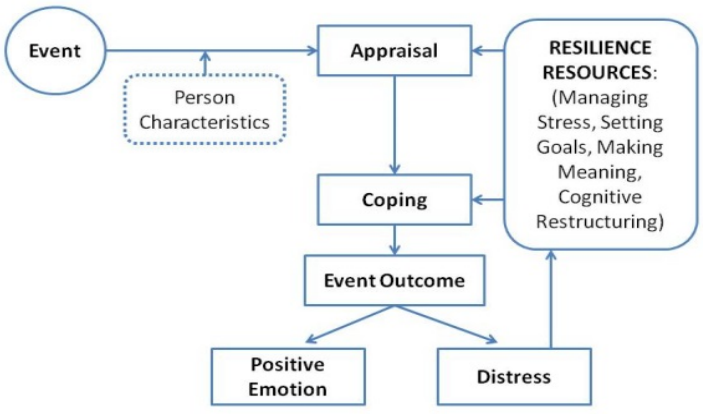
AYAs may have not yet developed the skills to navigate the adversities of cancer. In this regard, positive psychological resources are important because they may mitigate negative outcomes.[52,53] "Resilience" implies an ability to bounce back from adversity, and is evidenced by emotional and physical well-being after significant stress.[54] The study of resilience in cancer has lacked consensus of either definitions or outcomes indicative of resilience.[54,55] However, several personal resources are consistently associated with resilience among AYAs and older adults,[12,53,56] and parents of children with cancer.[16,17] These include skills in stress-management, problem-solving, goal-setting, benefit-finding, and meaning-making. Bio-behavioral models suggest these resources relate to HRQOL, health behaviors, self-advocacy, and immune function.[13]

We term these variables "resilience resources," and believe they represent an additional unmet need.

Practical challenges limit the success of traditional behavioral interventions. Time-commitments of cognitive behavioral therapy (CBT) may be prohibitive for AYAs. The average refusal rate in adolescent chronic disease settings is 37%; subsequent attrition is up to 32%.[57] Shorter skills-based interventions may be more successful.[58] AYAs learn and communicate differently than younger and older patients, necessitating age-appropriate language and educational methods.[59] Also, CBT is designed for patients with maladaptive coping, whereas AYAs may avoid maladaptive behaviors through brief preventive learning.

Stress and coping theory (**Figure 1**)[14] provides an excellent platform for intervention-development. Few interventions have obtained positive outcomes for AYAs, and fewer still have suggested mechanisms to build resilience resources.[53,60,61] Stress and coping theory suggests three categories of resilience resources: (1) dispositional factors (e.g., optimism); (2) situational factors (e.g., stress-management); and, (3) coping processes to create positive meaning (e.g., cognitive reframing). Among older adults with cancer, stress-management interventions show promise at the beginning,[62] middle,[63] and end of therapy,[64] and meaning-making improves HRQOL.[65] Among well AYAs, goal-seeking skills promote psychosocial well-being.[66] Among AYAs with chronic disease, positive re-appraisal of stressors reduces distress and improves adherence[66] and HRQOL.[67,68] Additionally, biobehavioral models suggest that resilience resources relate to long-term quality of life, health behaviors, immune function, and overall health and well-being.[13]

Figure 1. The Role of Resilience Resources on Appraisal and Coping



Adapted from Folkman S & Greer S; Psycho-Oncology 9:11-19 (2000)

Communication support is another unmet AYA need. AYAs with advanced cancer face added challenges with prognostic uncertainty and missed goals.[69] They understand death may be a consequence of their disease. Most report it would be

helpful, if not imperative, to discuss wishes, worries, and information to be shared with friends and family.[6-8] Only half engage in these discussions, however, and when they occur, discussions may be held too late for AYAs to accomplish their goals.[8,70] Indeed, despite guidelines for palliative care integration to facilitate psychosocial support and communication,[9-11] barriers remain. These include misconceptions of "palliative care," leading to late referrals,[36,71] and a lack of evidence-based, AYA-specific interventions.[72] Existing interventions are limited for 2 important reasons: (1) Although they show promise in promoting AYA-parent agreement about later, hypothetical decisions, they have only been tested in AYAs with early stage cancer.[73] (2) They tend to target advance care planning in the transition from cure-to-comfort directed care.[74] However, the experience of AYA advanced cancer may last years, and families' prognostic understanding (and corresponding advance care planning) is often delayed.[36,75] As a result, AYAs with already advanced cancer miss early, ongoing opportunities to explore their hopes and worries.[37]

AYA cancer has broad family- and public health-level implications. For AYAs with advanced cancer, missed opportunities to identify and articulate hopes, worries, and corresponding treatment decisions contribute to patient suffering, parent distress, and decisional regret.[73,76-78] Further, parent-child HRQOL is reciprocal.[78-80] Parent perceptions of patient wellbeing are associated with parent sleep disturbances, impaired physical health, and financial hardship.[81] Parents of AYAs with advanced cancer are at risk for serious psychological distress,[82] family dysfunction, and poor health behaviors,[17] which may affect them for decades.[83] Importantly, short-term parental distress and perceived quality of oncology care are related to long-term parental adjustment, whatever the outcome of the child's illness.[84-86] These data underscore the need to understand associations between patient-directed interventions and parent outcomes.[87]

The Promoting Resilience in Stress Management (PRISM) Intervention has the potential to meet these needs and improve outcomes. As described below, PRISM was developed based on stress and coping theory to be a brief, skills-based intervention targeting AYA resilience resources. Results from a phase II randomized controlled trial (RCT) suggest it is associated with increased AYA patient-reported resilience and HRQOL. It also provides opportunities for AYAs to articulate goals and meaning from their cancer experience, thereby facilitating communication and patient-activation.

2.1.2 *The Promoting Resilience in Stress Management (PRISM) intervention*

Our central hypothesis is that promoting resilience resources will improve outcomes for AYAs with advanced cancer and their families. We followed a stepwise approach to testing this hypothesis.

2.1.2.2 *Concept and survey development*. First, we conducted a cross-sectional, mixed-methods study to explore the construct of resilience in pediatric and AYA oncology. Qualitative findings directed the development a conceptual framework[16] and a survey comprised of validated instruments to measure corresponding patient-centered outcomes [the "Resilience in Pediatric Cancer

Assessment" (RPCA)].[16,17,88] Quantitative findings confirmed associations between lower resilience resources and higher distress, lower social function, and poorer health behaviors.[17]

2.1.2.3 *Prospective study of AYA perceptions of resilience*. Second, in the "Resilience in Adolescents and Young Adults with Cancer" study, we collected survey data and conducted consecutive 1:1 semi-structured interviews with AYA patients at the time of their diagnosis, 3-6 and 12-18 months later.[12,89,90] Several participants had advanced cancer at the time of the study. Thematic analyses suggested that AYAs endorse the need for strong resilience resources, but that they lack the skills. Specifically, AYAs stated stress-management, goal-setting skills, "staying positive," and "making meaning" from adversity were essential to their well-being.[12]

2.1.2.4 *Intervention Development.* These studies provided rationale for the design of a novel intervention to promote resilience resources, the "Promoting Resilience in Stress Management" (PRISM, **Table 1**).[18] PRISM is based on stress and coping theory (**Figure 1**),[14] our prior research, and successful interventions described in other populations. It is manualized (i.e., it has been standardized via comprehensive protocols). The initial design was refined with expert opinion and interviews with patients, psychologists, and social workers. Details are described below. Briefly, PRISM's overall objective is to increase resilience resources at times of high stress, thereby alleviating distress and improving quality of life.

Table 1. Original PRISM intervention content

Topic	Details	Format
1. Managing Stress	Mindfulness techniques, relaxation strategies, obtaining social support	One-on-One
2. Goal-setting	Setting specific, realistic, desirable goals, planning for roadblocks	
3. Positive Reframing	Recognizing negative self-talk, replacing with positive, realistic, manageable ones	
4. Meaning Making	Identifying benefits, purpose, meaning, or legacy from cancer experience	
5. Coming Together	Discussion about what was learned, what helped, what they can do to help	Family meeting
6. Boosters	In-person/digital/video conference modules to practice, further develop, and track skills.	One-on-One
7. Practice Opportunities	Paper-pencil and app-based modules to practice and further develop skills	Digital or Paper
Note: Sessions delivered approximately every 1-2 weeks, arranged in advance in conjunction with clinic and hospital visits.		

2.1.2.5 *Feasibility and Acceptability study of PRISM Intervention.* We completed a formative study of PRISM among 24 AYAs to determine the optimal content and timing of PRISM sessions. We found it to be feasible and highly valuable to AYA patients and parents.[18] Eighty percent of AYA participants completed the intervention and feedback was universally positive: "This was so helpful, I wish we had done this sooner," or "I think it's good techniques to use, definitely. I am teaching my little sister. I'm sure it can help her, too."

2.1.2.6 *PRISM Phase II RCT (clinicaltrials.gov NCT 02340884).* Next, in a phase II RCT testing PRISM efficacy among AYAs with new or recurrent cancer, we refined processes of enrollment, randomization, implementation, and data collection. We completed our target enrollment of 100 AYAs with either new or newly

recurrent cancer 2-months ahead of schedule. At the time of enrollment, 27 patients had recurrent cancer. Enrollment rates were 78% and similar among patients with new versus recurrent cancer. Thirteen experienced progressive disease during the study observation period, and 18 died of disease or treatment-related mortality prior to the 6-month end-point, including 5 of the 27 who enrolled with recurrent cancer. Attrition among surviving participants was similar on the PRISM (25%) and usual care (14%) arms, and primarily due to medical complications. Of 49 AYAs assigned to PRISM, 48 completed ≥1, and 43 completed all scheduled sessions. Only 2 PRISM and 6 usual care patients declined continued participation due to the burden of intervention sessions or surveys.

The primary objective of the phase II RCT was to assess patient-reported resilience 6 months following enrollment. Secondary outcomes included psychological distress and HRQOL at the same time-point. Final pilot results (n=92 with intention-to-treat analyses) suggest the intervention was associated with improved patient-reported resilience, distress, and quality of life scores with moderate effect sizes (**Table 2**).[91] Exploratory analyses suggested a stronger intervention effect among AYAs who enrolled with advanced cancer (**Figure 2**). Taken together, these findings are promising because: (a) meta-analyses suggest even small effect sizes of positive psychology interventions are associated with clinically meaningful patient-centered outcomes;[92] (b) we demonstrated feasibility among the sickest patients with advanced cancer; and, (c) the intervention may be even more impactful in this high risk group of patients.

Table 2. Results from completed pilot RCT among AYAs with new or newly recurrent cancer (n=74)

	Usual Care (mean, SD)			PRISM (mean, SD)			**Effect Size** (Cohens' d, 95% CI)	
Instrument	Baseline	6-months	**Change**	Baseline	6-months	**Change**	For change	For 6-month
CDRISC (Resilience)	28 (6)	28 (6)	**-1 (3)**	29 (6)	30 (5)	**+2 (5)**	**0.6 (0.1, 1)**	**0.4 (0, 0.9)**
K6 (Psychological distress)	8 (5)	7 (5)	**0 (5)**	6 (5)	5 (3)	**-1 (5)**	**-0.2 (-0.6, 0.3)**	**-0.5 (-1, 0)**
PedsQL (generic HRQOL)	59 (21)	60 (19)	**0 (20)**	62 (16)	67 (15)	**+6 (21)**	**0.3 (-0.2, 0.7)**	**0.4 (-0.1, 0.8)**
PedsQL (cancer-specific)	65 (17)	64 (20)	**-2 (13)**	66 (16)	72 (11)	**+ 8 (16)**	**0.7 (0.2, 1.2)**	**0.5 (0.1, 1.0)**

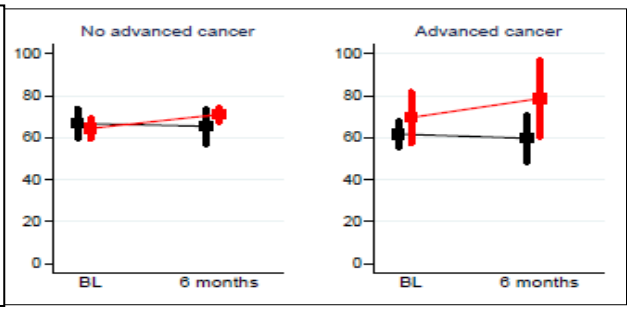


Figure 2. Mean cancer-specific HRQOL scores at baseline (BL) and 6-months), by advanced cancer status (red = PRISM; black = usual care)

2.1.2.7 *Adaptation of PRISM for patients with advanced cancer.* The phase II RCT included embedded requests for feedback regarding PRISM's usefulness and potential for improvement. Thematic comments from patients who entered the

study with advanced cancer and those who experienced progressive disease during the study period suggested PRISM should remain essentially the same, but that individual modules could include language relevant to the advanced cancer experience. For example, the goal-setting session could include opportunities to explore holistic hopes and how they could translate to actionable goals, the positive reframing exercises could include language about how negative self-talk can help identify worries about the future, and the meaning-making sessions could focus on what AYAs identify as important. All of these minor changes were thought to have potential to facilitate later conversations about AYA wishes, worries, and priorities. A more significant suggestion was to add an additional module to formally begin the process of advance care planning, in particular to focus explicitly on AYA values and perceptions of quality of life. Hence, we expanded the intervention script to reflect minor suggestions while adding a new session to introduce simple, evidence-based, and age-appropriate advance care planning exercises (select excerpts from *Voicing my Choices)*[74].

2.1.3 Rationale for this Study

Taken together, the background literature and our prior experiences underscore **three critical knowledge gaps**: (1) Although PRISM is feasible, our pilot RCT was not powered to test its impact specifically among AYAs with advanced cancer. (2) Although AYA and parent well-being are related, associations between AYA-PRISM and parent outcomes are unknown. And, (3) although PRISM enables AYAs to identify stressors and goals, how it translates to patient activation and subsequent engagement is unclear. Additionally, we will explore whether PRISM is associated with measurable biomarkers of stress and resilience. We propose to address these gaps in the current proposal.

3.0 Inclusion and Exclusion Criteria

3.1 Recruitment and Screening:

We will recruit AYAs and their primary caregivers from outpatient Clinics and inpatient wards of Seattle Children's Hospital, Texas Children's Hospital (Baylor), Children's Hospital Los Angeles (CHLA), and University of Pittsburgh Medical Center Children's Hospital. Research Associates (RAs) at each site will screen patients via review of the new diagnoses lists, tumor board rosters, attendance at weekly team rounds, clinic rosters and sign-outs, communication with clinicians, and/or overnight call lists, followed by a medical chart review to verify eligibility. Staff will verify the patient's diagnosis with a trained oncology provider.

Recruitment will occur either in person (inpatient hospital rooms and/or outpatient clinic) or by phone/video call/text (i.e., direct contact by study staff). Patients will either be approached inpatient/in clinic (including initial approach by the patient's nurse or other known member of clinic team) or will be mailed a letter or e-mail introducing them to the study and giving them the opportunity to "opt out" of future contacts if desired. If potentially eligible patients who receive the letter or email do not opt-out of being approached about the study, we may call them to assess their interest and arrange to discuss the study by phone/video or meet them in-person at an upcoming clinic visit. Study staff will reach out to potential participants (by phone/video, email,

text, or in clinic) to try and gauge interest in the study for a maximum of six attempts (with a maximum of 3 attempts wherein direct communication is achieved, such as leaving a voicemail message or having a conversation with the potential participant). Text communication will occur only after initial contact is made with a family via a non-text method.

Regarding privacy, hospital inpatient rooms and clinic rooms are all private. When by phone/video, patients and parents will be asked if they have time to talk and if there is a quiet space to discuss the study.

There will be a flyer posted in inpatient units and clinic areas. The flyer may also be handed out to potential participants before or during the consent conference if it occurs in person.

The RA will approach families and ask if they are interested in learning about a research study. Study personnel may contact patients and their parents to discuss the project, and answer questions by phone (and in advance of their clinic visit) or while at a regularly scheduled outpatient visit or inpatient. Should families prefer to continue to discuss the study in person, we will arrange a follow-up conversation regarding the study at the time of their clinic visit or inpatient admission, or while they plan to be at the hospital. If it is not feasible to conduct the consent conference in person, consent discussions will occur by phone call or video conference call (WebEx, Zoom, or Skype). Consent conferences will not be recorded. Study staff will use a phone guide for consent discussions over the phone/video. All consent methods will be used, in order to accommodate all patients, as well as to maximize recruitment to achieve study goals. Some patients come to clinic once every few months. The rationale for conducting the consent conference over the phone/video includes that in-person consenting may pose an infection risk to this subject population, e.g. COVID-19. In addition, in-person consenting may cause unnecessary subject burden, while obtaining consent by phone/video would achieve the same purpose without reducing subject informedness. Consenting by phone/video also allows potential subjects more time to consider participation. Furthermore, when speaking to potential subjects in person, providers may interrupt the consent conference to provide important clinical care, clinic or inpatient staff may advise us that the day is not “good” for the family to be approached, or illness status may preclude the patient from being cognitively able to provide consent/assent that day. When recruitment is done in person, the CRA will explain informed consent in a private area (e.g., clinic room, inpatient room).

Patients and families will be given an addendum to the consent form to participate in the optional heart rate variability component of the study. We will emphasize there will be no penalties if patients or families opt out of the HRV portion of the study. This optional procedure will be presented at the time of the consent conference. All patients fitting the eligible criteria 3.2.1.1-3.2.1.4 and 3.2.1.6-3.2.1.8 will be eligible for the HRV component of the study. In other words, patients will only be eligible for the HRV component at the Seattle Children’s site. Parents do not take part in the HRV component. In cases where it is necessary to minimize in-person contact with participants to minimize exposure risk (i.e. during COVID-19 pandemic), the HRV component will not be offered.

We recognize potential risks for adolescents involved in recruitment; there could be embarrassment or discomfort for adolescents if asked to participate. Adolescents may feel coercion to be part of the study. To mitigate these risks, we will emphasize the voluntary nature of the study to adolescents and parents and that the study will in no way impact or influence

clinical care. We will let adolescents know that their information will be kept confidential and that audio transcripts will be de-identified and audio recordings destroyed after transcribing. We will let adolescents know that they can change their mind about participating and may decide to withdraw from the study at any time.

Each of the participating sites has significant experience with clinic recruitment for studies and has developed processes to ensure best practices with study recruitment. These procedures and scripts also emphasize that any potential coercion on the part of parents should not take place, and that adolescents' decision for or against participation in the study does not affect the clinical care they receive.

The investigators and staff will be available to answer any questions from potential participants and participants via phone or email throughout the study. Any issues or concerns raised during enrollment processes will be reviewed by the PI and/or Co-Investigators and resolved within a timely fashion. We will emphasize that the decision of whether or not to be part of this study does not affect patients' ongoing care at their respective institutions.

3.2 Eligibility Criteria:

3.2.1 Inclusion Criteria FOR AYA PATIENTS (RCT & Run in)

3.2.1.1 Age 12-24 years

3.2.1.2 Patient aged 12-17 years: has signed informed assent and their parent/legal guardian has signed informed consent for study participation.

3.2.1.3 Patient aged 18-24 years: has signed informed consent for study participation.

3.2.1.4 Diagnosed with advanced cancer (progressive, recurrent, refractory disease, or any diagnosis associated with <50% survival), or any other progressive/recurrent brain or solid tumor, at least 2 weeks prior to enrollment.

3.2.1.5 Receiving care at Seattle Children's Hospital (SCH), Texas Children's Hospital/Baylor College of Medicine (BCM), Children's Hospital Los Angeles (CHLA), or University of Pittsburgh Medical Center Children's Hospital (UPMC)

3.2.1.6 Able to speak English language (for PRISM sessions)

3.2.1.7 Able to read English or Spanish language (for completion of surveys)

3.2.1.8 Cognitively able to participate in interactive interviews, PRISM sessions, and survey completion, as deemed by medical staff.

***Note: Concurrent parent participation is not required for AYA patient participation**

3.2.2 Exclusion Criteria FOR AYA PATIENTS:

3.2.2.1 Patient refusal to participate (any age), or parental refusal to participate for patients less than 18 years of age

3.2.2.2 Cognitively or physically unable to participate in interactive interview

3.2.2.3 Patient unable to read in the English or Spanish language

3.2.2.4 Patient does not have a diagnosis of advanced cancer or any other progressive/recurrent brain or solid tumor as defined in inclusion criteria.

3.2.3 Inclusion Criteria FOR PARENTS or GUARDIANS OF AYA PATIENT PARTICIPANTS to participate in SURVEY-COMPLETION (RCT phase only)

3.2.3.1 AYA Child of parent or guardian agrees to participate in study.

3.2.3.2 AYA child participant provides verbal assent or verbal consent if 18 or over for parent or guardian to complete surveys.

3.2.3.3 One parent per patient parent dyad.

3.2.3.4 Parent/guardian is cognitively and physically able to participate.

3.2.3.5 Parent/guardian is able to speak and read English or Spanish language.

3.2.3.6 Parent/guardian participant has signed informed consent for study participation

***Note: Parent survey-completion occurs ONLY in the RCT phase of the protocol (not in the run-in phase). Parent survey completion is not required for AYA patient participation.**

****Note: Only one parent may complete surveys.**

3.2.4 Inclusion Criteria FOR PARENTS, CAREGIVERS, GUARDIANS, SPOUSES, OR SIGNIFICANT OTHERS to participate in PRISM SESSION 6, "Coming Together" (where eligible) (RCT phase & Run in)

3.2.4.1 AYA meets above criteria listed in sections 3.2.1, AND

3.2.4.2 AYA participant randomized to PRISM intervention arm of study in RCT phase of study, AND

3.2.4.3 AYA participant provides verbal assent or verbal consent if 18 or over for parent, guardian, spouse, and/or significant other to be present during this session.

3.2.4.4 Parent/Caregiver/Spouse/Significant other is cognitively and physically able to participate

3.2.4.5 Parent/Caregiver/Spouse/Significant other is able to speak and read in English or Spanish

3.2.4.6 Parent/Caregiver/Spouse/Significant other has signed informed consent for study participation

3.2.5 Exclusion Criteria for PARENTS or GUARDIANS of AYA PATIENT PARTICIPANTS

3.2.5.1 AYA refusal to participate

3.3 Special populations: Please see section 17 for details about special populations including adults unable to consent, minors (individuals who are not yet adults), wards of the state, pregnant women, and prisoners.

4.0 Study-Wide Number of Subjects

4.1 Number of subjects:

Run-In PRISM-AC development, feasibility, and acceptability testing: We will enroll up to 30 AYAs on a "run-in" pilot trial to refine process measures in conducting the newly added 5th session that is part of PRISM-AC. This phase of the study will be conducted ONLY at Seattle Children's Hospital. Briefly, this "run-in" is designed as a cohort study to be conducted prior to launching the RCT phase of the study at Seattle Children's and is expected to last approximately 6-12 months.

Parent/Caregivers/spouses/significant others may participate in PRISM session 6 (family meeting called "coming together") but are otherwise not active study participants in this phase of investigation.

RCT phase: The target sample size is N=144 AYA participants (72/arm). Based on our prior work and characteristics of AYAs at participating centers (**Table 3**), we estimate identifying a total of 120 eligible AYAs/12-months (300 over the 30 months of enrollment). Assuming a conservative enrollment rate of 65% (versus 78% in phase II RCT), we expect to enroll and randomize 78 AYAs/12-months (target enrollment n=195 over the 30-months of recruitment). With a conservative attrition rate of 26% (due to medical complications as seen in pilot), we expect complete data collection on 144 AYAs (72/arm). This sample size achieves 80% power to detect an increase of 8.1 in mean Total PedsQL score, the main study outcome. Parent/Caregivers will also be invited to participate in this RCT phase of investigation as additional study subjects to complete surveys and participate in the PRISM session 6. Parents will complete surveys at the same time points as the AYAs. In our prior studies including AYA-parent dyads, >90% of caregivers participated. Hence, we expect complete data from a minimum of 128 caregivers (64/arm). Only one caregiver will be invited to complete questionnaires, and will be designated at enrollment.

Table 3. Annual number of AYAs with advanced cancer (12-25 yrs-old) who are eligible, enrolled, and evaluable at 3 months for RCT				
Site	Total	Eligible	Enrolled	Evaluable
Seattle Children's	45	35	23	17
Texas Children's	55	35	21	16
Children's Hospital, Los Angeles	55	30	21	16
Children's Hospital, University Pittsburgh Medical Center	35	20	13	9
Total/12-months	**190**	**120**	78	58
Total for 30-month recruitment period:			195	144

This is a 6-year study, including a 6-12 month run in, and a 5-year RCT of PRISM-AC compared to usual care among AYAs with advanced cancer or a progressive/recurrent tumor and their caregivers (6-mo preparation, 30-mo rolling recruitment, 12-mo follow-up, 12-mo data analyses and manuscript preparation). Study-wide, we intend to enroll a total of 174 AYAs (30 for run-in and 144 for RCT). Only SCH-based patients will enroll in the run-in. The RCT will be conducted at a 4 sites: Seattle Children's Hospital (SCH), Texas Children's Hospital/Baylor College of Medicine (BCM), University of Pittsburgh Medical Center Children's Hospital (UPMC), and Children's Hospital, Los Angeles (CHLA).

5.0 Study-Wide Recruitment Methods

All recruitment methods will be conducted and overseen by local sites per local practices. There are no study-wide recruitment methods (e.g., no call centers or national advertisements); however, the trial will be listed at clinicaltrials.gov and therefore identifiable by national search engines. Please see section 3.1 for more information about recruitment methods and screening.

6.0 Multi-Site Research

6.1 Enrolling sites. We will recruit consecutive AYAs and their primary caregivers from outpatient clinics and inpatient wards at the 4 participating sites (SCH, BCM, UPMC, and CHLA)

6.2 Coordinating site responsibilities. The Seattle lead CRA will ensure the following:

6.2.1 All required approvals have been obtained at each site (including approval by the IRB of record or any other contingencies and rules required by the NIH).

6.2.2 All sites have the most current version of the protocol, consent documents, and HIPAA authorization.

6.2.3 All modifications have been communicated to sites, and approved (including approval by the IRB of record and/or any other regulatory requirements) before the modification is implemented.

6.2.4 All engaged participating sites will safeguard data as required by local information security policies.

6.2.5 All local site investigators conduct the study appropriately.

6.2.6 All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

6.3 Study oversight.

Overall study oversite remains the responsibility of Dr. Abby Rosenberg at the Dana-Farber Cancer Institute. Due to her new engagement at Dana-Farber, she will have frequent check-ins with the coorninating center, Seattle Children's, to monitor progress on enrollment, intervention delivery, data completion, and protocol adherence. She will also be involved in monthly multisite calls to maintain up to date on study progress.

Seattle Children's will remain the coordinating center and maintain the following responsibilities on Dr. Rosenberg's behalf. The SCH lead CRA will have at minimum monthly meetings with each site to review and troubleshoot trial conduct and questions, including (but not limited to) regulatory oversight, recruitment, data collection, intervention delivery, clinical concerns and/or other concerns. The lead CRA will review current documents and any changes that are upcoming or approved. The lead CRA will review any interim results or necessary information the sites should have as well as all study procedures, including modifications, updates, study closure, etc. The DFCI lead interventionist (Junkins) will have at minimum twice monthly meetings with interventionist(s) to administer re-training as needed and review intervention delivery and fidelity. A lead SCH study team member will conduct yearly on-site or remote monitoring of participating sites for review of study documents and databases. This will include verification of consent/assent forms, documentation of eligibility, completeness of Case Report Forms (CRFs), and regulatory submissions and approval.

7.0 Study Timelines

Study activities include start-up, conduction and oversight, followed by dissemination of results. Projected activities and deliverables are described in Table 4.

Table 4. Anticipated timeline of research activities

Activities	Year 1				Year 2				Year 3				Year 4				Year 5				Year 6			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Run-In Feasibility and Acceptability																								
IRB Protocol Submission																								
PRISM-AC development																								
Recruitment																								
Analysis																								
RCT Implementation Activities																								
IRB Protocol Modification																								
Design of Case Report Forms and RedCap database																								
Conduct of PRISM RCT for AYAs with cancer																								
Recruitment																								
Follow-up																								
Monitoring and Analyses																								
Monitoring of PRISM intervention fidelity																								
Interim data analysis (design, program, and run)																								
Full data analysis (design, program, and run)																								
Manuscript submission and dissemination																								

8.0 Study Endpoints

8.1.1 Primary Endpoint: 3-month follow-up of last AYA participant including patient-reported outcome survey completion.

8.1.2 Secondary Endpoints:

8.1.2.1 3-month follow-up of last parent participant including parent-reported outcome survey completion.

8.1.2.2 3-month data collection of "palliative care activation" measures, including surveys, medical record data extraction.

8.1.2.3 12-month follow-up of last participant for exploratory cohort.

9.0 Procedures Involved

9.1 Enrollment

9.1.1 Once consent documents are signed and all questions addressed, the consenting RA or study staff will register the patient in the REDCap system. For the RCT (all participating sites), randomization will not occur until after baseline Resilience in Pediatric Cancer Assessment (RPCA) surveys are collected (see below). Site RAs will maintain original copies of all consent forms when possible. Consent forms completed electronically will be saved and stored on a restricted research drive.

9.2 Randomization (RCT only)

9.2.1 As a quality control measure, a randomization log will be maintained at SCH to track the participant ID, stratum, randomized assignment, and date of randomization. Patients will be randomized only after completion of baseline surveys and in a 1:1 ratio to receive usual, non-directive, supportive care without PRISM ("control" arm) or with PRISM ("experimental" arm). Randomization will be stratified by age (patients ages 12-17 versus ages 18-25) and site. Biostatisticians who will conduct data analysis will be blinded from the treatment group allocations.

9.2.2 Throughout the screening period until allocation of the control or PRISM, participants will be assigned a screening number, according to the chronological order of screening. Once enrolled, the participant will be assigned a study ID.

9.3 Scheduling of study procedures with participants

9.3.1 Run in

Upon enrollment, study staff will return to all participants to deliver the baseline RPCA survey and create a study calendar outlining survey due-dates and PRISM sessions. Staff will query participants about preferred survey completion; all patients will be offered electronic surveys in their preferred language. If English, the survey will first be offered by email via REDCap or via REDCap on a study team iPad. Spanish instruments will be available in paper-pencil form only. To compare survey data to our prior historical cohort studies, surveys in the run-in group will be collected at baseline, week 6 and week 12

(Figure 3A). Parent proxy report (as an option in cases where patients cannot fill out surveys) will not be offered in the Run-in.

Figure 3A. Schedule of Run-In Cohort Activities by Week Post-Enrollment

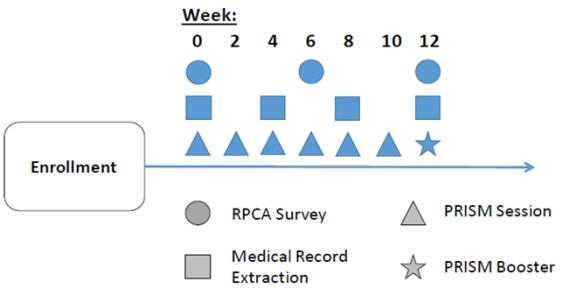
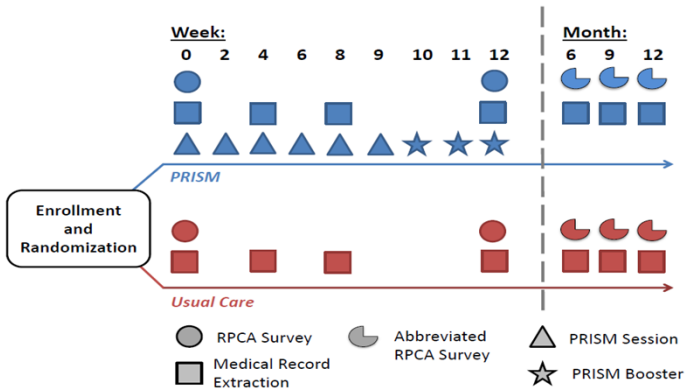


Figure 3B. Schedule of RCT Activities by Week Post-Enrollment



9.3.2 RCT participants:

9.3.2.1 Baseline Survey Completion. Upon enrollment, study staff will deliver the baseline survey in participant's preferred language (English or Spanish). The study will first be offered by email via REDCap or via REDCap on a study team iPad. Upon request, staff will offer paper-pencil versions and/or interview-based versions.

9.3.2.2 Randomization. Patients will be randomized following completion of baseline RPCA surveys. Staff will aim for the RPCA surveys to be completed immediately following enrollment. Baseline surveys will be collected within the two weeks. If surveys are not completed within this time-frame, staff will return to the participant to confirm interest and offer a digital (or, when requested paper-pencil or interview-based) survey to be completed. If participants do not complete the survey at that time, they will be removed from the study. For those who do complete the survey, following completion, staff at each site will register participants and receive their randomization allocation. They will then return to patients and families to relay this information and create a study calendar outlining survey due-dates and, where relevant, PRISM sessions. Where relevant, PRISM-sessions will be scheduled approximately every other week, beginning within the first week of enrollment following survey completion.

9.4 Overview and Session Details of Intervention Arm.

The original Promoting Resilience in Stress Management (PRISM) intervention consists of four, 30-50 minute, one-on-one, in-person sessions approximately 1-2 weeks apart, plus a session for AYA and caregivers, together (**Table 1**). Supplemental materials (e.g., media-links to resources, worksheets, text-based reminders, and a digital app to track and practice skills) are provided between sessions. The digital app is an interactive platform to practice the same PRISM exercises that are taught in the PRISM intervention script. Please note that the app's visual content is "fixed"/does not move. As such, all VISUAL components of the app are available in the PRISM App Screenshots document. All AUDIO content of the app is available in the PRISM App script appendix. The app is not being evaluated for safety and/or efficacy. Data

about the app will not be submitted to or held for inspection by the FDA. All digital data collected by the app is de-identified; we cannot connect data to individual users. We only know by population how often a given 'page' of the application is opened.

To increase translation and wider application of PRISM in the future, a trained non-clinical research associate administers it, as described in previous models and our pilot studies.[18,93] The 1st session occurs within 2 weeks of enrollment. Other sessions are scheduled around patient clinic and/or hospital visits (depending on concurrent illness and medical needs). Following the "Coming Together" session, intervention participants will be offered every other week "booster" contacts until they reach the 3 month point from enrollment. Although in person visits are preferred for all of the PRISM sessions, if a patient explicitly requests or if scheduling barriers preclude in-person visits, sessions may be done via phone or other web based communication (Zoom, WebEx, or Skype).

Details of the sessions are listed in **Table 1**. Briefly, session 1 ("Stress-management") focuses on mindfulness skills including deep breathing and relaxation techniques, and building awareness and acceptance of stressors. Session 2 ("Goal setting") teaches simple goal-setting skills (e.g., identifying realistic, concrete and actionable goals, planning steps towards their achievement, preparing for roadblocks and identifying alternative pathways). Session 3 ("Cognitive Restructuring") trains patients to recognize negative emotions and demoralizing self-talk and helps them develop skills to reframe these in a positive light. Session 4 ("Benefit Finding") focuses on finding meaning and/or benefit from difficult situations (including cancer).

For this study and the development of PRISM-AC, we will add a 5th main session focused on early advance care planning, using the age-validated and widely used *Voicing My Choices: A Planning Guide for Adolescents and Young Adults* (VMC, see full copy in appendix)[74]. Briefly, VMC was designed in partnership with AYA patients, parents, and *Aging with Dignity (agingwithdignity.org)* to mimic legal advance directives available for older adults. The document has been tested for feasibility and acceptability among AYAs with cancer and other life-limiting illness, and is the established standard of care for advance care planning in this age group. The instrument is designed to be introduced by trained staff (including research staff and non-medical personnel), and completed by AYAs either with such staff present, with family, or independently, depending on AYA preferences. For the purposes of the present study, we consulted with VMC creators regarding a recommended approach and ideal VMC content to be included in PRISM-AC.

Because PRISM sessions 1-4 build skills to identify goals and values, VMC is an appropriate culmination of skills and offers concrete examples of how to utilize them. For this reason, PRISM-AC will introduce specific VMC pages (see appendix) as examples of how such skills might be helpful in cases of advanced cancer and progressive/recurrent tumors, and then offer opportunities to practice them in real time. Interventionists will only complete up to four specific pages with AYAs: page 4 "My Comfort", page 5 "My support", page 8 "My Friends and Family to Know", and page 9 "My Spiritual Thoughts". If AYAs express a desire to do any of the other pages, we will redirect them to their medical team, social work, and/or their parents. Specifically, we will introduce the VMC booklet and then highlight the pages and allow participants to choose the one(s) that resonate with them "a la carte" (see appendix). Although advance care planning includes sensitive topics like end-of-life planning, this booklet was selected specifically because they are more generic and applicable to all AYAs with illness. If an AYA has no specific preferences, the interventionist will direct the patient to the page about "my comfort" (VMC page 4) and complete that page during the session.

Introductory scripts were approved by VMC developers and are provided in the Voicing My Choices Session appendix document. Following the completion of VMC pages during the PRISM-AC session 5, AYAs will keep their booklet and have opportunities to continue exercises on their own, with family, with study staff during return visits (see "boosters" below), or with medical staff, as appropriate and/or desired. Again, interventionists will only do the four selected pages with the AYA and will redirect as appropriate if the AYA wishes to complete other pages. Finally, at the close of the fifth session, AYAs will be given a checklist of all the skills and topics covered throughout PRISM-AC, including VMC content. Staff will ask what they would like to share with their parent(s), spouses, significant others, or guardians during the final session (see "coming together" below) such that the interventionists can prepare to facilitate the final session.

The final session ("Coming together") allows patients to reflect on the skills they have learned, to identify those that resonate and work for them, and to share their thoughts with parents, family-members, and loved ones. During this last session, parents, spouses, caregivers, and/or significant others are explicitly asked to join and listen to the discussion. Study personnel will review and share with attendees the explicit skills endorsed by patients on the aforementioned checklist and encourage shared conversation about how parents/patients can support one another. As above, for families where parents prefer Spanish or another non-English language, this final session will be conducted with a trained interpreter of the native language of the parent. In the phase II RCT, the majority of the PRISM arm opted into the fifth session even though it was an optional study procedure in that study (n = 38 out of 40 who completed all four PRISM sessions). Because advance care planning requires parent participation and an aim of this study is to determine if the additional PRISM session #5 will enable those discussions, we have opted to include the coming together as a standard in this and all future projects. However, patients may still opt out of the coming together session if they request to do so explicitly. We will continue to follow them and offer an optional booster session with the interventionist in lieu of the family meeting in these cases. Additionally, the coming together session may not be feasible if parents/caregivers/guardian/spouse/significant others have not agreed to be a part of the study. In such cases, we will re-offer participation in real time. If parents/caregivers/guardians/spouses/significant others still decline, then we will skip the family meeting.

Sessions may be combined (maximum 2 modules/session) based on patient preference/ research discretion for reasons including (but not limited to): illness severity/progression or patient availability.

All of the sessions of the PRISM will be audio-recorded as possible, barring issues with the recorder or refusal of the patient to be recorded. Sessions will not be recorded through WebEx, Zoom, or Skype platforms. Administrators of PRISM will explain that the sessions will be taped and reviewed by the study team with the goal of assessing adherence to the protocol, inclusion of required elements, and presence/absence of additional information with the exception of the feedback questions. As possible, the PI or supervising team member will review the first 6 sessions for each interventionist, and score them for fidelity using a standardized tool (see appendix). After the first 6 sessions are reviewed for each interventionist, approx. one in every 5 sessions will be randomly selected to be monitored for fidelity, with feedback and re-training regarding adherence to protocol and approach to be refined if needed.

Participants on the intervention arm will also receive once every other week "booster" contacts until they reach the 3 month point from enrollment, for both the run in and the RCT. These will include brief (10-20 minute) in-person contacts in clinic, in the hospital, via phone or other web

based communication (Zoom, WebEx, or Skype) or by email and will consist of opportunities to practice specific skills (at the patient's discretion). Study staff will contact patients to coordinate such visits and will prompt them by asking: "Would you like to review or practice any of the resilience skills?" [If needed, staff will remind patients of all 5 sessions. If patients are willing, study staff will ask,] "Which one?"

Finally, in order to practice skills between sessions, all participants with smart phones assigned to the PRISM will be invited to download the PRISM app. This platform is available in both the iTunes Store as well as the Google Play Store, however, the content within the app is only accessible with a password that will be provided by the PRISM team. App passwords are a short code specific to site and group arm (i.e. PRISMAC_SCH_Control) that participants are prompted to enter immediately upon opening the PRISM app. The app includes digital content of all paper-pencil "cheat sheets" and worksheets (see manual in appendix for paper versions and screen-shots of app). Participants will be given access to both types of materials. Use of the app is optional for study participation. Where relevant (i.e., for participants without a smartphone), we will provide iPads to be used in hospital settings. Note these participants may need to establish email account for such purposes if they do not already have one.

Each site's interventionist(s) will be responsible for delivering PRISM to their site's participants in the majority of cases. In rare circumstances (e.g., interim coverage for unexpected lapses in staffing), trained interventionists from SCH or DFCI may deliver sessions to other sites' participants pending approval from the site's IRB. In these instances, the site coordinator will be responsible for scheduling the session and setting up a videoconference using the site's own HIPAA compliant software (i.e., Zoom, WebEx) for session delivery. Thus, no contact would occur between SCH or DFCI interventionists and site participants outside of session delivery. At the start of the session, the site coordinator will briefly join the video call in order introduce to the patient and SCH or DFCI interventionist using first names only. Any correspondence between site coordinators and SCH or DFCI interventionists regarding session scheduling will use study ID numbers only. All interventionists will have a Bachelor's degree or higher and will be trained according to Section 21.1.

9.5 Data collection schedule for study staff.

9.5.1 For the AYA and caregiver survey schedules for both the run in and RCT, please see Figures 3A and 3B.Medical record data will be collected at baseline and monthly until the 3-month mark in both the run in and RCT. Additional medical record abstraction will occur for the RCT at 6-, 9, and 12-months. The caregiver to complete the surveys will be designated at enrollment. RA's at each site will prospectively abstract information from the medical record using a study-specific case report form (CRF) adapted from prior studies.[94] This will include: (1) AYA participation in goals of care conversations: dates of documented conversations with medical team regarding prognosis, treatment decisions, and/or goals of care, whether or not AYA was present, and if there is documented active AYA participation. (2) Benchmarks of Palliative Care Utilization: number and frequency of documented psychosocial and palliative care referrals and meetings, hospice referrals, limitation-of-resuscitation orders, completion of advance care planning documents, and end of life details (i.e. location of death, clinical involvement and family support (sibling & financial assessments)). (3) Clinical covariates: the AYA's diagnosis, cancer/tumor-directed treatments, and intensity in the past month,[38] number of and reason for hospital days

(anticipated and unanticipated), prescription psychiatric and/or mood altering medications, prescription opioids and other pain medications, and number of documented palliative care/psychosocial encounters. These variables were selected based on prior evidence that child well-being and family psychosocial needs affect immediate psychosocial outcome metrics (e.g., psychological distress and quality of life).[38,95]

9.6 Resilience in Pediatric Cancer Assessment (RPCA) Survey (all participants, including AYAs of run-in cohort):

Patient (and parent)-reported outcomes (PROs) will be measured with the Resilience in Pediatric Cancer Assessment (RPCA), a comprehensive survey comprised of age-appropriate validated instruments (**Table 5**). The RPCA was designed with AYA and parent stakeholders to capture patient-reported outcomes associated with resilience resources.[16] We have successfully used it in several of our prior studies.[16,17,88-90,96] The survey includes embedded validated instruments as well as standard demographics (age, sex, and race/ethnicity, education, income, number of children in the home). For the present study, we added an ad-hoc checklist querying the number and duration of discussions the family has had with health-care, psychosocial, or palliative care teams regarding concepts of prognosis, treatment goals, AYA hopes, worries, or concerns, and to what degree AYAs were involved in such discussions.

Table 5. Resilience in Pediatric Cancer Assessment (RPCA) Instruments

Objective	Concept	Instrument(s)	Source
Aim 1 (AYA Outcomes)	HRQOL (Primary Outcome)	PedsQL Generic Core and Cancer Modules (PedsQL)[20,21]†‡	AYAs
	Anxiety/ Depression	Hospital Anxiety and Depression Scale (HADS)[22]†‡	
	Symptom Burden	Memorial Symptom Assessment Scale (MSAS)[24]†‡	
	Hope	Hope Scale[25]†	
	Resilience	2-item Connor-Davidson Resilience Scale[97]	
		10-item Connor-Davidson Resilience Scale[94]†	
Aim 2 (Parent Outcomes)	Anxiety	Generalize Anxiety Disorder Screener (GAD-7)[26]	Caregivers
	Depression	Patient Health Questionnaire (PHQ-8)[27]	
	HRQOL	Medical Outcomes Study Rand Short-Form 36[29]‡	
	Family Experience	Family Experience Survey (HCAHPS)[30]	
Aim 3 (Activation)	Activation	Decision Making Involvement Scale[31]‡	AYAs and Caregivers
		Survey of Caring for Children with Cancer (SCCC) †‡	
		Patient Activation Measure (PAM-13)[120] †	
		Benefit Finding[121] †	
	Demographic Questionnaire	Demographic information †	AYAs and Caregivers
	COVID-19 Impact	The COVID-19 Impact Questionnaire ‡	AYAs and Caregivers
	Quality of Care Checklist	Quality of Care Checklist †	AYAs

† Included in RPCA for "run-in"
‡ Included in abbreviated RPCA surveys

The full RPCA survey will be administered at baseline and week 12 in the RCT. (**Figure 3**). In order to optimize engagement, patients in both arms of the study will be asked to complete the abbreviated Resilience in Pediatric Cancer Assessment (aRPCA) during the

prospective longitudinal follow-up period (months 6, 9, and 12). The aRPCA will assess only selected outcomes (patient outcomes of HRQOL & symptoms, parent outcomes of HRQOL, and family activation variables), as described below. For those on the non-intervention arm of the study, staff will schedule a "study check-in" visit to coordinate the aRPCA completion and thank families for their continued participation.

In both arms of the study, if any participant declines to complete the full RPCA survey and/or if participants or family members report participants are unable to complete the survey due to illness complications, staff will offer in the following order: (a) an in-person (English-speaking, interview based) survey session, and (b) abbreviated versions of the questionnaire for patients to complete. Only at follow-up timepoints and in cases where participants are too ill to provide self report in writing or interviews, staff will offer abbreviated versions of the survey for *parents* to complete as proxy respondents. These options will be offered in an effort to collect full data for primary endpoint assessment, including the aRPCA or even a survey containing only the primary outcome of HRQOL.

Participants in both arms of the study will be scheduled for their surveys at the time of enrollment and then reminded prior to each survey due-date. Participants will be contacted by phone, email or mail to receive their RPCA survey. If we have not received a response within a day of initial contact, participants will receive up to 4 follow-up phone calls, texts, and/or emails (approximately once weekly) within a 28 day window before and after surveys are due. Participants will remain eligible for subsequent survey completion and follow-up even if surveys are missing and the same procedures will be conducted for each survey due-date until the 12-month follow-up point.

9.6.1 **RPCA item details**

9.6.1.1 AYA Version (not included in parent surveys):

9.6.1.1.1 Pediatric Quality of Life (PedsQL) Generic and Cancer Module Teen Reports. The PedsQL 4.0 Generic and 3.0 Cancer Module include 50 items evaluating HRQOL of AYAs with cancer. Queries assess physical, emotional, social, and school well-being, plus cancer-related pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance, and communication. Scales are available for teens and young adults,[20,21] and have been used successfully with low rates of refusal and minimal missing data.[98] Items are rated on a 5-point Likert scale and total scores transformed to a 0-100 scale with higher scores representing better HRQOL. Internal consistency ranges from 0.75 to 0.92.[21] These instruments are included in all surveys, including the full surveys for the run-in Cohort and RCT, and the abbreviated survey for the RCT.

9.6.1.1.2 Hospital Anxiety and Depression Scale (HADS). The HADS assesses mixed affective symptoms in patients with serious illness.[22] It has been validated in AYAs with chronic illness[99] as well as AYA cancer survivors.[100] The scale has excellent reliability (α=0.83-0.82).[22] It consists of 7 questions for anxiety and 7 for depression. Each is scored from 0-3, for a total range of 0-21 points per subscale. "Caseness" of anxiety and depression is defined as ≥8 points, with sensitivity/specificity of 0.8/0.9 for anxiety and 0.8/0.8 for depression.[22] This

instrument will be included only in PARTICIPANT surveys. It will be included in both full and abbreviated surveys (RPCA and aRPCA) in order to optimize primary outcome data collection in the event of illness complications or death.

9.6.1.1.3 Memorial Symptom Assessment Scale (MSAS). The MSAS measures the presence, severity, frequency, and extent of bother from symptoms with high consistency (α>0.8).[23,24] For the run-in, we will use the Pediatric-validated MSAS instrument (32-items) and for the RCT, we will use a version of the MSAS that has been previously developed for and used among children with advanced cancer (26-items Likert scales assess physical (pain, fatigue, drowsiness, nausea, anorexia, cough, diarrhea, vomiting, itching, skin issues, constipation, dysphagia, dry mouth, numbness, sweating, dyspnea, and dysuria), and psychological (irritability, sleep disturbance, nervousness, sadness, worrying, difficulty concentrating, and image issues) symptoms. Total- and sub-scores are calculated as an average, with higher scores representing higher symptom burden. This instrument is included in all surveys, including the full surveys for the run-in Cohort and RCT, and the abbreviated survey for the RCT

9.6.1.1.4 Hope Scale. The Snyder "Hope" Scale contains 8 hope items plus 4 "filler" questions, and measures "the overall perception that one's goals can be met."[25] The instrument was named based on patterns of hopeful thought and assesses patient-reported efficacy by assessing the ability to generate a route to one's goals (termed "pathway" thoughts) and the ability to initiate and maintain the actions necessary to reach a goal (termed "agency" thoughts). Prior studies performed among AYA cancer patients have shown that high-hope individuals have improved psychosocial outcomes. The instrument has been validated in both adult and pediatric settings and is scored on an 8-point Likert scale. Higher scores imply greater levels of hopeful thought patterns. Cronbach's alphas for the whole scale range from .74 to 0.84. This instrument is included in the full (not abbreviated) surveys for both the run-in cohort and the RCT.

9.6.1.1.5 Connor-Davidson Resilience Scale. The Connor-Davidson Resilience Scale is a reliable and widely used instrument to measure inherent resiliency.[97] Questions revolve around personal problem-solving and approaches to adversity. The 10-item instrument has high internal consistency (Cronbach's alpha = 0.85), and has been used in diverse populations including adolescents, parents and cancer patients.[97,101] Correlative studies have evaluated the scale with other psychosocial measures such as psychological distress,[102] PTSD,[103] and social support.[104] It also has been used in pharmacologic and other intervention studies to model modifiable outcomes Each item consists of a 5-point Likert scale (scored from zero to four) for total of 40 points. The mean score among well US adults is 31.8, with higher scores reflecting greater resilience. This instrument is included in the full (not abbreviated) surveys for both the run-in cohort and the RCT.

9.6.1.1.6 Patient Activation Measure. The 13-item PAM includes 3 domains to measure AYA or parent knowledge, confidence, and willingness to act regarding the AYA's health.[39,105,106] It is well-validated among chronically ill and healthy

adult populations, and studied among AYAs and parents of children with cancer.[106] Both patient and parent versions have acceptable internal consistency and reliability (α=0.86 and 0.85, respectively). Items are scored on a 4 point Likert scale; responses are summed and transformed to 0-100.[107] Higher scores suggest higher activation and thresholds distinguish 4 categories: (1) staying the course; (2) taking action; (3) confidence and knowledge to take action; and (4) believes active role important. This survey is only included in the run in.[39]

9.6.1.1.7 Benefit/Burden Scale for Children: The Benefit/Burden Scale for Children (BBSC) was adapted by pediatric psychosocial clinicians from the Benefit Finding Scale for Children.[108] BBSC measures benefit finding, illness-perceived burdens and psychological functioning in children. Factor analysis revealed a two-factor solution and each subscale had strong internal validity; benefit finding (α = .852; 10 items) and illness-related burden (α = .804; 10 items). All items are answered on a 5-point Likert scale ranging from "not at all" to "very much." This survey is only included in the run in.

9.6.1.1.8 Quality of Care. The run in will include a check list asking AYAs about quality of care from their care team.

9.6.1.2 Parent version (not included in AYA surveys)

9.6.1.2.1 Generalized Anxiety Disorder Screener (GAD-7). This 7-item survey is commonly used to identify cases of generalized anxiety disorder and to assess symptom severity.[26,109] Participants are asked how often during the last two weeks they have been bothered by each of the 7 core symptoms of generalized anxiety disorder. Response options include "not at all," "several days." "more than have the days," and "nearly every day," scored as 0, 1, 2, and 3, respectively. Therefore, GAD-7 score range from 0 to 21, with scores of ≥5, ≥10, and ≥15 representing mild, moderate, and severe anxiety symptoms levels, respectively. Internal consistency was acceptable (α=0.89). Inter-correlations ranged from r = 0.45 to r = 0.65.This instrument is included in the full (not abbreviated) surveys for the RCT.

9.6.1.2.2 Patient Health Questionnaire (PHQ-8). This 8-item survey is widely used among general populations, patients with chronic illness, and in parents of children with cancer.[27,28,110-113] It is identical to the also widely used PHQ-9, with the exception that PHQ-8 deletes a question about suicidal ideation. Research indicates that the deletion of this question has a minimal effect because self-harm thoughts are relatively rare and this item is the least commonly endorsed item on the 9-item survey. Furthermore, the original validation studies of the two instruments demonstrate similar psychometrics and identical thresholds for depression severity. The instruments have excellent psychometric properties (α=0.86-0.89). Each item is scored on a 4-point Likert scale and the sum (0- 27) indicates the degree of depression, with scores of ≥5, ≥10, and ≥15 representing mild, moderate, and severe depression. Scores correlate with functional status and are sensitive to behavioral interventions.[113,114] This instrument is included in the full (not abbreviated) surveys for the RCT.

9.6.1.2.3 Medical Outcomes Study Rand 36-item Health Survey (SF-36). The SF-36 is the most widely used generic measure of HRQOL among U.S. Adults.[115] It incorporates 8 concepts: physical functioning, body pain, limitations due to physical health problems, role limitations due to personal or emotional problems as well as emotional well-being and social functioning, energy, fatigue and general health perceptions. It includes a single item regarding perceived change in health.[29] Internal reliability ranges from α=0.78-0.93. This instrument is included in both the full and abbreviated surveys for the RCT.

9.6.1.2.4 Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS). This survey is a widely used and standardized tool to measure patient and family perspectives on hospital care.[30] It has been endorsed by the National Quality Forum (NQF) in order to allow for cross-hospital comparisons. The survey includes a core set of questions that can also be combined with customized project- or site-specific items. For this study, we have included domains regarding care for teenaged patients, communication and child-centered care, and overall hospital ratings. All items are scored on a Likert Scale (for example, to the question "During this hospital stay, how often did providers involve your child in discussions about his or her health care?" response options include "Never," "Sometimes," "Usually," and "Always." This instrument is included in the full (not abbreviated) surveys for the RCT.

9.6.1.3 Both AYAs and Parents

9.6.1.3.1 The Decision-Making Involvement Scale (DMIS). The 30-item DMIS was developed to assess child and adolescent involvement in decisions having to do with illness management.[31] Specifically, items assess child- and parent-behaviors that reflect the way children are involved in decisions, regardless of who ultimately makes the decision. Both AYAs and parents are asked to reflect on an important conversation from the past month and then respond to items based on a 4-point Likert Scale. Although there is a potential total score, instrument authors suggest scoring based on subscales assessing specific dimensions of involvement, including "child seek," "child express," "parent seek," "parent express," and "joint/options." Range of scores for each subscale = 0-4 and Cronbach's alpha = 0.68-0.71. This instrument is included in full and abbreviated surveys for the RCT.

9.6.1.3.2 The Survey about Caring for Children with Cancer (SCCC). This questionnaire was developed from literature and focus groups of parents and medical providers to identify key domains relevant to caring for children with advanced cancer. Items were adapted from existing validated surveys[116] and evidence-based guidelines.[117] The survey has been extensively tested for content, wording, response burden, and cognitive validity.[118] It has been used in multiple pediatric palliative care clinical trials, with several key analyses conducted by the PI.[82,119,120] For this study, we included select items to assess parent-/patient- perceptions of prognosis, treatment goals, ability to express hopes and worries, as well as questions assessing satisfaction with overall care, and an ad-hoc checklist querying the number and duration of discussions the family has with health-care, psychosocial, or palliative care teams regarding prognosis, treatment goals, AYA hopes and worries, and to what degree AYAs

were involved in such discussions.[75,121] This instrument is included in full and abbreviated surveys for the RCT and the run-in.

9.6.1.3.3 The COVID-19 Impact Questionnaire. (COVID-IQ) This 7-item, self-report questionnaire was developed for this study to assess perceived impact of the COVID-19 pandemic on AYAs and parents. Items assess worry/anxiety related to COVID-19, life events as a result of COVID-19 (e.g., loss of job, missed school), lifestyle changes (e.g., social distancing), and known COVID-19 symptoms/diagnoses/treatments of self and family members. Respondents are invited to provide free text responses for two additional items: 1) "What is helping you through the COVID-19 pandemic" and 2) "Please tell us about other effects of COVID-19 on yourself, your child(ren) and/or your family, both negative and/or positive." Lastly, respondents are asked to rate the extent to which their responses to other survey questionnaires were impacted by the COVID-19 pandemic.

9.7 Optional Heart Rate Variability Procedures

9.7.1 Data Collection

HRV will be measured using the Actiheart 5 external device (CamnTech, Inc, UKFDA class 2, 510(k) number K052489). The Actiheart 5 is an FDA-approved, lightweight, wireless electrocardiogram (ECG) monitor that attaches to a patient's torso via two standard ECG electrodes. Patients who consent to the optional HRV measurement portion of the study will be given their Actiheart monitor at enrollment. A study CRA or investigator will place the monitor on the patient and ensure adequate ECG signal acquisition, or a study CRA will instruct the patient on placing the monitor themselves. The patients will wear the monitor for a 24h period, and then return the device to a study team member. The devices will be collected at the next planned clinic appointment if outpatient, or the next day if inpatient.

The HRV monitoring would not be expected to affect the subject's usual clinical care. Subjects could undergo lab draws, clinic visits, receive chemotherapy, and maintain their usual level of activity without interference from the HRV monitor. If a subject needed to undergo emergent imaging of the chest (where the HRV device may obstruct some of the visual field), or an emergent surgical procedure while wearing the monitor, it would simply be removed. The study team would otherwise coordinate HRV monitor placement so that it does not overlap with planned chest imaging or surgical procedures. If a subject need to remove the monitor for any reason, we would not expect the subject to replace and wear the monitor again during that 24-hour recording period.

9.7.2 Data Collection Schedule

HRV data will be collected at clinically relevant and study specific time intervals where possible (**Table 6**). When not possible, HRV data collection will be scheduled at the patient's convenience.

Table 6. HRV data collection schedule					
Time Point	T1 (Baseline)	T2 (PRISM session #1)	T3 1 month (survey timepoint)	T4 3 months (survey timepoint)	T5 6 months (survey timepoint)
Where?	In clinic/at home OR inpatient	In clinic/at home OR inpatient	In clinic/at home OR inpatient	In clinic/at home OR inpatient	In clinic/at home OR inpatient
How long?	24 hours	24 hours	24 hours	24 hours	24 hours

10.0 Data and Specimen Banking

10.1 Data Storage and Confidentiality

De-identified data (including medical record, RPCA survey data, and transcripts of recorded sessions and/or interviews) will be stored indefinitely within a database saved on a password protected server at Seattle Children's Research Institute. Upon completion of data collection, SCH will transfer the limited dataset to DFCI per the Data Transfer Agreement. Original surveys will be saved at SCH for 10 years or until final analyses are completed, whichever occurs last, in order to ensure data quality. Only study staff with human subjects training will have access to the data, subject to approval by the SCH site PI, Dr. Yi-Frazier. De-identified study data will be banked indefinitely for future use by the group of investigators conducting the study and access will be controlled by the PI's. PIs will verify that additional analyses have IRB approval. No data will be withdrawn from the study database. Results of initial analyses will be shared with participants if participants request on the consent form that they would like a summary of study results.

10.2 Data and/or Sample Sharing

Data will not be shared outside the group of investigators conducting the study but will be fully shared during and after the study with investigators in the group. When other investigators are interested in new analyses, the PIs will verify they have IRB approval to conduct additional analyses. De-identified study data will be banked indefinitely for future use by the group of investigators conducting the study and access will be controlled by the PI's. Future studies will formally test the intervention once its feasibility is confirmed. Should the intervention be effective, it will be made publicly available for use by the broader medical communities caring for AYAs with serious illness.

11.0 Data Analysis/Management

11.1 Run-In Cohort*:* Data will be analyzed descriptively, including demographic and clinical characteristics of participants (i.e., age, sex, cancer or tumor-type, time since diagnosis, number of days in hospital during PRISM study). Eligible AYAs who decline to participate will be asked to provide a reason for declining the study and the above characteristics will be obtained from the medical record; such that we can compare participants and non-participants to determine biases in enrollment preferences.

11.2 "Feasibility" will be defined as: (1) at least 70% enrollment of approached and eligible patients; and (2) at least 70% completion of the 5 main PRISM sessions (not including "Coming

Together," as we have done for prior feasibility determinations) among enrolled patients. "Acceptability" will be assessed qualitatively, as we have done in all prior pilot studies of PRISM's development. Briefly, prior to each session (beginning with session #2), interventionists will solicit feedback regarding the usage and utility of the prior learned skill(s). Following the final session, we will solicit more detailed feedback regarding timing and value of the intervention and its content (see PRISM manual and Voicing My Choices session in appendices). Because the additional session involving early advance care planning is new for this study, we have designed additional pointed questions to gather user feedback about these exercises, including their perceived value, format preferences, timing, and if/how the session compares to the other skills (See Voicing My Choices appendix document). Finally, baseline and follow-up RPCA scores will be determined and these data will be entered into the secure database. For this pilot study, we will describe pre-and post-intervention scores and score changes for each instrument, with effect sizes calculated accordingly.

11.3 Randomized Controlled Trial (RCT): The primary statistical analyses will be intention-to-treat to avoid confounding by non-random participant attrition. Demographics, clinical characteristics, and items within the RPCA will all be summarized at each time-point using descriptive statistics: frequencies and proportions for categorical variables, means and standard deviations for continuous variables, or median and interquartile range if distribution is skewed. All analyses will be adjusted for patient age and site, as randomization is stratified by age and site, as well as baseline characteristics clearly imbalanced between groups. Additional baseline characteristics we consider as potential confounders include sex, race, and primary language spoken at home.

11.3.1 Sample Size Determination and Power

11.3.1.1 Our focus for sample size estimation is *the primary outcome: AYA PedsQL generic core scores at 3-month observation.* Sample size is based on published data from the pediatric advanced cancer population, where baseline scores were normally distributed with mean 70.9 and standard deviation 17.2.[122] Assuming 26% attrition, we will randomize 195 AYAs (98 per arm) to obtain an evaluable sample size of 144 AYA participants (72 per arm). This sample size achieves 80% power to detect an 8.1 point difference in the mean 3-month total PedsQL score (Table 6).

11.3.1.2 Power calculations for select secondary AYA outcomes are listed in Table 6.

11.3.1.3 Parent Reported Outcomes*:* Assuming >90% caregiver participation (as in our prior studies), we anticipate a minimum sample size of 128 caregivers (64 per arm). This caregiver sample size achieves ≥80% power to detect reasonable effects for parent outcomes, based on standard deviations and other parameters from our preliminary data and published literature (Table 7).

Table 7. Detectable Differences in selected Mean Instrument Scores Between Groups Given 80% Power and 5% Type I Error Rate						
Aim	**Sample (N)**	**Outcome (Instrument)**	**Sample Mean (SD)**	**Source**	**MCID***	**DD (SD)**
1	AYAs (144)	Quality of Life – General (PedsQL 4.0)	70.9 (17.2)	Published Data[122]	4.4	**8.1 (17.2)**
		AYA Quality of Life – Cancer (PedsQL 3.0 Cancer)	65.3 (16.3)	Phase II RCT	(not published)	**7.7 (16.3)**
		Anxiety (HADS-A)	5.9 (3.4)	Phase II RCT	1.3-1.8	**1.6 (3.4)**
		Depression (HADS-D)	5.2 (3.6)	Phase II RCT	1.5	**1.7 (3.6)**
		AYA Hope (Hope Scale)	Mean 50 (8.3)	Phase II RCT	(not published)	**3.9 (8.3)**
2	Parents (128)	Anxiety (GAD-7)	2.95 (3.4)	Published Data[26]	(not published)	**1.7 (3.4)**
		Depression (PHQ-8)	3.3 (3.7)	Published Data[123]	5	**1.8 (3.7)**
		HRQOL-physical (SF-36 PCS)	50.3 (6.9)	Published Data[124]	3-5	**3.4 (6.9)**
		HRQOL-mental (SF-36 MCS)	42.9 (11.9)	Published Data[124]	3-5	**5.9 (11.9)**
*Legend: MCID: Minimal Clinically Important Difference (*reported when published); DD: Detectable Difference in Mean*						

11.4 Randomization

11.4.1 The randomization algorithm will be constructed by the study statistician using a permuted blocks scheme with varying block sizes; only the statistician will be aware of the block sizes until completion of the study. A statistician independent of the study will prepare the final randomization list, which will be administered by a clinical research associate independent of the study using the SCH/UW REDCap. Randomization will be stratified by age (patients ages 12-17 versus ages 18-25) and site.

11.5 Analysis Plan

11.5.1 Overview. The primary statistical analyses will be intention-to-treat to avoid confounding by non-random participant attrition. Demographics, clinical characteristics, and items within the RPCA will be summarized at each time-point using descriptive statistics: frequencies and proportions for categorical variables, means and standard deviations for continuous variables, or median and interquartile range if the distribution is markedly skewed. All analyses will be adjusted for site and patient age, as randomization is stratified by these 2 variables, as well as baseline characteristics clearly imbalanced between groups.

11.5.2 Primary Outcome. Our primary outcome is *AYA reported HRQOL* at 12 weeks. Because the amount of change depends strongly on the initial HRQOL at baseline we will control for baseline HRQOL as a covariate in the regression. Regression models will be used to estimate mean-level differences and 95% confidence

intervals comparing scores in the PRISM intervention to those in usual care. The mean total PedsQL generic core score will be the outcome, and the PRISM intervention the predictor, of interest. A generalization of the two-sample t-test based on a contrast of the regression model will examine if there is an increase in PedsQL scores from baseline for PRISM versus usual care at the primary time point of interest, 3 months following enrollment. The same analysis will be undertaken for the domain subscales of PedsQL (physical and psychosocial), the cancer-specific module, and secondary outcomes included in AYA surveys. Subgroup analyses will explore whether the effect of the intervention is modified by medical covariates, symptom distress, and/or concurrent parent distress. Response type (survey, interview, or parent proxy) will be included in sensitivity analyses and data reported separately if indicated. The rationale for these subgroup analyses is grounded in prior findings suggesting symptoms and parent wellbeing are associated with patient HRQOL.[83,122]

11.5.3 Secondary Outcomes

11.5.3.1 The goal for parent outcomes is to evaluate the effect of the intervention on *parent psychological distress* and HRQOL. Mean total scores from each parent instrument at 12 weeks will be the secondary outcomes of interest. We will model distress and HRQOL separately and follow a similar approach to the analyses for continuous outcome measures in Aim 1. As sex and baseline patient HRQOL may be predictors of these outcomes,[78,125] each will be included if imbalanced between arms.

11.5.3.2 To compare patient and caregiver *activation*, we will measure patterns in multiple domains: AYA- and parent-reported Decision-Making Involvement Scores, AYA participation in goals of care conversations, and formal palliative care service utilization including documented referrals for hospice and charted decisions to limit resuscitative efforts. For all outcomes, results between trial groups will be compared using analysis of variance with trial group as the factor of interest. We will explore whether change in activation scores are correlated within families and/or modified by parent/child characteristics (sex, psychological distress scores, cancer/tumor-type, among others) using ordinal logistic regression models with cumulative logits, where change activation level is categorized as negative, null, or positive.

11.5.3.3 **Exploratory analyses** will evaluate prospective and longitudinal survey and clinical data beyond month 3 (primary endpoint) at months 6, 9, and 12 of the study. Comparisons between groups will still use an intention to treat approach as described above. Additionally, we will explore the relationship between biomedical variables and patient reported anxiety and depression through a combination of paired and unpaired t-tests, chi-squared (or Fisher's exact) tests, and linear and logistics regression. HRV will be measured in 24-hour increments using both time and frequency domain parameters as established by the international Cardiology task force

guidelines.[126] Means and standard deviations will be compared to published normative data in adolescents.[46]

11.5.3.4 Additional analyses will include process evaluations that include: (a) intervention fidelity; (b) satisfaction queries; and (c) mediation analyses to evaluate relationships between PRISM, family activation, and outcomes. For example, the intervention effect on parent outcomes may be mediated by parent activation. If we find a positive intervention effect on parent psychological distress, we will explore activation mediation using the counterfactual framework with indirect mediation effects computed through G-estimation and incorporating confounders of the mediator-outcome association.[127] Finally, we will conduct a planned interim analysis for data-safety monitoring purposes when half of AYA participants have reached the primary endpoint (see Human Subjects).

11.5.3.5 Multiple comparisons. Multiple comparisons are a concern since we are collecting multiple measures from both patients and caregivers and are interested in several hypotheses. We minimize this problem by specifying a limited number of main hypotheses for each aim. False Discovery Rate criterion will be used to correct for multiple testing in analyses that are not pre-specified. Likewise, in manuscripts and presentations, we will report the number of tests performed and interpret results within this context.

11.5.3.6 Considerations regarding missing data. Effective data collection at scheduled times will be monitored and attrition minimized as described below. While our goal will be to minimize missing data, data may still be missing due to patients/families skipping individual items, omissions in medical records, lack of follow-up, medical complications, or death. We will quantify the amount of missing data, evaluate the association of participant characteristics with missing data, and minimize bias and increase efficiency in the associations of interest by applying appropriate methods to account for missing data.[128-130] For example, where missing at random (MAR) is a plausible assumption, we will use multiple imputation or inverse probability weighting, depending on the statistical model being considered. For missing not at random (MNAR), we will use sensitivity analyses. In all cases, we will assess the robustness of estimates due to assumptions.

12.0 Confidentiality

12.1 Data Storage. All information collected for research purposes will be de-identified. Identifying information (names, addresses and phone numbers) will be used initially only to identify potential patients to approach. The only link between the participant identifiers and their study identifier will be kept on a password protected database and in a locked filing cabinet. There are no patient identifiers collected and retained for research purposes. Feasibility data will represent only frequencies and percentages.

12.2 Patient Identifiers within stored data. No participant identifiers will be kept with or included in the study data. All identifying patient information will be stored on a secure database, or in a locked filing cabinet with the study team. This data will be stored and maintained for a minimum of ten years or until final analyses are completed, whichever occurs last, in order to ensure data quality.

12.3 Study-wide data management. Individual sites will be responsible for original source data (surveys, Case Report Forms) until study completion. All such materials will be stored in a locked file cabinet or other office with access only to study staff. Upon study completion (last data collection for last patient), all materials will be de-identified (labeled only with study ID) and faxed or scanned to the coordinating center for electronic storage. As described above, monthly site data collection responsibilities will include monitoring of local data completeness and troubleshooting with the coordinating center for data completion, if necessary. Per the Data Transfer Agreement, a Limited Data Set will be transmitted by Seattle Children's research staff to external collaborators using a secure, institutionally approved method. Any data provided from SCH to Dr. Rosenberg and DFCI for oversight purposes during active data completion will also be limited.

When Zoom is used, the following actions will be taken to protect confidentiality and privacy:

1. The latest version of Zoom that is available will be used.
2. The meeting room will be set to private.
3. A password/passcode will be required for meeting entry.
4. The private chat function will be disabled.
5. The General chat function will be used. Examples of General chat use may include sharing approved resources and PRISM app passwords (as described in Section 9.4), communicating if there are technical difficulties, and the accommodation of specific needs by participant's request (e.g. if a patient has a medical reason that may impact verbal communication).

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

13.1 Data collection

Data collection will occur at each of the 4 enrolling study sites: SCH, BCM, UPMC, and CHLA. Data collection will consist of self-report questionnaires and electronic ECG recordings from HRV monitors. Research material collected will be in the form of data from standardized questionnaires, digital ECG files, and also from medical record information extracted from the patient's electronic medical record. Protected health information (PHI) is accessible only by site PIs and key study personnel.

13.2 Data Management

Research material collected will be in the form of data from the standardized questionnaires, digital ECG files and medical record information. Protected health information (PHI) is accessible only by the site PIs and key study personnel, and the on-site monitoring from the coordinating site (SCH). A variety of measures will be utilized to ensure participant privacy. Minimal paper records, such as consent forms, will be kept in a locked drawer in the site PIs' research offices. No identifiable patient information will be labeled on the surveys or ECG

files; all will be identified with a study-specific identifier with assigned identifier kept on a password protected encrypted server. Data will be stored in an electronic database (REDCap -Research Electronic Data Capture) using the participant's study identifier. REDCap data collection projects rely on a thorough study-specific data dictionary defined as an iterative self-documenting process by all members of the research team. We have conducted the iterative development and testing process previously, resulting in well-planned data collection. REDCap servers are housed in a data center and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to researchers at various institutions by both Privacy Officers and Institutional Review Boards. REDCap has been disseminated for use locally and at other institutions and currently supports over 300 academic/non-profit consortium partners on six continents and over 20,000 research end-users (www.project-redcap.org). The REDCap data record may contain some identifying information. Subjects will be tracked using their study identifier. The identifiable data will be designated as "PHI" in the REDCap database which will allow us to exclude access to the identifiable information as necessary.

13.3 Survey Data

The study questionnaire ("Resilience in Pediatric Cancer Assessment", RPCA) and the intervention ("Promoting Resilience in Stress Management", PRISM) may address sensitive matters. Participants may be prompted to think about the threat to their life posed by their cancer/tumor, as well as other difficult topics such as psychological distress, grief, bereavement, and health behaviors. The topics to be covered may provoke sadness, anxiety, depression, fear or doubt.

While surveys will be coded to protect anonymity and do not include instruments to directly measure suicidal ideation or other self-harming behaviors, they will be reviewed within 72 hours by the site study team for (a) missingness (see 13.4.1 below); and (b) unanticipated immediate threats to participants' or others' safety. As part of their informed consent process, participants will be made aware of the survey-review timeline as well as the fact that confidentiality may be broken in the case that providers see an immediate threat to the patient's or another's safety. No physical risks are expected to arise from the study.

If indicated, referral for consultation will include a direct phone call (or in-person consultation) by PI or research team member to recommend further help. This would include alerting: a) current therapist (if they have one), and b) their oncology social worker. The participant will also be given the phone number to the Seattle Children's, Baylor College of Medicine, or Children's Hospital of Los Angeles outpatient psychiatric clinic. County-specific crisis line phone numbers will also be provided as needed.

In the event of other concerns from interventionists and/or other study staff based on interactions with AYAs and families, as well as in other cases of concern for patient or others' safety, the same processes will occur, including immediate referrals to the site PI, and the patients' primary medical and social work teams for in-person evaluation or referral to the appropriate mental health professional if warranted. After hours, the site PI and on-call providers from the medical teams will be notified. All study-related concerns for patient or other person's safety will be reported as an adverse event (AE) to the IRB and Data Safety Monitoring Committee (DSMC, see "Data Safety Monitoring Plan"), within 1 week of study staff awareness. In addition, the PI will review the potential risks and reported findings at least once monthly with study staff from all participating sites. While this is not a pharmacologic

trial and we do not anticipate medical complications, sites will nevertheless notify the IRB and DSMC of all participant deaths at the time of study renewal (annually). Unanticipated (non-medical) participant deaths will be reported to the DSMC within 1 week with a determination if the event might be attributable to the study. In such cases, the DSMC chair may convene the committee and/or suspend the study for additional review (see section 13.5 below).

13.4 Heart Rate Variability Data

Following a 24-hour recording, a study team member will collect the Actiheart monitor from the patient (either in clinic or while in the hospital). De-identified data from the device will be uploaded into the Actiheart software (CamnTech, Inc), which will be installed on one computer located in the locked office of the study PI. Data will then be transferred to the above mentioned encrypted RedCap database.

13.5 Data Collection Procedures/ Internal Site Monitoring plan

The coordinating center will be responsible for systematic data collection, quality control, and data-management procedures including: (1) oversight of ongoing data collection; (2) rigorous training and ongoing monitoring of adherence to protocols; (3) regular review of questionnaire response rates and missing items to identify and correct problems; (4) verification of all data through computerized data entry systems restricting invalid/out-of-range responses; (5) at minimum monthly meetings and progress reports to provide feedback to study staff concerning difficulties and follow-up to ensure problems are resolved quickly; and, (6) yearly on-site monitoring of participating sites

13.5.1 Survey data. To optimize collection, all participant surveys will be available by paper or online via the REDCap system, a secure HIPAA-compliant, high-quality data collection tool. Surveys may also be completed in person with a study team member. The rationale for offering both paper-pencil and electronic versions is based on our prior experience where participants preferred the former,[90] which in turn facilitated more complete data collection. To ensure primary outcome data, we will offer an interview and/or abbreviated survey with only the PedsQL for those who do not complete all assessments or who request to drop out or who are too ill to complete the entire survey. To ensure data quality, a RA will review RPCA surveys within 72 hours of their completion for missing fields and call participants sites to clarify and query/complete individual missing items verbally.

13.5.2 Medical record data. RA's will collect and upload CRF data monthly for both the run in and RCT 3 months post baseline. CRF data will also be collected at 6-, 9-, and 12-monthsfor the RCT only. To ensure reliability and validity of abstracted medical record data, we will use our current methods for training and quality, including guided practice abstraction and independent abstraction with reconciliation by a trainer. A 10% random sample will be dual abstracted. A RA assignment will monitor and reconcile case report forms with RedCap data once monthly.

13.5.3 Heart Rate Variability Monitors

Staff investigators and RA's will be trained on recognizing adequate signal acquisition on the Actiheart monitors when the patient initially has the device placed. If there is suboptimal recording identified, the team member placing the device will be able to recognize in real time and make appropriate adjustments to the equipment based on Actiheart user manual suggestions.

13.6 Safety and Compliance Monitoring

This is a small multisite clinical trial of a supportive care intervention with no more than a minor increase over minimal risk and the prospect of direct benefit. As such, data monitoring will be primarily carried out by the Lead RA at the coordinating site (SCH) and a small, external Data Safety Monitoring Committee (DSMC).

13.6.1 Data and Safety Monitoring Plan. Safety monitoring will be the responsibility of a 4-member Data Safety and Monitoring Committee (DSMC) composed of professionals across the country representing different disciplines and expertise (see table below). All members are independent of the protocol. The committee will be convened at the beginning of the study and then twice annually via conference calls, to provide input and guidance on the study evaluation and intervention protocols, including quality assurance and safety issues related to the protocols, as well as data handling activities. As above, in the event of an unanticipated patient death, the committee may convene an ad-hoc session and/or suspend the study to assess patient risk and/or necessary revisions to the protocol.

13.6.2 Data and Safety Monitoring Committee

Member Name, Title	Discipline	Research Expertise
Leanne Embry, PhD (Associate Professor, Pediatrics University of Texas, San Antonio)	Pediatric Psychology	Behavioral Science, Adolescent and Young Adult Oncology
Donna Johnston, MD (Professor, Pediatrics Children's Hospital, Eastern Ontario)	Pediatric Oncology and Palliative Care	Pediatric Oncology and Palliative Care, Clinical Trial Design, Patient-Reported Outcomes
Barbara Jones, PhD, MSW (Professor, Pediatrics University of Texas, Austin)	Pediatric Social Work	Psychosocial Oncology, Pediatric Palliative Care, Adolescent and Young Adult Oncology
Kira Bona, MD, MPH (Assistant Professor, Pediatrics, Boston Children's Hospital & Dana Farber Cancer Institute)	Pediatric Oncology	Pediatric Oncology and Palliative Care, Patient-Reported Outcomes

13.6.3 Monitoring study safety. DSMC members will provide input and feedback to the PI and Co-investigators, via e-mail and conference calls, related to (a) accrual rate, (b) study eligibility determination issues, (c) data completion rates including conformance with informed consent requirements, (d) intervention fidelity indicators, (e) adverse events, and (f) compliance with data management procedures. The lead statistician will oversee the summarization of online data to evaluate data completeness and protocol adherence. The Lead RA will also send monthly reports summarizing recruitment and other site specific data (such as indicators of intervention delivery, occurrence of adverse events, and conformance with IRB requirements).

The committee will also receive information on questionnaire data, presented for the participants overall rather than by study group. This study will not have pre-set stopping rules, but the DSMC will have the option of requesting the data be unblinded and considering altering the study or stopping the study early. Although the full committee will meet twice-yearly, the chair will be free to assemble the full committee

at any time if the chair believes it is important. Because committee members may be located at various sites, the committee meetings may be conducted by phone.

Data safety monitoring for the intervention will focus on assuring that subjects are not experiencing any significant or unexpected distress and that they are satisfied with the intervention components; we will monitor all complaints about the study. We do not anticipate stopping the study early for efficacy or harm, but the DSMC will have the option to consider such action in the event of a highly unexpected result. The DSMC will review the draft questionnaires to be sent to subjects and review any complaints that may be received from patients, family members, clinicians, or others. We do not anticipate any external factors such as findings from ongoing trials that will affect the safety of participants or the ethics of this research study.

13.6.4 Identification, review and report of adverse events and unanticipated problem. Adverse events information will be collected at all assessment points and recorded on standard forms. We will collect information on all potential types of adverse events. Consistent with NIH and the sites IRBs policies, adverse events will be promptly reported in writing to the NIH, individual IRBs, and the DSMC chair. The DSMC will modify or stop the study if any such complaints represent a legitimate concern about the study procedures or methods.

13.6.5 Compliance with monitoring requirements. Compliance with the monitoring plan will be ensured through the Lead RA's close supervision. The Lead RA will hold no less than monthly calls with the sites to monitor recruitment and protocol adherence. Site RAs will gather required information on an ongoing basis and send monthly written reports to Lead RA. The Lead RA will schedule yearly on-site monitoring visits as the coordinating site for data completeness and accuracy. Site RAs will assist in providing on-site monitors with appropriate access to all study related charts and databases during the visit.

13.6.6 Assessment of relevant external factors. Given the characteristics of the intervention, it is unlikely that a breakthrough result from another study will change the course of this study.

13.6.7 Interim analysis plan. A primary endpoint interim analysis to assess for safety and missingness will be led by the study statistician after half of the targeted sample size of participants have reached the primary endpoint. The DSMC will determine a priori stopping occurrence of serious events, including (but not limited to) stopping the study for efficacy if interim analysis is significant. For efficacy endpoint, if an effect were found, the DSMC will be presented with unblinded results (i.e. they will be able to ascertain which results correspond to the intervention arm). Based on these results, the DSMC will present recommendations to the study team regarding early stopping or continuation of the trial. There are no pre-planned stopping rules for adverse events since these are not anticipated.

14.0 Withdrawal of Subjects

14.1 Plan for Non-Responders

Response to the intervention will be determined upon study completion (not in "real-time,"). All participants, including those on the intervention arm, will continue to receive usual care, including as-needed referrals for professional psychology services.

14.2 Early Withdrawal of Subjects

All participants may choose to withdraw from the study at any time. We will track date of discontinuation and request a brief reason to be recorded for tracking purposes. In the event of serious medical complications (or death) precluding participation, participants will be censored after 2 months of missing data. In all other cases, staff will continue to request surveys until 2 months following the study endpoint (12 months for RCT, 3 months for Run-In), as described above.

14.3 When and How to Withdraw Subjects

In this intention-to-treat analysis plan, all participants who fill out a baseline survey will be included in analyses. As above, withdrawal will be determined by study staff only in the event of medical complications or death.

14.4 Data Collection and Follow-up for Withdrawn Subjects

Unless explicitly indicated by participants who withdraw their consent, baseline data for all eligible patients will be maintained and utilized in analyses.

15.0 Risks to Subjects

The intervention ("Promoting Resilience in Stress Management", PRISM) and our surveys may address sensitive matters in that it they patients to identify stressors and negative thoughts. Adolescent and young adult participants may be prompted to think about the threat to their life posed by their cancer/tumor. During the coming together session and/or while completing surveys, parents may be prompted to think about the threat to their child's life by their cancer/tumor. The topics to be covered may provoke sadness, anxiety, depression, fear or doubt for AYAs and/or their parents. Any spouse, caregiver, significant other, caregiver, etc. who participates in the coming together session may be also prompted to think about the threat to the AYA's life posed by their cancer/tumor and these topics may provoke sadness, anxiety, depression, fear or doubt for AYAs and/or their parents.

Administrators of the intervention will be trained to inform the patient's primary social work and/or medical teams if the patient and/or parents/guardians/spouses/significant others endorses thoughts of self-harm or harm to others. As part of their informed consent process, participants will be made aware of this policy, as well as the fact that confidentiality may be broken in the case that providers see an immediate threat to the patient's or another's safety. Patients who participate in the optional HRV measurement component of the study may experience some mild physical discomfort or skin irritation associated with wearing the ECG monitor. The risk is minimal, as this process is identical to standard ECG measurements obtained for clinical purposes, of which all participants will have undergone. No significant physical risks are expected to arise from the study. The primary risk to participants will be concerns about confidentiality, and stress of discussing the topic of their or their child's cancer/tumor experience. While the potential risks to participants are low, we will take steps to ensure that all potential risks are handled appropriately as described

below. Due to the nature of the PRISM intervention, all staff and participants will be unblinded from the time of randomization.

We recognize the unique risks of data collection for an AYA population. The major risk is compromise of personal data. Thus, confidentiality procedures for all data will be a priority for this study. All data will be maintained on secure computers or in locked offices at Seattle Children's Research Institute (data collection center). The study results will be kept for at least ten years or until final analyses are completed, whichever occurs last, in order to ensure data quality. The subject's consent to use or share PHI does not expire. Access to the building where the study data will be kept at Seattle Children's Research Institute is limited to authorized personnel. The Lead RA and other researchers involved in this project have years of experience and has received ongoing training at Seattle Children's Research Institute on confidentiality as well as HIPAA confidentiality standards. Our and other previous trials have kept their data at Seattle Children's Research Institute in the recent past, and the security and confidentiality of the data have never been compromised.

15.1 Alternatives: Patients may opt not to participate in the research. Their care will not be affected in any way should they decline participation.

16.0 Potential Benefits to Subjects

We hypothesize that patients who receive the intervention will have diminished psychological distress and greater quality of life. We also hypothesize that parents/caregivers/significant others/spouses will benefit similarly from their child's/partner's participation because prior experience in pediatric cancer studies suggests it is personally important for some patients and caregivers to share their perspectives, challenges and growth experienced during their cancer. However, there may be no direct benefit for participating in this study if our hypotheses are wrong. More broadly, information gained from this study may heighten the understanding of the AYA cancer and progressive/recurrent tumor experience and elucidate strategies that foster resilience and promote better quality of life in this group of high risk patients. These strategies could be extended to the care of other AYA patients facing non-cancer or tumor-related life-threatening illness. This research has the potential to contribute to the research base concerning the promotion of optimal quality of life and mental wellness for all AYA patients.

17.0 Vulnerable Populations

17.1 This study includes the following vulnerable populations:

A. Individuals who are not yet adults (children, teenagers): Pediatric patients with serious illness are at risk for poor outcomes and may benefit from resilience-enhancing interventions in the future. We justify the inclusion of children in this project because the implementation of those interventions requires feasibility information and patient feedback. This study will provide those crucial data. Patients enrolling in this study may, in fact, benefit from the intervention; however, at the time of consent, we will ensure that all patients and families understand the objective of this study are to test the feasibility of this intervention such that it may be used prospectively in the future (see risks/benefits above).

B. Pregnant women: There is a chance that a parent or spouse/significant other of a patient participant is pregnant and therefore could participate in the survey and/or 'coming together' portion of this study. This study does not involve interventions/invasive procedures to the woman or fetus and does not involve fetuses or neonates as subjects.

17.2 This study will not include:

17.2.1 Prisoners
17.2.2 Cognitively impaired adults
17.2.3 Wards of state

18.0 Community-Based Participatory Research

N/A

19.0 Sharing of Results with Subjects

19.1 Following completion of the study, a written summary of the main results will be provided to all interested participants.

20.0 Setting

20.1 Patients will be identified and recruited at their home institution (SCH, BCM, UPMC, CHLA). See section 23 for specifics.

20.2 Study visits may be done in person at the hospital/clinic, in the inpatient room or in the outpatient clinical research center. PRISM sessions may also be conducted by phone or other web based communication (Zoom, WebEx, or Skype).

20.3 There will not be an involvement of any community advisory board.

20.4 All local research will be conducted via patients' home institution (i.e., in Seattle, research activities will occur within Seattle Children's Hospital and Clinics; however as above, patients/families may be at home and participate remotely via video call.)

21.0 Resources Available

21.1 **Interventionist Training and Fidelity**. PRISM has been standardized through the creation of comprehensive protocols for those who implement it. Session-by-Session details are provided in the PRISM manual and in the Voicing My Choices Session Appendix document; on outline of each main section is listed in **Table 1.** All interventionists undergo at least 4 hours of training including role-playing and progressive mastery of intervention materials. The fidelity of all sessions will be systematically assessed via audio-recording. As possible, the PI or supervising team member will review the first 6 sessions for each interventionist, and score them for fidelity using a standardized tool (see appendix.) Interveners will receive feedback regarding adherence to protocol and approach will be refined with additional training, if needed.

21.2 Refer to **Table 3** for annual numbers of AYAs. We will consecutively enroll patients at SCH, BCM, UPMC, and CHLA.

21.3 Refer to 'Table 4' for the Timeline of conducting and completing the research.

21.4 The local research teams will work closely with the Hematology/Oncology medical and social work teams if outside resources or needs arise.

22.0 Prior Approvals

22.1 N/H R01 CA222486-01A1 was reviewed by the relevant study section. The final notice of award was received 8/1/13.

23.0 Participant Incentives

For the Run-In, participants will be receive $20 for each survey (total $60 for 3 surveys) following the completion of each survey No parent incentives or compensation will be offered as parents are not participants in the run in study.

For the RCT, all active patient participants will receive $50 in total, in multiple installments. The total amount of $50 will either be administered in two installment payments in the form of a $25 gift card or five installment payments in the form of a $10 gift card during the 12-month duration of the study. For example, for participants who are very ill or for whom survival is unlikely, we would provide the payment installments at earlier time points (e.g., baseline survey, 3-month survey). Per HRP-316: a) credit for payment will accrue as the study progresses as all participants will be paid in separate installments in conjunction with completion of a survey, b) payment will not be contingent on completing study procedures as the first payment installment would occur prior to the final study component (12-month survey). C) The amount of payment and the proposed method and timing of disbursement is neither coercive nor presented undue influence.

Participants will also receive small, non-monetary items, such as pens, lanyards, or tote bags throughout the study. Parents and guardians will also be offered non-monetary items such as pens, bags, stress balls, mugs, etc. Patients will receive payment regardless of if they complete the full RPCA, aRPCA, or the primary outcome measure only. Patients will not be paid more for participation in the optional HRV procedures.

Patient participants who complete both the baseline and 6-month surveys will also be entered in a raffle to win an iPad. At each site, raffles will take place once per year or after 10 participants have completed all study procedures, whichever occurs first. Each participant in the raffle will therefore have 10% or greater chance of winning an iPad.

24.0 Use of Social Media

We will not use social media for this study.

25.0 Local Number of Subjects

See section 4.1.

26.0 Provisions to Protect the Privacy Interests of Subjects

When recruitment is done in person, the study team will use a private room to discuss potential participation and the use of an intermediary (as needed) if the subject does not know the researcher. When recruitment is done via phone/video call, patients and parents will be asked if they have time to talk and if there is a quiet space to discuss the study. Emphasis will be made to ensure that subjects know that not participating will not impact patient care.

When possible, texting participants will occur on a secure, HIPAA-compliant platform. If a HIPAA-compliant platform is not available or allowable per specific site restrictions, research staff will not include PHI in texting communications with participants and families. Depending on the texting platform used, subjects may be able to send text messages back to the study team. Any texting platform used (depending on local site requirements) that allows research staff to receive text messages from subjects will be HIPAA compliant and will protect all information received from subjects.

The study team will warn the participant of the possibility of sensitive subject matter before the session. The study team will be sure to emphasize to the participant that this study is completely optional and the participant has the right to not answer any questions that they feel uncomfortable with, that they can withdraw their participation at any time, and that their refusal to participate in this research will not impact their care.

The study team will have access to any patient/participant information that could pertain to study participation or that has an influence on how a participant participates.

27.0 Compensation for Research-Related Injury

There is no compensation for research-related injury.

28.0 Economic Burden to Subjects

28.1 We strive to complete these visits with patients while they are already at the hospital. As above, intervention sessions may be conducted via phone or other web-based communication (e.g., Zoom, WebEx, or Skype) or via phone.

Study visits will be scheduled in conjunction with other medical visits as much as possible to minimize additional hospital/clinic visits or burdens to families. Prior experience suggests some families prefer to come back to the hospital/clinic for these visits, even when they require additional time. No additional incentives or financial support will be provided in such cases (e.g., gas-cards or transportation), unless requested by families and considered on a case-by-case basis by study staff.

Patients and families will be asked if they would like to receive text messages from the study team for study participation coordination (e.g., enrollment, survey reminders, intervention session scheduling, payment). Standard text messaging rates from mobile phone providers may be incurred. The study team will inform patients and families of potential charges in the consent conference and give them an opportunity to opt out to avoid potential charges.

29.0 Consent Process

We will request a waiver of consent for screening purposes for this study and a waiver of documentation of consent for study enrollment in cases where in-person consent conferences are not feasible. This will be done so that CRAs may identify potential and

eligible patients prior to their scheduled clinic visits and to ensure that recruitment is possible whilst protecting participant safety.

Consent Conferences. The consent meeting between the CRA and eligible participants (with parents if applicable) will include an explanation of the study in developmentally appropriate lay-language. All AYA participants will provide either written informed consent (if aged 18 years or more (or assent (if <18 years-old). Parents of teens (<18 years-old) will provide written informed consent. As described in the inclusion/exclusion criteria above (Section 3), participants must speak English fluently; however, they are eligible if English is not their primary language spoken at home (or if it is not their first language). In cases where parent consent is required and parents do not speak English fluently (or prefer another language), all conferences will be had in the presence of a trained medical interpreter either in person or via phone interpreter. All participants and parents will be provided an opportunity to read the consent/assent form in their preferred language (English or Spanish), to ask questions about the study and have those questions answered by the research team member before deciding about study participation and signing the consent/assent form. Parental permission for study participation will be obtained first if the patient is under 18, then patient assent will be obtained for all patients 12-17 years of age. If a patient indicates that they do not want to participate in the study that non-assent will override the parent's permission and the patient will be recorded as a refusal. The research team member will redirect any parent who attempts to convince their child to participate in the study and remind them of their child's right as a potential research participant to refuse participation without coercion. Consent to study participation will be obtained from patients 18 years of age and above. The CRA will emphasize to all patients and parents in developmentally appropriate lay-language that being in the study is their choice, and that they may choose not to participate or may change their mind at any time and it will not affect how their nurses or doctors care for them.

When conducting the consent conference in person, those who agree to participate will sign a paper consent form. When the consent conference is conducted over the phone/video, those who agree to participate will complete an electronic consent form via the REDCap database using the REDCap e-consent framework. Study staff may also email a copy of the consent form to subjects if requested. The body of the consent form will be identical, whether on paper or in REDCap. A link to the electronic consent form will be e-mailed to participants prior to the phone/video consent conference. Study staff will answer any questions about the study, and those who agree to participate will provide an electronic signature, date, and time on the REDCap form to indicate their consent. The REDCap e-consent framework allows participants to create an electronic signature using their cursor and provides a timestamp. This framework also automatically generates an extra certification page for participants to confirm the correctness of their responses before submitting; stores a static copy of their responses as a PDF in the study's file repository. Subjects will also be prompted to download a copy of their signed consent form from REDCap, or study staff can e-mail the signed form.

After conducting the consent conference either in person or by phone/video, RAs will create a consent process note for REDCap and the EMR. Included in this note will be the date of the consent conference, the names of the patient and parent (if applicable),

the name of the person obtaining consent, the fact that the subject agreed to participate and that all risks and opportunities of the study were explained, and that the subject had adequate opportunity to have their questions answered. If an interpreter is used, the name of the interpreter will be documented.

The rationale for separate consents from parents is as follows: parents/caregivers/spouse/significant other will provide an addendum to the AYA consent/assent to acknowledge that they may participate in the 'Coming Together' portion of the study. Parent/guardian separate consent will be obtained because parents will be completing their own study questionnaires and will be disclosing their own financial and quality of life information in surveys. Parents/guardians may still be involved in the 'Coming Together' portion of the study and not want to sign consent to complete questionnaires and vice versa, they may want to complete questionnaires and not participate in the 'Coming Together' portion of the study either by their or the patient's choice or patient may be on control arm and will not have the option of the 'Coming Together' visit.

There will be an addendum to the consent form for the optional HRV measurement component of the study. Patients and families will be presented this consent form during their consent conference.

For eligible patients who are visually impaired, the font size on consent forms and other documents will be enlarged according to patient preferences. If eligible patients with visual impairment cannot read large print text, the consent materials will be explained to the subject in the presence of an impartial witness who observes the entire consent process. In that case, sufficient time will be allowed for questions to be asked and answered, to ensure that the subject comprehends the consent information. The presence of the witness will be documented in the chart note and on the consent form.

29.1.1 Non-English Speaking Subject:

29.1.1.1 Patients who speak English but have non-English speaking parents/guardians/caregivers/ spouses/significant others will be eligible to participate. Procedures for screening, approach, and enrollment of these families will be similar to above, except as follows:

29.1.2 For Spanish Speaking Parents:

29.1.2.1 For patients < 18 years-old: Spanish-English translations of the consent and assent forms will be provided for parents during discussions of the study and consent conferences and all discussions will occur with trained medical interpreters**.**

29.1.3 For patients 18 years and older:

29.1.3.1 Spanish-English translations of the consent will be provided for parents during discussions of the study and consent conferences at patients' requests. Likewise, if patients wish their parents/guardians/ caregivers/spouses/significant others to participate in session 6, "coming together," they will be invited to sign a Spanish version of the coming together addendum. All discussions involving Spanish (non-

English) speaking participants will occur with trained medical interpreters.

29.1.4 For all patients:

29.1.4.1 Session 6 (“Coming together”) will be offered in the presence of an interpreter in the parents'/guardians/ caregivers/spouse/significant other's first language. All other 1:1 sessions will still be conducted in English with English-speaking, trained interventionists.

29.1.5 For Other Non-English Speaking Parents, on a case-by-case basis:

29.1.5.1 Discussions of study will occur with interpreters in the appropriate language. If families and patients are interested in participation, informed consent forms would be translated into the native language of the parent.

29.1.5.2 Everything pertaining to Spanish speaking parents would be the same for other non-English speaking parents except that discussions, conferences, and Session 6 would be in the native language of the parent, spouse, caregiver, significant other, etc.

29.2 If a patient is still active on study, however is no longer coming to clinic on a regular basis and turns 18 years old or needs to re-consent due to a modification with the protocol (or other cause), study staff will mail or email the consent to the participant and will call the participant (and parents if applicable) and go over study changes. When sent via mail, the consent mailing will include a pre-paid return mailing envelope so the participant can sign and return to return to study staff. The study staff will make note of the date of the re-consent conference. When the participant/parent-signed form is returned, the researcher will then sign and date it with the current date. The researcher will add a notation that the actual consent conference took place on the date noted via telephone. Similarly, if participants move away from a study center, staff will query their continued interest in study participation and offer all study activities remotely via phone or other web based communication (skype, Blue Jeans, go to meetings, WhatsApp, etc.) to encourage continued participation. Additionally, staff will ask that participants provide a contact number or email of their new clinical team such that issues of safety can be communicated. Per the Certificate of Confidentiality, patients do not need to sign a Release of Information for us to contact their provider in issues of safety to themselves or others.

29.3 Waiver or Alteration of Consent Process (consent/parental permission will not be obtained, required information will not be disclosed, or the research involves deception); Waiver or Alteration of HIPAA

29.3.1 We will request a Waiver of HIPAA Authorization for recruitment and Alteration of HIPAA Authorization: The research involves no more than minimal risk to the subjects.

29.3.1.1 The waiver of HIPAA is being requested for preliminary screening purposes. Preliminary screening procedures are minimal risk; they include a basic review of the patient’s medical records to identify whether or not the patient meet basic eligibility requirements. No study

activities occur prior to the documentation of informed consent by patient and/or parent participants. In addition, an alteration is being requested for cases in which it is necessary to conduct consent remotely (via phone or video-conference) because we cannot approach eligible patients in person due to patient safety concerns (e.g. during COVID-19 pandemic). Many of our participants are immunocompromised, and there will be many cases unrelated to or after the COVID-19 pandemic in which it would be much safer to approach patients remotely (e.g., when staff are ill, when participants are receiving immunosuppressing treatment, when participants are very ill). In these cases, we will follow remote consent procedures outlined above, and patients/parents will indicate their willingness to participate both verbally and via digital signature on the REDCap forms. In-person approaches and consent conferences will be prioritized when they are possible, and in those cases written signatures will be obtained. Research coordinators will collaborate with the site PIs to determine when remote consenting is necessary. Site PIs will make the final determination as to when remote consenting is needed.

29.3.1.2 The waiver or alteration will NOT adversely affect the rights and welfare of the subjects. Provide protocol specific findings justifying this determination: The confirmation of eligibility relies in part upon the expertise of clinicians and by the patient's medical record. This is information that the patient's clinicians would have as a part of the patient's clinical care. The information collected is narrow in scope and will not affect a potential participant's insurance, employability, or lead to stigmatization. Screened patient information will be stored in a database and will be used for demographic tracking purposes and for preventing re-approach. All publication or presentation of research results will be done in a manner that would not reveal an individual's identity. In remotely conducted consent conferences, we will explain the study in as much detail as we would in person and ask questions throughout the discussion to ensure participant comprehension. Therefore, conducting consent conferences remotely will not be significantly different from in-person consenting or have significant adverse impacts.

29.3.1.3 The research could NOT practicably be carried out without the waiver or alteration. Provide protocol specific findings justifying this determination: We need to have the waiver in order to determine potentially eligible participants for this study. If we did not confirm eligibility with the clinicians giving care, confirmation of eligibility would be dependent upon the patient and parents. It is likely that they would be able to confirm the eligibility criteria but there is the possibility that some may not be able to do so for all of the study criteria. It is also possible that they may be uncomfortable being asked to confirm the eligibility criteria or wonder why it is that they are being asked to do so.

We also need this alteration to be able to consent participants in cases where in-person consent conferences may pose risk to the patients, particularly within this immunosuppressed, high-risk population. The advanced cancer and progressive/recurrent tumor patients we are attempting to enroll are often highly immunocompromised, with a much higher risk for infection by a multitude of transmissible illnesses, and these patients are susceptible to substantially worse symptoms and outcomes from such illnesses than a person of average health. For example, as of Spring 2020, the COVID-19 pandemic has significantly impacted our ability to approach patients and conduct consent conferences in person; therefore, this has led us to revisit our previous practices for in-person consenting, and determine that, in order to protect patient safety while still giving all eligible patients the opportunity to participate in this potentially beneficial research, we need the option to enroll patients remotely.

In addition, both of our previous procedures for remote consent conferences are no longer feasible in this circumstance, as follows: 1) When a remote consent conference was requested by patients or families, we had previously mailed consent forms prior to a phone consent conference and requested that families sign the forms and return via mail. However, during this unique time, families of individuals in our target population are likely exercising extreme caution to protect their at-risk child's health, meaning many may prefer to avoid sharing of physical documents via mail. Furthermore, requiring families to return documents via mail may pose additional risk and burden as they will need to leave their homes to locate mailboxes or visit the post office. 2) We had also previously e-mailed consent forms to families and requested that they print, sign, scan and return to us via email. However, we have found that this option is very often not doable for families in this population as it requires them to have access to a printer and scanner, which the majority do not (e.g., families not living at home, when the AYA in inpatient, etc.) Therefore, in order to continue to recruit for this study whilst ensuring patient safety and minimizing any burden or stress on families, providing an electronic means for families to review consent forms and indicate willingness to participate (via digital signature) is necessary.

29.3.1.4 Whenever appropriate, the subjects will be provided with additional pertinent information after participation. Provide protocol specific findings justifying this determination: Study participants will be provided with any additional information that may become known during the course of the study which may influence their decision to be in the study.

29.3.2 Waivers for participants who turn 18:

29.3.2.1 We will re-approach and consent participants if they turn 18 while they are still actively participating in the study. However, we request the waiver of consent & HIPAA for patients that turn 18 if no further data collection and study related activities are occurring, as their data is limited to the continued use of existing data.

29.4 Subjects who are not yet adults (infants, children, teenagers)

29.4.1 Consent/assent will be obtained for all patients 12 years-old and older (written assent for those ages 12-17, and written consent for those 18 years and older). These consent conferences will be documented in the patient's medical record. If patients indicate that they do not want to participate in the study, that non-assent will override the parent's permission and the parent will be recorded as a refusal. The research team member will redirect any parent who attempts to convince their child to participate in the study and remind them of their child's right as a potential research participant to refuse participation without coercion. The CRA or PI will emphasize to all patients and parents in developmentally appropriate lay-language that being in the study is their choice that they may choose not to participate or may change their mind at any time and it will not affect how their nurses or doctors care for them.

29.4.2 Since this is a minimal risk study, consent will be obtained by one parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

29.4.3 We will re-approach and consent the children of participants if they turn 18 while they are still actively participating on study. However, we request the waiver of consent & HIPAA for patients that turn 18 if no further data collection and study related activities are occurring, their data is limited to the continued use of existing data, which entails minimal risk to the subjects. Subjects will have assented to participate in the study as minors and provided assent on the consent form, so the rights of subjects who turn 18 while the study is ongoing will not be affected by continuing to use the data after contact has ceased. Given that active participation in the research would be complete, it would not be practicable to seek consent because of the potential difficulty locating subjects, or it may be inappropriate to re-approach the subjects due to their health status.

29.5 Cognitively Impaired Adults

29.5.1 NA

29.6 Adults Unable to Consent

29.6.1 NA

29.7 Consent for use of HUD

29.7.1 NA

30.0 Process to Document Consent in Writing

Consent documents are attached in the appropriate section of the Click smart form, including the identical REDCap consent forms for remote consenting. We are following the SOP as written with the exception that we will ask 12 & 13 year old patients to co-sign the consent form with their parents. As described in Section 29.0, we will also enlarge the print on consent forms and other study documents if we have an eligible patient who is visually impaired.

We will obtain written assent/consent from participants whenever possible, as a wet ink of signature. When this is not possible, we will obtain a digital signature to indicate willingness to participate. Upon enrollment and randomization, the PI or Co-I's will place a research note in the medical record to document the discussion and participants. Additionally, we will ask for a waiver of documentation of consent for providing updated information about text messaging approved with MOD00009623.

31.0 Drugs or Devices

N/A

32.0 Good Clinical Practice

We are committed to conduct the described study per International Center for Harmonization of Good Clinical Practice (ICH-GCP).

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