PROTOCOL TITLE:

The Promoting Resilience in Stress Management (PRISM) Intervention: a multi-site randomized controlled trial for Adolescents and Young Adults receiving Hematopoietic Cell Transplantation

SPONSOR: Dana-Farber Cancer Institute

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AYA	Adolescent and Young Adult
CRA	Clinical Research Associate
DNE	Days to Neutrophil Engraftment
CTRA	Conserved Transcriptional Response to Adversity
HCT	Hematopoietic Cell Transplantation
HRV	Heart Rate Variability
GVHD	Graft versus Host Disease
MEMS	Medication Electronic Monitoring System
PRISM	Promoting Resilience in Stress Management
RCT	Randomized Controlled Trial

PROTOCOL REVISIONS (Original Approval Version 02/15/2018)

Protocol Revision (Version) Date	Revision	Rationale
8/10/2018 (PRIOR TO STUDY LAUNCH)	Updated Study Team	Personnel Change
	Addition of secondary aims to examine additional patient-reported outcomes	Preliminary data from concurrent studies suggested clinically relevant patient-reported outcomes influenced by intervention; scientific interest
	Addition of secondary aims to examine parent outcomes	Preliminary data from concurrent studies suggested parents interested in participation; scientific interest
	Adherence aim changed to exploratory	Final statistical calculations and discussion with pharmacists & consultants suggested insufficient power to detect associations.
	Procedures clarified	Consistency of institutional practices
	Statistical plan clarified	Final (pre-launch) statistical plan confirmed with study team
	Centralized PRISM Manual	Single document used between PRISM studies for consistency and generalizability of the PRISM intervention.
10/17/18	Changed RPCAs wording, formatting, and some questions	Consistency of study procedures
	Updated risks in protocol	Changing how study staff query suicidal/self harm thoughts as study staff are not trained to fully complete suicide assessments
	Consent forms	implement app language to include iTunes and Google Play
	Added recruitment flyer	Aid with recruitment
1/2/19	Add CD RISC 10	Study design update
	Add phone consent	Maximize recruitment for infrequent clinic patients
	Allow session #1 to be done remotely	Flexibility of study procedures
1/30/19	Add HRV as exploratory outcome of interest	Scientific Interest
6/20/2019	Changes to payment schedule	Optimize enrollment and retention through individualized incentive structure
	Adding raffle to win iPad	Optimize subject retention with non-monetary incentive
	Allow for combining intervention sessions	Address feasibility challenges identified in prior studies associated with critically ill patients
8/26/2019	Including St. Jude Children's Research Hospital and University of Alabama, Birmingham, as additional study sites.	Augment recruitment to reach accrual goals.
	Including annual on-site monitoring for participating sites	Quality assurance and data monitoring of non-primary sites.
	Expanding window for	Optimize subject retention and data completion

	baseline survey completion	
10/3/2019	Add CTRA as exploratory outcome	Scientific Interest
1/13/2019	Add autologous HCT to inclusion criteria	Augment recruitment to reach accrual goals.
	Removing costs of care & adherence questionnaires from AYA surveys	Minimize participant burden
5/1/2020	Add opt-out approach letter	Augment recruitment to reach accrual goals by minimizing need for in-person contact (e.g., during COVID-19 pandemic)
	Add electronic consenting procedures/request waiver of consent documentation & alteration of HIPAA	Promote participant safety by minimizing need for in-person contact
	Add COVID-19 impact instrument for AYAs and parents	Scientific Interest
8/25/2020	Clarifying language for phone approaches	Clarification/specificity
	Clarifying language re: HRV monitor placement	Clarification/specificity
	Making Spanish instruments available in REDCap	Promote equity by offering electronic surveys for Spanish-speaking participants
11/3/2020	Allowing SCH PRISM interventionists to deliver sessions remotely to St Jude patients	Fulfill interim staffing needs so enrolled patients can continue to receive intervention on schedule
3/05/2021	Clarifying eligibility to include patients receiving HCT for any malignancy	Clarify and augment enrollment goals to make up for limited accrual during the COVID-19 pandemic
	Expanding eligibility to include patients with bone marrow failure syndromes with predisposition (risk) for later malignancy	
10/24/2021	Expanding eligibility criteria for optional procedures to include Spanish-speaking individuals	Promote equity for Spanish-speaking participants

	Text reminders to participants	Augment survey completion
	Enabling zoom chat during zoom-based PRISM sessions	Optimize ability to communicate with participants during virtual study activities
	Accommodations in consent process for visually impaired individuals	Promote equity for visually-impaired participants
	Additional incentive for survey completion	Augment survey completion
	Clarification regarding survey administration procedures	Minimize participant burden, augment survey completion
	Change medication adherence monitoring to optional procedure	Minimize participant burden
2/18/2022	Update study team member information	Reflect change in CHLA site PI
	Add additional variables to be extracted from medical record for patients participating in HRV and/or CTRA optional components	Scientific interest
11/28/2022	Update study team member information – change Principal Investigator	Reflect PI personnel change at primary site
12/16/2022	Editing to reflect that DFCI is the sponsor site.	Reflect Abby Rosenberg's move to DFCI.
2/3/2023	Added language to clarify sponsor (DFCI) and coordinating site (SCH) responsibilities.	Fulfill sponsor's regulatory requirements.
03/21/2023	Updating study team member information	Removing team members from protocol

1.0 Objectives

1.1 Overview

The experience of hematopoietic cell transplantation (HCT) among Adolescents and Young Adults (AYAs) with cancer is particularly difficult because age-related developmental challenges of identity, relationships, and vocation may add to the burden of cancer. Compared to other age-groups, AYAs have poorer psychosocial outcomes including increased anxiety and depression and poorer adherence to oral immunosuppressive medications. These outcomes may, in turn, predispose AYAs to disease-related morbidity and mortality such as graft-versus-host disease (GVHD) and/or cancer-relapse. A potential barrier to improving these experiences may be that AYAs have few opportunities to develop the personal resources needed to handle adversity. We have previously developed the "Promoting Resilience in Stress Management" (PRISM) intervention for AYAs with serious illness. This manualized, brief intervention is delivered in 4, 30-60 minute, one-on-one sessions, followed by a Parent/ Caregiver/ Spouse/ significant other inclusive meeting. It targets skills in stress-management and mindfulness, goal-setting, positive reframing, and meaning-making. All of these skills are associated with improved patient well-being in other populations, and preliminary findings from a recently closed pilot randomized controlled trial among AYAs with newly diagnosed cancer suggest PRISM is associated with improved health-related quality of life. This study will build on our prior experience and fill a critical knowledge gap regarding PRISM's impact among AYAs receiving HCT. Thus, we will conduct a multi-site randomized controlled trial among N=70 AYAs (n=35 PRISM and n=35 usual care; ages 12-24 years), with the primary trial outcome of patient-reported symptoms of anxiety and depression. Secondary outcomes will include the cost-effectiveness of the intervention in this population and the impact of the intervention on parent well-being. Exploratory outcomes will assess patient adherence to oral GVHD medications, as well as three biomedical variables associated with psychological distress; heart rate variability (HRV), days to neutrophil engraftment (DNE), and development of acute GVHD. We hypothesize that AYAs who receive PRISM will report fewer mixed affective symptoms, demonstrate better adherence, and show improved biomedical outcomes, while their parents report improved quality of life and psychological distress. We also anticipate the intervention will be cost-effective. In sum, this study offers an opportunity to expand the body of knowledge regarding methodologically rigorous and evidence-based psychosocial interventions and standards of care for AYAs with hematologic and other malignancies. Ultimately, this research has the potential to reduce the burden of cancer in these vulnerable populations.

1.2 Purpose of the Study Protocol

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

1.3 Primary Aim: Evaluate the effect of PRISM compared to usual care on symptoms of anxiety and depression.

Primary Outcome Measure: AYA-reported mixed affective (anxiety and depression) symptoms 6-months post enrollment (measured with the Hospital Anxiety and Depression Scale).[1]

Primary Hypothesis**:** PRISM will be associated with lower anxiety and depression compared to usual care.

1.4 Secondary Aims:

1.4.1 Evaluate PRISM's impact on other key patient-reported outcomes 6-months following enrollment.

Outcome Measures: (a) Symptom Burden (measured by the Memorial Symptom Assessment Score)[2]; (b) Health-Related Quality of Life (measured with the Pediatric Quality of Life [PedsQL] 4.0 Generic and 3.0 Cancer Modules)[3,4]; (c) Hopeful patterns of thought (Hope Scale)[5]; and, (d) resilience (Connor Davidson Resilience Scale, CDRISC-10).[6,7]

Hypothesis: PRISM will be associated with (a) lower total symptom burden; (b) *higher* quality of life; (c) higher hope; and (d) higher resilience, compared to usual care.

1.4.2 Evaluate the cost-effectiveness of the PRISM intervention.

Outcome Measure: Cost per Quality Adjusted Life Years (QALY)

Expected findings**:** PRISM will be cost-effective compared to usual care, considering a standard willingness to pay threshold of $150,000 per QALY gained

Exploratory Outcomes: (i) PRISM's cost utility as a function of treatments related to patient-reported anxiety and depression; and, (ii) PRISM's cost per clinically relevant consequence such as change in mental health score or adherence.

1.4.3 Evaluate the impact of PRISM on parent outcomes 6-months following enrollment.

Outcome Measures: Health-Related Quality of Life (SF-36)[8]; anxiety (Generalized Anxiety Disorder Screener, GAD-7),[9] and depression (PHQ-8),[10,11]

Hypothesis: Parents of AYAs who receive PRISM will report higher quality of life and lower psychological distress compared to parents of AYAs in usual care.

Exploratory Outcome: Family Experience (selected items from Hospital Consumer Assessment of Healthcare Providers and Systems [HCAHPS] survey).[12]

1.4.4 Describe individual and group 6-month trajectories for patient reported outcomes of usual care and PRISM participants.

1.5 Exploratory Aims

1.5.1 Evaluate the effectiveness of PRISM compared to usual care in promoting adherence to oral GVHD prophylaxis.

Outcome Measures: (i) Medication Electronic Monitoring Systems (MEMS) cap electronic adherence assessments during the remaining 6 months following initial hospitalization for HCT.

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

Outcome Measures: (i) Days from HCT to neutrophil engraftment, (ii) prevalence and severity of GVHD (revised Seattle Criteria), (iii) heart rate variability (as measured by the interbeat interval (IBI), (iv) gene expression profile.

1.6 Rationale for the Selection of Outcome Measures

The primary outcome (patient-reported anxiety and depression symptoms) was selected not only because it is a prevalent and clinically important element of AYA wellbeing during and after HCT, but also because our pilot experience suggests PRISM may prevent the development of distress over time. Additional AYA patient-reported outcomes were selected because they are clinically relevant norms in psychosocial intervention research. Our prior experience suggests PRISM is associated with improved quality of life, hope, and resilience, for example, and the present study will confirm if these findings are generalizable in this new population of youth receiving HCT. We chose to measure cost-effectiveness with cost per QALY because this ratio has established thresholds with which to define value. We will capture additional measures of cost-effectiveness (e.g., cost as a function of anxiety/depression and cost-effectiveness for various levels of adherence)) in order to inform future clinical guidelines and research. Prior evidence suggests that parent and child outcomes are strongly correlated; it is thus important to determine if a child-centered intervention can also improve parent outcomes and experiences. Emerging data indicate anxiety and depression can impact cancer-related outcomes through immune-mediated mechanisms. Neutrophil engraftment and GVHD are both immunologic phenomena that have been associated with psychological disposition in the HCT literature, and are documented as part of clinical standard of care. HRV is a commonly used, noninvasive stress biomarker with published normative values. The “Conserved Transcriptional Response to Adversity (CTRA)” RNA transcription pattern is observed following exposure to stress, and results in increased inflammation, which is an important mediator of acute and chronic co-morbidities. Lastly, adherence was selected as a clinically important exploratory outcome because of its potential impact on late effects including GVHD.

2.0 Background

2.1 Prior Literature and Previous Studies

2.1.1 Outcomes and Barriers to Improvement among Adolescents and Young Adults with Cancer

Adolescents and Young Adults (AYAs) with cancer have high risks of poor physical and psychosocial outcomes, perhaps because cancer disrupts normal developmental experiences like establishment of independence, identification of

personal, social, and sexual identities, completion of education, and pursuit of vocational goals.[13-17] AYA survivors have ongoing challenges including physical impairment, psychological distress, infertility, and discrimination in employment and insurance.[18-20] These challenges impair survivors' abilities to contribute to society. Compared to adults without a history of cancer, AYA survivors have projected annual excess medical expenditures of $3170 and annual productivity losses of $2250 per person.[21] Extrapolating these costs across the lifetime of AYAs implies excessive societal economic burdens. Targeting AYA well-being may therefore improve AYA and societal outcomes.[22]

A potential explanation is that AYAs lack skills to navigate the adversities of cancer. Positive psychological resources may mitigate negative and facilitate positive outcomes.[23,24] "Resilience" is evidenced by sustained emotional and physical well-being after significant stress.[25] The study of resilience in cancer has lacked consensus of either definitions or outcomes indicative of resilience.[25,26] However, several personal resources are consistently associated with resilience among AYAs and older adults with cancer,[24,27,28] and among parents of children with cancer.[29,30] These include stress-management, problem-solving and goal-setting skills, benefit-finding, and the ability to make meaning from adversity. We term this group of variables "resilience resources."

Bio-behavioral models suggest that resilience resources relate to long-term quality of life, health behaviors, immune function, and overall health and well-being.[31] Pre-transplant depression has been associated with lower overall survival and higher risk of acute GVHD among HCT recipients. Additionally, studies of autologous HCT recipients suggest greater optimism and lower anxiety was associated with accelerated neutrophil engraftment following transplant. Genome science studies are beginning to map out the underlying molecular pathways responsible for these interrelated mental and physical health outcomes in cancer. Acute or chronic stress can induce a conserved transcriptional response to adversity (CTRA) gene expression profile - a systematic shift in gene expression that results in increased expression of genes involved in inflammation.[32-34] Conversely, positive psychological states can activate protective gene expression patterns that promote healthy immune system function, which is particularly salient in the HCT setting. Hence, skills-based interventions bolstering these resilience resources may improve both psychosocial and biological disease outcomes.[31]

These resources are particularly important in the setting of Hematopoietic Cell Transplantation (HCT). AYAs receiving HCT experience high burdens of medical morbidity and mortality, and comparatively poor health-related quality of life.[35-42] Anxiety is highly prevalent before the transplant, and 40% of patients experience depressive symptoms in the 6 months that follow. This "stress reaction" is associated with behavioral problems and peer isolation, and persists for a third of patients.[43] Assisting AYAs to navigate the early transplant period may minimize escalation to significant distress. Further, professional behavioral health

specialists may be scarce for the subset with serious distress.[44,45] Experts therefore suggest "universal" preventative psychosocial oncology care designed to "help patients help themselves."[44-46]

The first 6 months after HCT are important. Stress and distress before and in the first 6 months after HCT contribute to poor pharmaco-adherence, in turn increasing risks of cancer recurrence and Graft Versus Host Disease (GVHD).[41,47-49] Adherence rates among HCT-AYAs range from 40% to 90%; only 56% demonstrate "perfect adherence" and most take only 73% of their prescribed doses.[50] Although non-adherence is a well-described problem,[48,51,52] few interventions have improved it.[53] Early, psychosocial interventions targeting psychosocial wellbeing and self-efficacy may be more effective.[43,49,53,54]

Access to early psychosocial interventions is limited. Despite national recommendations for early integration of psychosocial care in pediatric and AYA oncology,[55-60] barriers remain. These include diverse models of assessment, service delivery, and staffing.[55] Pediatric cancer centers differ in size and location; they have variable, often limited, resources and funding for psychosocial services.[57,61,62] Some may not treat a sufficient number of patients to justify the costs of a comprehensive multidisciplinary team.[61,62] While centers may provide training for staff to effectively support patients and families (e.g., workshops on empathic listening, communication, problem-solving, and health literacy),[63-65] standardized, evidence-based, developmentally-appropriate interventions for AYAs with cancer are not well described.[16,55,56,66-68]

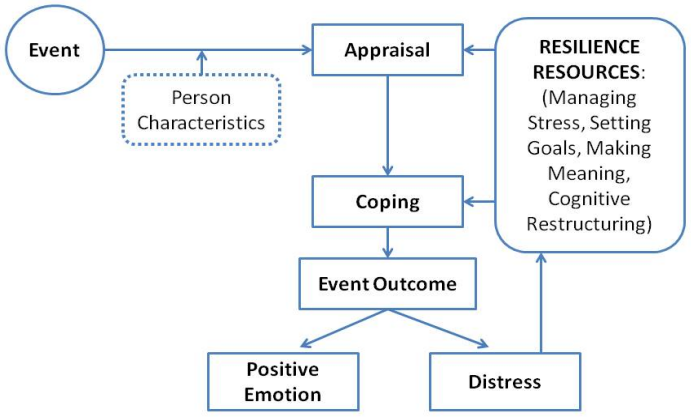
Practical challenges limit the success of traditional behavioral interventions. Time-commitments associated with traditional psychological interventions like cognitive behavioral therapy (CBT) may be prohibitive for AYAs. The average refusal rate for CBT in adolescent chronic disease settings is 37%; subsequent attrition is up to 32%.[69] Shorter skills-based interventions may be more successful.[70] Additionally, stigma and costs associated with traditional mental health services may hinder their uptake.[55-57,61,62,71,72] AYAs learn and communicate differently than younger and older patients, necessitating age-appropriate methods.[73] Furthermore, CBT is designed for patients with maladaptive coping, whereas AYAs may be helped to avoid maladaptive behaviors through brief preventive learning.

Psychosocial interventions must also be cost-effective. With increasing costs of healthcare, high quality and cost-effective interventions are critically important. Recent studies suggest psychosocial oncology interventions have favorable cost-effectiveness.[74-77] Economic analyses focusing on cost-utility, expressed in cost per Quality Adjusted Life Year (QALY) gained, have been recommended because they include standardized methods and established thresholds for willingness to pay (typically $150,000 per QALY gained).[77-80] However, cost per QALYs may not capture all outcomes important to patient-stakeholders.[81] Corresponding cost-consequence analyses may better align with informational demands of decision-makers because they list and compare all relevant direct

and indirect costs and consequences (e.g. cost per change in anxiety and depression scores). For this reason, the Second US Panel on Cost-Effectiveness in Health and Medicine recommends both approaches.[78]

Stress and coping theory (Figure 1)[82] provides an excellent platform for intervention development. This theory suggests three categories of resources to maintain psychological well-being during and after serious illness: (1) dispositional factors (e.g., optimism); (2) situational factors (e.g., stress-management and goal-setting skills); and, (3) coping processes to create positive meaning (e.g., cognitive reframing). Among older adults with cancer, stress-management shows promise at the beginning,[83] middle,[84] and end of treatment,[85] and meaning-making may improve quality of life.[86] Among well AYAs, individual differences in goal-seeking and problem-solving are associated with psychosocial well-being.[87] Among AYAs with chronic disease, positive re-appraisal of stressors reduces distress, improves adherence,[87] and optimizes quality of life.[88,89]

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



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

2.1.2 The Promoting Resilience in Stress Management (PRISM) intervention

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

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[30] and a survey comprised of validated instruments to measure corresponding patient-centered outcomes [the "Resilience in Pediatric Cancer Assessment" (RPCA)].[29,30,90] Quantitative findings confirmed associations between lower resilience resources and higher distress, lower social function, and poorer health behaviors.[29]

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.[28,91,92] Several participants received HCT during 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.[28]

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**).[93] PRISM is based on stress and coping theory (**Figure 1**),[82] 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. 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 with parents/caregiver/spouse/significant other about what was learned, what helped, what they can do to help	Parent/Caregiver/ Spouse/Significant other inclusive meeting
6. Boosters	Personal contacts and/or digital modules to practice, further develop, and track skills.	One-on-One or Digital

Note: Sessions delivered approximately every 1-2 weeks, arranged in advance in conjunction with clinic and hospital visits or can be done via phone or other web based communication (i.e., zoom, WebEx, skype, blue jeans, go to meetings, WhatsApp, etc.) (with the exception of session 1).

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.[93] 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."

PRISM Pilot 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 ahead of schedule; enrollment rates were 78%.

Attrition (20%) was similar on the PRISM and usual care arms, and primarily due to medical complications.

The primary objective of the phase II RCT was to assess patient-reported resilience. Final analyses suggest PRISM improved patient reported resilience and quality of life, and reduced psychological distress (Table 2).

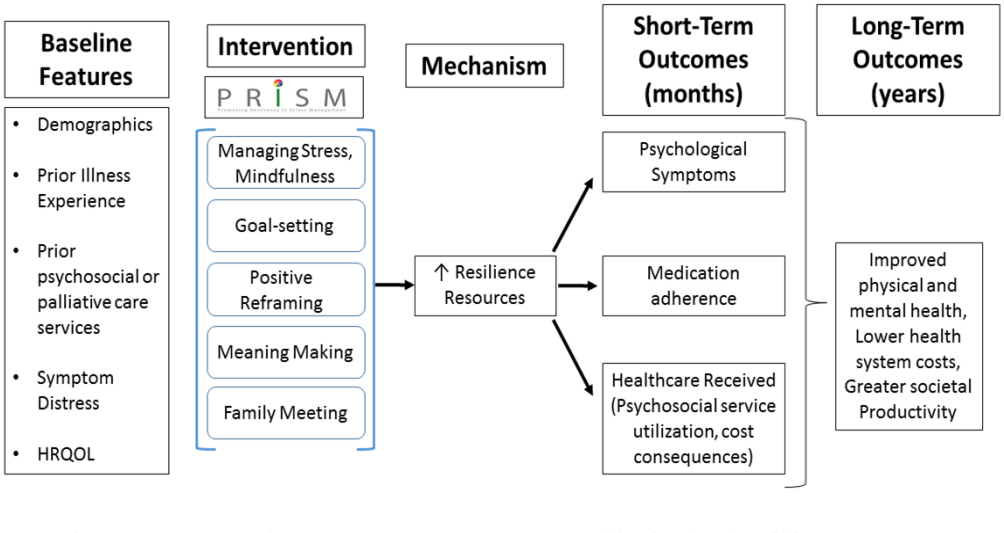
Table 2. Mixed linear model estimates of change in instrument scores associated with PRISM compared to usual care in phase II RCT

Outcome (instrument)	Beta (95% CI)	p-value
Resilience (CDRISC-10)	3.0 (0.5, 5.4)	0.02
Generic Quality of Life (PedsQL SF-15)	7.2 (-0.8, 15.2)	0.08
Cancer-specific Quality of Life (PedsQL Cancer)	9.6 (2.6, 16.7)	0.01
Global Psychological Distress (Kessler-6)	-2.1 (-4.1, -0.2)	0.03

2.2 Rationale for this Study

While these findings suggest PRISM is effective**, key questions remain**: (1) Does supportive care with PRISM prevent clinically important symptoms of anxiety and depression among AYAs receiving HCT?; (2) Is PRISM cost-effective compared to supportive care without PRISM?; (3) Does it promote medication adherence? and, (4) Is PRISM associated with measurable biomarkers of stress and resilience? These questions are important because high-value interventions must not only provide clinical benefit, but also be cost-effective.[94] The current study will build on our prior success and expertise to answer these questions. (**Figure 2**).

Figure 2. Conceptual Model for Study



Legend: *PRISM: Promoting Resilience in Stress Management; HRQOL: Health-Related Quality of life*

3.0 Inclusion and Exclusion Criteria

3.1 Recruitment and Screening:

We will recruit consecutive AYAs and their primary caregivers from outpatient Clinics and inpatient wards of Seattle Cancer Care Alliance (Seattle Children's Hospital and Fred Hutchinson Cancer Research Center),Children's Hospital Los Angeles (CHLA), St. Jude Children's Research Hospital (SJCRH), and University of Alabama at Birmingham (UAB). Research Associates (RAs) at each site will screen patients via review of the new transplant arrivals list, clinic rosters and sign-outs, communication with clinicians, and attendance at HCT conferences, followed by a medical chart review to very eligibility.

For Seattle Children's Hospital participants, recruitment will be conducted as follows: The study will be initially introduced to eligible families through either a study information flyer or opt-out letter. When possible, BMT clinic staff will distribute flyers to patients on intake day with the message that "someone will be contacting you to talk about this more" message. RAs will then conduct in-person recruitment in clinic waiting rooms, at clinic visits and/or inpatient hospital rooms. RAs will then discuss the project with patients and their parents and answer questions. Consent conference may be conducted directly following the approach or at a later date, depending on family preference.

Phone-based recruitment methods will be used in cases where in-person recruitment is not possible/feasible. This includes instances when in-person interaction would pose infection risk to patients (e.g., **during COVID-19 pandemic**), instances where patients are coming to clinic infrequently, or when in-person recruitment may cause unnecessary subject burden and obtaining consent by phone/video would achieve the same purpose without reducing subject informedness. This includes instances such as providers interrupting the consent conference, when the day is "not good" for the family to be approached, or when illness status in which the patient is not cognitively able to provide consent/assent that day. In these instances, eligible patients (or parents, when patient is under 18) will be mailed a letter or sent an e-mail introducing them to the study and giving them the opportunity to "opt out" of future contact if desired. If potentially eligible patients who receive the mailing do not opt-out of being approached about the study, an RA will then call them to assess interest. RAs will call a maximum of six times until contact is made, with a maximum of 3 voicemails. Once direct contact is made (i.e., having a conversation), follow up calls or texts will only occur if the family expresses interest in the study or requests a callback. Once they contact the family, the RA will use a phone approach script to explain the study. If the family is interested, the RA will e-mail or mail a copy of the consent form to the family and schedule a later time for a phone/video consent conference. Should families approached via phone prefer to continue to discuss the study or consent in person, we will arrange a follow-up conversation regarding the study at the time of their clinic or inpatient hospital visit or

while they plan to be at the hospital. Text communication will occur only after initial contact is made with a family via a non-text method.

Consent conferences will be conducted in a private consult room, clinic room or in the patient room (in-hospital) or via phone or videoconference. Videoconference will only be used if specifically requested by the participant, via WebEx or Zoom. Videoconference or phone-based consent conferences will NOT be recorded. Patients and families will be given an addendum to the consent form to participate in the optional heart rate variability,CTRA gene expression (blood draw), or medication adherence monitoring components of the study. We will emphasize there will be no penalties if patients or families opt out of the optional portions of the study. These optional procedures will be presented at the time of the consent conference. All patients fulfilling eligibility criteria will be eligible for the HRV and CTRA components of the study. Only patients receiving allogeneic HCT will be eligible for the medication adherence monitoring component. . Parents do not take part in the optional components. In cases where it is necessary to minimize in-person contact with participants to minimize exposure risk (e.g., during COVID-19 pandemic), the HRV component will not offered and families will be verbally informed of this justification.

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 qualitative interview 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 for participant 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 via phone or email throughout the study. We will emphasize that the decision of whether or not to be part of this study does not affect participants' involvement in the PRISM study, or their ongoing care at their respective institutions.

3.2 Eligibility Criteria:

3.2.1 Inclusion Criteria FOR AYA PATIENTS:

3.2.1.1 Age 12-24 years

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

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

3.2.1.2 Receiving allogeneic or autologous HCT for treatment of malignancy or bone marrow failure syndrome at Seattle Cancer Care Alliance (Seattle Children's Hospital and Fred Hutchinson Cancer Research Center),Children's Hospital Los Angeles (CHLA), University of Alabama at Birmingham (UAB) or St. Jude Children's Research Hospital (SJCRH).

3.2.1.3 Within 4 weeks of their HCT date ("day zero") (if prior, their planned HCT date)

3.2.1.4 Patient able to speak in the English language

3.2.1.5 Patient able to read in the English or Spanish language

3.2.1.6 Cognitively able to participate in interactive interviews

*****Inclusion criteria for medication adherence component only:** Patient receiving allogeneic HCT (i.e., receiving standard prophylaxis against Graf*t-Versus-Host Disease [GVHD]).*

***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 speak in the English language

3.2.2.4 Patient unable to read in the English or Spanish language

3.2.2.5 Patient not receiving allogeneic or autologous HCT for treatment of malignancy or bone marrow failure syndrome.

*****Exclusion criteria for medication adherence component:** Patient receiving autologous HCT (i.e., not receiving standard prophylaxis against Graf*t-Versus-Host Disease [GVHD]).*

3.2.3 Inclusion Criteria FOR PARENTS or GUARDIANS OF AYA PATIENT PARTICIPANTS to participate in SURVEY-COMPLETION

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

3.2.4 Inclusion Criteria FOR PARENTS, CAREGIVER, SPOUSES, OR SIGNIFICANT OTHERS of AYA PATIENT PARTICIPANTS to participate in PRISM SESSION 5, "Coming Together"

3.2.4.1 AYA agrees to participate in study

3.2.4.2 AYA randomized to PRISM intervention arm of study

3.2.4.3 AYA provides verbal assent or verbal consent if 18 or over for parent, caregiver, 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 participant has signed informed consent for study participation

3.2.5 Exclusion Criteria for PARENTS, GUARDIANS, CAREGIVER, SPOUSES, OR SIGNIFICANT OTHERS of AYA PATIENT PARTICIPANTS in SURVEY COMPLETION or PRISM SESSION 5, "Coming Together"

3.2.5.1 AYA refusal to participate

3.2.5.2 Parent/Guardian/Caregiver/Spouse/Significant other participant is <18 years of age

3.2.6 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

Number of subjects: We will enroll and randomize a total of n=90 AYAs from the four sites in order to reach our target n=70 of evaluable patients with complete data at the primary endpoint (Table 3). Note that both AYA patients and their parents/legal guardians will be enrolled when possible in order to collect accurate costing data. The rationale is that much of the day-to-day costs such as transportation and missed work will be experienced by PARENTS rather than AYAs.

Table 3. Annual number of AYAs (12-24 yrs-old) who are eligible, enrolled, and evaluable at 6 months

Site	Total	Eligible	Enrolled	Evaluable
SCCA	18	16	11	10
CHLA	12	11	7	6
St. Jude	10	9	6	4
UAB	10	8	6	4
Total/Year	**50**	**44**	**30**	**24**
Total for 36-month recruitment period:			**90**	**>70**

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 identified by national search engines.

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 Seattle Cancer Care Alliance (Seattle Children's Hospital and Fred Hutchinson Cancer Research Center), Children's Hospital Los Angeles (CHLA), St. Jude Children's Research Hospital (SJCRH) and University of Alabama at Birmingham (UAB). The lead study team member from SCH will travel to each participating site for site initiation where study teams will participate in minimum a day long training.

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

6.2.1 All sites have the most current version of the protocol, consent document, and HIPAA authorization.

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

6.2.3 All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) 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 (Junkins) lead interventionist will have at minimum twice monthly meetings with interventionists 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 approvals.

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. Timeline of research activities

	Year 1				Year 2				Year 3				Year 4				Year 5			
Activities	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Study Implementation Activities																				
IRB Protocol Submission)																				
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 Primary Endpoint: 6-month follow-up of last AYA participant including patient-reported outcome survey completion.

8.2 Secondary Endpoints:

8.2.1 6-month follow-up of last parent participant including parent-reported outcome survey completion.

8.2.2 6-month costing data collection including parent- and parent-reporting costing forms, and medical record extraction

6-month follow-up of last AYA participant by Medication Electronic Monitoring System (MEMS) cap electronic adherence assessment.

9.0 Procedures Involved

9.1 Enrollment. Once consent documents are signed and all questions addressed, the consenting RA or study staff will register the patient in the RedCap System. Randomization will not occur until after the baseline Resilience in Pediatric Cancer Assessment (RPCA) surveys are collected (see below). Site RAs will maintain original copies of all consent forms and fax/email copies to the coordinating center for secure storage and tracking purposes.

9.2 Randomization.

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 the 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 18-24 and site. Biostatisticians who will conduct data analysis will be blinded from the treatment group allocations. 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 Baseline Survey Completion Upon enrollment, study staff will deliver the baseline survey in participant’s preferred language (English or Spanish). For both English and 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 (interviews only available in English).

9.3.2 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 first 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 in real-time. 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 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.

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 5th session for AYA and selected parent/caregiver/ spouse/significant other 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 during the in-person sessions with the same intervention script (please see training manual and fidelity document for script). 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.[93,95] 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 5th session, intervention participants will be offered every other week "booster" contacts until they reach the 6 month point from enrollment. Although in person visits are preferred, if a patient explicitly requests or if scheduling barriers preclude in-person visits, all sessions and boosters may be done via phone or other web based communication (i.e., zoom, WebEx, skype, blue jeans, go to meetings, WhatsApp, etc.) .

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 benefitting from difficult situations (including their cancer).

The final 5th 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. During this last session, selected parent(s)/caregiver(s)/ spouse/significant others are explicitly asked to join and listen to the discussion. Study personnel will review and share with parents/caregivers/ spouse/significant others the explicit skills endorsed by patients and encourage shared conversation about how parents/caregiver/spouses/significant others and the patients can support one another. For families where parents prefer Spanish or another non-English language, this final session will be conducted with a certified 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). 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 parent/caregiver/ spouse/significant other inclusive meeting in these cases. Additionally, the coming together session may not be feasible if the parent/caregiver/spouse/significant other has not agreed to be a part of the study. In such cases, we will re-offer participation in real time. If parents/caregivers/ spouse/significant other still decline, then we will skip the parent/caregiver/spouse/significant other inclusive meeting.

Sessions may be combined (maximum 2 sessions per meeting) 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. Administrators of the 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 at Seattle Children's will review the first of each 5 sessions for each interventionist, and score them for fidelity using a standardized tool (see appendix.). After the first 5 sessions are reviewed for each interventionist, one of each 5 subsequent sessions will be randomly selected to be monitored for fidelity, with feedback and re-training regarding adherence to protocol and approach will be refined if needed.

Participants on the intervention arm will be offered every other week "booster" contacts until they reach the 6 month point from enrollment. These will include brief (10-20 minute) in-person contacts in clinic, in the hospital, by phone or other web based communication (i.e., zoom, WebEx, skype, blue jeans, go to meetings, WhatsApp, etc.) by email, or by digital text based modules that 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 4 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.. The app includes digital content of all paper-pencil "cheat sheets" and worksheets (see manual in appendix for both 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 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 video-conference using the site's own HIPAA compliant software (i.e., Zoom, WebEx) for session delivery. Thus, no contact would occur between SCH 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 interventionist using first names only. Any correspondence between site coordinators and SCH interventionists regarding session scheduling will use study ID numbers only.

9.5 MEMS cap and adherence assessments.

For patients who are eligible and consent to the optional medication adherence monitoring portion of the study, we will use the medication electronic monitoring system (MEMS) monitoring device to evaluate real-time medication adherence for oral immunosuppressive medications (standard prophylaxis against Graft-Versus-Host Disease [GVHD]). The MEMS system employs a microelectronic technology to record actual medication vial openings (date and time) as a measure of dosing. It is widely considered the gold standard of medication-adherence methodology.[96,97]

Beginning 2 weeks following the date of discharge from initial HCT hospitalization and for the final duration of the remaining 6 months on study, participants will store prescriptions for their primary GVHD prophylaxis (typically either tacrolimus or cyclosporine), in study-dispensed MEMS bottles and caps. A patient supply kit containing a MEMS cap and bottle will be dispensed to all study participants by the institutional RA no more than 7-10 post discharge. The patient will receive instructions directing them to put their primary GVHD prescription into these bottles and to take their prescription using the MEMS medication bottle. The patient will be instructed that any additional refills of their GVHD prophylaxis required during the study period are also to be added to their MEMS medication bottle. When possible, the study RA will meet with families in person approximately 2 weeks post-discharge to verify new prescription has been dispensed in these bottles and to review procedures. A study coordinator will

contact study participants monthly by phone, email, text or in person to answer any questions or concern the patient may be having.

The following instructions will be included in the patient supply kit:

1. In the next 1 -2 days, please put your main GVHD prophylaxis medication into your MEMS medication bottle. If you are unsure what medicine this is, please check with your study team.
2. Once you have filled your bottle, before you take your next dose of your GVHD medication, please replace the regular cap with the MEMS TrackCap you received in your study kit.
3. All doses of your GVHD medication should be taken from the MEMS medication bottle with the MEMS TrackCap while you are on this study.
4. Please take your GVHD medication exactly as your doctor has ordered.
5. Open the medication bottle ONLY when it is time for you to take your GVHD medication.
6. Close the medication bottle right after taking the GVHD medication.

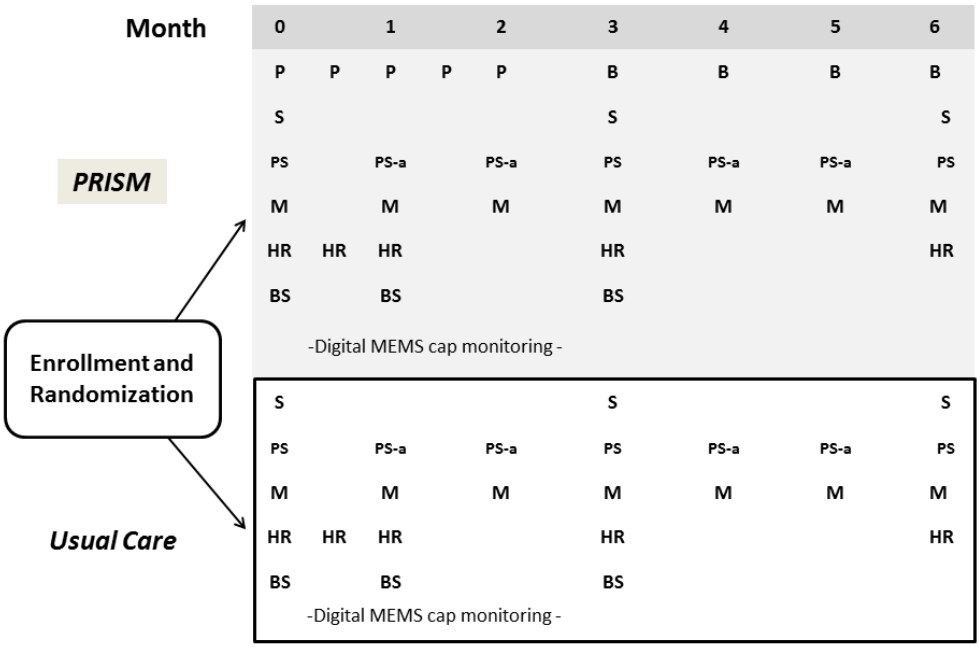
- To **refill** your GVHD medication while on this study, follow these instructions.
  - Only refill your medication when you need to take a dose of your GVHD medication!
    - Open the old bottle and take out a dose of medication.
    - Refilled bottle with your GVHD medication using your prescription bottle from your pharmacy.
    - Replace the electronic Trackcap onto the newly refilled bottle of your GVHD medication.
    - Please do not refill or open your MEMS cap when you are not taking your medicine.

If medications are dispensed in a blister package, if possible, study participants will be asked to place blister packages into medication bottles and take as above. Because most AYAs can take tablets, use of liquid formulations will be rare. However, when indicated or requested by patients, pharmacists will dispense oral, crushable tablets for compounding. Those study participants will, however, be asked to open their MEMS bottle at the same time as taking their GVHD medication. Patients will be instructed not to open the container unless taking a dose of the medication and to remove only the prescribed dose. After the final 6 months of study participation, study participants will be asked to return their MEMS track cap to their study coordinator.

9.6 Data collection schedule for study staff.

Caregiver reported costs of care and medical record data will be collected monthly (Figure 3). Details about staff-data collection are as follows:

Figure 3. Schedule of Study Activities by Month Post-Enrollment



LEGEND: P=PRISM Session, B=PRISM Booster, S=Survey, PS = Parent Survey, PS-a = Parent Survey, abbreviated, M=Medical Record Abstraction, HR=Heart Rate Variability, BS = Blood Sample

9.6.1 Digital pharmaco-adherence. Medical record abstraction will include prescription details including medication-name, frequency, and dosing.

9.6.2 Health care utilization. The Case Report Form (CRF, appendix) will capture the following variables through medical records and billing systems: (1) Intervention time: visit time related to case management and PRISM sessions; (2) mental health utilization: number, location, and duration of formal psychosocial clinician visits, psychological diagnoses, number of prescription psychiatric medications; and, (3) additional relevant utilization: number of supportive care medications (including acute and chronic pain medications and sleep-aids), number of and reason for unplanned hospital days, Emergency Department, outpatient clinic visits; resource use associated with additional health problems and diagnoses such as medical treatments an procedures, additional hospital services, distance between home and primary care facility (documented by home zip code), etc.

9.6.3 Additional covariates. RA's at each site will prospectively abstract the following clinical covariates from the medical record (using study-specific CRFs, appendix): the AYA's diagnosis, GVHD-directed treatments (and modifications), and treatment-intensity in the past month.[98] These variables were selected to capture relevant costs and based on prior evidence that AYA well-being and family psychosocial needs affect immediate psychosocial outcome metrics (e.g.,

psychological distress and quality of life).[46,98] In addition, RAs at each site collecting biomarker data (i.e., heart rate variability and/or blood samples) will abstract additional clinical covariates to provide needed context as to the conditions under which the corresponding biologic data were collected. These data will only be collected for participants who consented to the HRV and/or CTRA optional components of the study. Sites collecting heart rate variability (HRV) data will abstract the following clinical information for participating patients: cardiac medications, diagnostic cardiac test data, and patient weight, height, and Body Mass Index (MBI). Sites collecting blood samples will abstract the following information for participating patients: date of conditioning chemotherapy and/or radiation start, transplant date, and blood test information.

9.7 Resilience in Pediatric Cancer Assessment (RPCA) Survey (both arms):

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.[30] We have successfully used it in several of our prior studies.[29,30,90-92,99] The survey includes embedded validated instruments as well as standard demographics (age, sex, and race/ethnicity, education, income, number of children in the home).

The full RPCA survey will be administered to patients and parents at baseline, month 3 and month 6 (**Figure 3**). In order to optimize engagement, parents in both arms of the study will be asked to complete the abbreviated Resilience in Pediatric Cancer Assessment (aRPCA) at months 1, 2, 4, and 5. The aRPCA will assess only cost-consequences, as described below. In the rare case that a patient is their own money manager, AYA patients will be asked to complete cost-consequence questionnaires at each month in lieu of parents. RPCA and aRPCA surveys will be administered via REDCap or pencil-and-paper, depending on participant preference. If administered via REDCap, participants will be sent an email containing the survey link. Email language will include all text described in the IRB-approved template (see "PRISM BMT Survey letter – REDCAP") though additional personalized text may be included to reflect participants' specific needs. Paper-and-pencil surveys will be delivered in-person or via mail. If patients or parents specifically request to opt-out of aRPCA surveys (i.e., cost consequences assessments), study staff will no longer administer aRPCA surveys for the remainder of the study. In these cases, patients/parents will remain eligible to complete RPCA surveys.

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. If patients and parents have not completed any interval study questionnaires, we will still invite them to complete the 6 month questionnaire regardless of how many intermediate questionnaires they have completed. If patients and parents

are reluctant to fill out the full RPCA at 3 month and/or 6 months, we will offer a shortened RPCA assessing the primary outcomes only. If patients are still reluctant to complete the questionnaire due to length, we will provide a HADS only questionnaire option. Patients and parents will be given up to 4 weeks to complete the 6 month questionnaire before deemed 'off study'.

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 version (primary outcome only – HADS questionnaire only) of the questionnaire for patients to complete. Only 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 proxy questionnaires would be the patient questionnaire given to the parent to complete on behalf of their child. In such cases of proxy-completion of surveys, staff will note this distinction in the database and proxy-completion will be included as a potential confounding variable in subsequent analyses. These options will be offered in an effort to collect full data for primary endpoint assessment.

Participants in both arms of the study will be scheduled for their surveys at the time of enrollment and then reminded 1 week and 2 days prior to each survey due-date. Participants will be contacted in person, by phone, email, text or mail to receive their RPCA/aRPCA surveys. If we have not received a response within a day of initial contact, participants will receive up to 4 follow-up phone calls, texts or emails (approximately once weekly) within a 28 day window before and after surveys are due. Follow-up surveys not received within 28 days of their due-date will be considered missing. 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.

Table 5. Resilience in Pediatric Cancer Survey Domains	
AYA Surveys	Anxiety & Depression: Hospital Anxiety and Depression Scale (HADS)[1]
	Symptom Burden: Memorial Symptom Assessment Scale (MSAS)[2]
	Quality of Life: PedsQL Generic Core and Cancer Modules (PedsQL)[3,4]
	Hope: Hope Scale[5]
	Resilience: Connor-Davidson Resilience Scale[6]
	Health Utilities: Health Utilities Index[100-104]
	Demographics
Parent Surveys	Proxy Health Utilities (Health Utilities Index)[100-104]
	Costs of Care Checklist
	Quality of Life: Medical Outcomes Study Rand Short-Form 36[8]
	Anxiety: Generalize Anxiety Disorder Screener (GAD-7)[9]
	Depression: Patient Health Questionnaire (PHQ-8)[10]
	Family Experience Survey: HCAHPS[12]
	Demographics

9.8 RPCA item details

9.8.1 AYA Version (not included in parent surveys)

9.8.1.1 Hospital Anxiety and Depression Scale (HADS). The HADS assesses mixed affective symptoms in patients with serious illness.[1] It has been validated in AYAs with chronic illness[105] as well as AYA cancer survivors.[106] The scale has excellent reliability (α=0.83-0.82).[1] 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.[1] This instrument will be included in the full (non-abbreviated) RPCA survey as well as the 3 and 6 month shortened RPCA.

9.8.1.2 Memorial Symptom Assessment Scale (MSAS). The MSAS measures the presence, severity, frequency, and extent of bother from 26 symptoms with high consistency (α>0.8).[2,107] For this study, we will use a version of the MSAS that has been previously developed for and used among children with advanced cancer.[98,108] 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 will only be included only in full (non-abbreviated) RPCA surveys.

9.8.1.3 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,[3,4] and have been used successfully with low rates of refusal and minimal missing data.[109] 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.[4] This instrument will only be included only in full (non-abbreviated) RPCA surveys.

9.8.1.4 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."[5] 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 will only be included only full (non-abbreviated) RPCA surveys.

9.8.1.5 Connor-Davidson Resilience Scale. The Connor-Davidson Resilience Scale (CD-RISC) is a reliable and widely used instrument to measure inherent resiliency.[6] 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.[6,110] Correlative studies have evaluated the scale with other psychosocial measures such as psychological distress,[111] PTSD,[112] and social support.[113] 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 will only be included only full (non-abbreviated) RPCA surveys.

9.8.2 Both AYA and Parent Version

9.8.2.1 Health Utilities Index (HUI). The HUI is a multi-attribute preference-based health-status classification system validated in AYA cancer populations.[100-104] The index consists of 15 total queries to assess 2 systems - cognition, emotion, fertility, mobility, pain, self-care, and sensation (HUI2); and, ambulation, cognition, dexterity, hearing, emotion, pain, speech and vision problems (HUI3). Scoring is based on standard gamble utilities, with scores from 0 (health-state preference equivalent to death) to 1 (perfect health). Parents will be asked to complete the survey as a proxy for their AYA participant. Patient data will be used unless unavailable; only in cases where patient data is unavailable will parent proxy data be used for data analysis. This instrument will be included in the full (non-abbreviated) RPCA surveys as well as the 3 and 6 month shortened RPCAs.

9.8.2.2 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. This instrument will be included in the patient and parent RPCA surveys.

9.8.3. Parent Version (not included in AYA surveys)

9.8.3.1 **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.[9,114] 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 will only be included only full (non-abbreviated) RPCA surveys.

9.8.3.2 **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.[10,11,115-118] 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.[118,119] This instrument will only be included only full (non-abbreviated) RPCA surveys.

9.8.3.3 **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.[80] 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.[8] Internal reliability ranges from α=0.78-0.93. This instrument will only be included only full (non-abbreviated) RPCA surveys.

9.8.3.4 **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.[12] 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 a small subset of questions from 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 will only be included only full (non-abbreviated) RPCA surveys.

9.8.3.5 Patient costs. A study-specific cost-of-care checklist was adapted from consensus guidelines for cost-effectiveness analyses.[78] It will be embedded within RPCA surveys and query parent-estimates of: (1) direct costs: time costs (travel/wait time, time with providers), out-of-pocket expenses (gas/travel, other child-care needs); (2) indirect costs: time-lost from vocation or employment (see appendix). It will be included in the full and abbreviated surveys (RPCA, aRPCA and the 3 and 6 month shortened RPCA) in order to minimize recall bias and accurately collect monthly costing data from then perspective of parent/guardian caregivers. Due to recall bias, parents will be able to complete this questionnaire in real time over the course of the month. Parents will be given the questionnaire at the beginning of each month to have on hand to complete. If parents do not fill it out in real time, they will have the chance to complete in based on recall during their monthly visit in their embedded RPCA/aRPCA

9.9 Optional Procedures

9.9.1 Heart Rate Variability 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 team member (licensed medical provider or CRA with appropriate certification, per site requirements) will place the monitor on the patient (left chest) and ensure adequate ECG signal acquisition OR a study CRA will instruct the patient (no physical patient contact from CRA). 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.

9.9.2 Blood Samples

Whole blood samples will be sent to the University of California Los Angeles (UCLA) Social Genomics Core for transcriptome profiling using RNA sequencing.[120] The Clinical Research Associate will work with inpatient or outpatient staff to obtain subject's blood. A total volume of 5 ml of blood will be collected from subjects at the time of any clinical blood draw or intravenous access near the planned study time point. For smaller

children, we will follow clinical guidelines regarding volume of blood draws. Blood samples needed for clinical purposes will be prioritized over research lab collection.

Biospecimens (blood samples) will be temporarily stored in secure freezers at Seattle Children's Hospital Research Lab Services (RLS). The specimens will be labeled only with study identification numbers. Blood samples will be stored until 20 samples have been collected (anticipate <6 months depending on enrollment), and then will be shipped to the UCLA laboratory for analysis. No biospecimens will be banked.

Following quality assurance testing of suitable mass (Nanodrop ND1000) and integrity (Agilent Bioanalyzer RNA Integrity Score), mRNA will be converted to cDNA (Illumina TruSeq), and >10 million sequence reads will be obtained on an Illumina HiSeq 4000 instrument in the UCLA Neuroscience Genomics Core.

9.9.3 Data Collection Schedule

HRV data and/or blood samples will be collected at clinically relevant and study specific time intervals where possible (**Table 6**). When not possible, HRV and/or blood sample data collection will be scheduled at the patient's convenience, and/or during the next scheduled clinical lab draw. .

Table 6. Biological data collection schedule

Time Point	T1 (Baseline)	T2 (PRISM session #1 OR 1 week post enrollment)	T3 1 month (survey timepoint)	T4 3 months (survey timepoint)	T5 6 months (survey timepoint)
24-hour HRV Recording	X	X	X	X	X
Blood Sample	X		X	X	

10.0 Data and Specimen Banking

10.1 Data storage

All pharmaco-adherence, medical record, health care utilization, HRV, blood samples, RPCA survey data, and audio transcriptions will be coded and labeled with study identification numbers. All will be stored in original (hard copy) forms in locked cabinets (where relevant) and/or password-protected secure databases (for all electronic survey data) 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. Coded electronically saved 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. Only study staff with human subjects training will have access, subject to approval by the SCH site PI, Dr. Taylor. 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. Coded 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 dissemination and implementation potential of the intervention once its efficacy is confirmed. Should the intervention be effective, the intervention will be made publicly available for use by the broader medical communities caring for AYAs with serious illnesses.

11.0 Data Analysis/Management

11.1 Overview

The primary statistical analyses will be intention-to-treat to avoid confounding by non-random participant attrition or crossover. Demographics, clinical characteristics, items within the RPCA, adherence data, and costing data 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.

11.2 Sample Size Determination and Power

Our focus for sample size estimation is the primary outcome (Aim 1): mean HADS scores at 6-month observation. In the following table we list minimum clinically important differences (MCID) for various outcomes and detectable differences (DD) with our proposed sample size. Sample size is based on preliminary data from our Phase II RCT suggesting AYA HADS scores are normally distributed with mean score of 11.1 (SD=6.2). Assuming 20% attrition, we will randomize 90 AYAs (45 per arm) to obtain an evaluable sample size of 70 AYA participants (35 per arm). This sample size achieves 80% power to detect a 4.2-point increase in the mean 6-month total HADS score. This means 35 per arm will provide us >80% power to detect MCID 3.1 in the primary outcome HADS. Detectable differences for secondary patient- and parent-reported outcomes given this sample size are shown in **Table 7**. Sample size calculations have limited roles in economic analyses due to wide variability in distribution of costs and corresponding to infeasibly large requirements based on traditional inference.[121,122] Economists therefore focus on determining cost-effectiveness, as described above, including confidence intervals to reflect the precision of estimates.

Table 7. Detectable Differences between groups (in primary and secondary aims including patient- or parent-reported outcomes measures) given 80% power and 5% Type I error rate

Aim	Outcome (Instrument)	Population norms	Source	MCID	DD (SD)
1	AYA Anxiety/Depression (HADS total)	Mean 11.1 (SD 6.2)	Phase II RCT	3.1	4.2 (6.2)
2A	AYA Symptom Burden (MSAS)	Mdn 8.5 (IQR 4.3-14.0)	Published Data[98]	(not published)	4.9 (7.2)
	AYA Quality of Life – General (PedsQL 4.0)	Mean 70.9 (SD 17.2)	Published Data[123]	4.4	11.7 (17.2)
	AYA Quality of Life – Cancer Specific	Mean 65.3 (SD 16.3)	Phase II RCT	(not published)	11.1 (16.3)
	AYA Hope (Hope Scale)	Mean 49.6 (SD 8.3)	Phase II RCT	(not published)	5.6 (8.3)
2D	Anxiety (GAD-7)	2.95 (SD 3.4)	Published Data[9]	(not published)	2.3 (3.4)
	Depression (PHQ-8)	3.3 (SD 3.7)	Published Data[10]	5.0	2.5 (3.7)
	Parent physical quality of life (SF-36 PCS)	Mean 50.3 (6.9)	Published Data[124]	3-5	4.7 (6.9)
	Parent mental quality of life (SF-36 MCS)	Mean 42.9 (11.9)	Published Data[124]	3-5	8.1 (11.9)

11.3 Randomization

The randomization algorithm will be constructed by the study statistician using a permuted blocks scheme with randomly varying block sizes, within strata defined by age group and sites. Randomized assignments will be administered by a research associate using REDCap. Randomization will be stratified by age (patients ages 12-17 versus ages 18-24) and site.

11.4 Analysis Plan

11.4.1 Primary Outcome (Anxiety and Depression [HADS scores]). Our primary outcome is AYA reported total HADS score at 6 months. Because the amount of change depends strongly on the initial score at baseline we will control for baseline score 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 total HADS score will be the outcome, and PRISM intervention indicator will be the predictor of interest. Baseline HADS score, age group, site and other unbalanced confounders will be covariates in the regression. With this model specification, the regression coefficient of PRISM indicator captures the difference in the average changes (from baseline to 6 months) for the HADS score between PRISM arm and usual care arm. Thus the primary hypothesis can be tested by applying the Wald t-test to the regression coefficient of PRISM indicator. The same analysis will be undertaken for the domain subscales of anxiety and depression (HADS-A and HADS-D subscale scores).

11.4.2 Secondary Outcomes

11.4.2.1 AYA patient reported outcomes. The same analysis as above will be undertaken for the secondary outcomes of symptom burden, generic- and cancer-specific quality of life, hope, and resilience.

11.4.2.2 Cost per Quality Adjusted Life Year (QALY). We will use a cost-effectiveness framework to evaluate the overall value of PRISM.[81] We anticipate that supportive care and PRISM will be cost-effective compared to supportive care alone. The main cost-analyses will determine the total, per-patient, 6-month costs of PRISM versus usual care. Using Quality-adjusted life years (QALYs) we will then estimate the incremental cost-effectiveness ratio (ICER)

Costs will be calculated with a micro-costing approach, multiplying resource use by unit costs.[80] Resource utilization will be valued through the Medical Expenditures Panel Survey[125,126] and the Healthcare cost and utilization project,[127,128] with additional information from the Federal Supply Schedule.[78,79] For example, PRISM utilization will be calculated by estimated cost per visit category (e.g., in-person check-in with/without formal session), plus estimated costs of intervention delivery (including facilities and overhead). We will add a fixed $50 per patient cost for caseload supervision and information support, consistent with prior analyses of collaborative psychosocial interventions.[129-131] Patient costs will be valued using opportunity cost methods and the proxy-good method in sensitivity analyses.[132]

We will calculate ICERs to provide information on the incremental cost for each additional unit of change in QALYs. Because the goal of cost-effectiveness analysis is to inform decisions about resource allocation and assess intervention value, traditional hypothesis testing is rarely utilized.[80] Uncertainty in all ICER estimates will be quantified using non-parametric bootstrapping and calculation of a 95% confidence interval (CI) with Fieller's method.[133,134] We will calculate QALYs with standard utility values (preference-based measures of quality of life ranging from 0 to 1, defined by the Health Utilities Index).[102] Sensitivity analyses will calculate QALYs with assigned values for HADS scores (1.0 for no, 0.8 for mild, and 0.6 for severe anxiety or depression) as described previously.[135-137] The rationale for this dual approach is that preference-based scoring in pediatrics has limitations because rapid developmental changes make it difficult to identify health attributes (and hence, utility values) relevant to all age groups.[138]

11.4.3 Parent Outcomes. The same analysis as above (primary outcome and Aim 2A) will be undertaken for the parent outcomes.

11.4.4 Patient Outcome Trajectories. We will use descriptive statistics to summarize patient-reported outcomes in each study arm at enrollment, 3 months and 6 months. We will plot individual patient trajectories across all time-points for each outcome measure and attempt to identify trajectory patterns (e.g., stable vs. temporary or sustained improvement or deterioration) within study groups. We will also plot outcome summaries across time by study group to assess between-

group differences in overall trajectories and variability.

11.5 Exploratory Analyses

11.5.1 Digitally (MEMS-cap) assessed medication adherence rates will be defined as [(# events of MEMS cap opening/# events prescribed)] x 100. Days when oral GVHD medications were held by the prescriber (captured via medical record abstraction) will be removed from the denominator, whereas "missed doses" will be defined as those where no cap was opened on a day medication was prescribed. Adherence will be calculated on a monthly basis and summarized both monthly, and as a 3-month average.

11.5.2 We will calculate **incremental cost consequence ratios** (e.g., the cost for each unit of improvement in average HADS scores or adherence) using the same costing numerators as above with the HADS and adherence change as the denominator. These will be included not as a threshold for cost-effectiveness, but as part of a comprehensive evaluation of both costs and consequences of the intervention.

11.5.3 To explore the contribution of different cost parameters to total healthcare costs, we will analyze disaggregated costs (e.g., formal-, informal-, and non-healthcare sector costs) from a payer and societal perspective.[78,139] A similar analysis will be completed from the societal perspective. An incremental analysis will estimate the arithmetic mean difference in costs between intervention and control patients using multivariable generalized linear analytic techniques to adjust for variability in outcomes based on baseline characteristics. Sensitivity analyses will model the potential range of cost impact based on variable fee-for-service and out-of-pocket expenses

To explore family experience scores, we will conduct descriptive analyses of categorical data. Comparisons will include standard hypothesis testing including chi-square tests for frequency data and Kruskal Wallis for non-parametric differences in distribution of responses.

11.5.4 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. DNE will be defined as the number of days from transplant to an absolute neutrophil count (ANC) of >500/mm2 for ≥3 days. Cumulative incidence and severity of Grade II-IV GVHD will be defined by the revised Seattle Criteria as documented by the patient's clinical provider. HRV will be measured in 24-hour increments using both time and frequency domain parameters as established by the international Cardiology task force guidelines. Means and standard deviations will be compared to published normative data in adolescents. CTRA scores will be divided into two groups (above and below the median). We will perform multivariable analyses, adjusting for age, sex, diagnosis, disease status at the time of transplant, conditioning intensity, and,

immunosuppressive medications/GVHD prophylaxis to examine the association between CTRA biology and HCT outcomes.

11.6 Additional analyses, confounders, and other considerations.

We will conduct interaction modeling and subgroup analyses to explore whether the effect of the intervention is modified by medical covariates, symptom distress, and/or adherence. The rationale for these subgroup analyses is grounded in prior findings suggesting symptoms, adherence, and overall well-being are associated.[140]

We will conduct a thorough process evaluation that includes: (a) intervention fidelity; and, (b) satisfaction queries. Multiple comparisons are a concern since we are collecting multiple measures from patients and are interested in several hypotheses. We minimize this problem by specifying a limited number of main hypotheses for each aim. The Benjamini-Hochberg procedure will be used to control the False Discovery Rate criterion at $\alpha=0.05$ to correct for multiple testing in analyses that are not pre-specified.[141] Likewise, in manuscripts and presentations, we will report the number of tests performed and interpret results within this context.

11.7 Missing Outcome Data

While our goal will be to minimize missing data, data may still be missing due to patients/families skipping individual survey items, omissions in medical records, lack of follow-up, medical complications, or death. We will quantify the amount of missing data, evaluate the pattern of missingness, 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.[142-144] For example, for outcomes 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) data, 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 and biospecimens collected for research purposes will be coded. 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. Blood samples sent to UCLA for analysis will not contain any participant identifying information, they will be labeled with study ID only. When sample analysis is complete at UCLA, results containing study ID only will be faxed or scanned to the coordinating center for electronic storage. Upon study completion (last data collection for last patient), all materials will be coded (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 deidentified. Individual site teams will make all study files available during the on-site monitoring of the study by the coordinating site. In this instance, PHI will be viewable by the monitor for data accuracy but will not be copied or stored.

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, 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 enrolling study sites: Seattle Cancer Care Alliance (Seattle Children's Hospital and Fred Hutchinson Cancer Research Center), Children's Hospital Los Angeles (CHLA), University of Alabama at Birmingham (UAB) and St. Jude Children's Research Hospital (SJCRH), with the exception of CTRA gene

expression, which will only be collected at the Seattle site. 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 the site PIs and key study personnel.

13.2 Data Management

Research material collected will be in the form of data from the standardized questionnaires, medical record information, digital ECG files, blood samples, and electronic MEMs cap medicine adherence data. Protected health information (PHI) is accessible only by the site PIs and key study personnel, and the on-site monitor 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, blood samples, 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. For the present study, we will use the REDCap system managed by the University of Washington Institute for Translational Health Sciences (ITHS). 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, 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 for (a) missingness (see 13.4.1 below); and (b) unanticipated immediate threats to participants' or others' safety.

As part of the 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 site's outpatient psychiatric clinic, and 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 MEMs Cap Medicine Adherence Data

The coordinating center will be responsible for uploading and maintaining the MEMS cap medicine adherence data. After each patient returns their MEMS cap following their study completions, the study coordinator will mail the track caps in padded envelope to the coordinating center - Seattle Children's Hospital Attn: Molly Taylor (1920 Terry Ave. M/S CURE-4, Seattle, WA 98101). The site coordinator will upload the data will be via the MEMS MAP modem (Aardex Group, Belgium), yielding a record of times and dates that the container was opened. These methods have been used successfully in prior pediatric and AYA adherence studies.[97,145,146]

13.5 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 abovementioned encrypted RedCap database.

13.6 Blood Samples

5 mL whole blood will be collected in a PaxGene (PreAnalytiX GmbH) blood tube at the time of a planned clinical blood draw. These biospecimens will be labeled with the subject's study ID only (no identifying information) and sent to the Seattle Children's Research Lab Services (RLS) Core (Seattle Children's Hospital, Seattle, WA) for storage. De-identified, batched blood samples will be shipped by RLS to the University of California Los Angeles (UCLA) Social Genomics Core Laboratory for analysis.

13.7 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.

13.7.1 **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. The rationale for offering both paper-pencil and electronic versions is based on our prior experience where participants preferred the former,[92] which in turn facilitated more complete data collection. To ensure primary outcome data, we will offer an abbreviated survey with only the HADS and HUI for those who do not complete all assessments or who request to drop out. To ensure data quality, a RA will review RPCA surveys within 72 hours of their completion for missing fields and call participants to clarify and query/complete individual missing items verbally.

13.7.2 **MEMS caps**:

One to two weeks following discharge from the initial HCT and the day after any subsequent hospitalizations, an RA will contact the family by phone to review the MEMS-cap system and, where relevant, confirm the MEMS-cap is being used. Where indicated, to identify obstacles and solutions to its use.

13.7.3 **Medical record data:**

RA's will collect and upload CRF data monthly. To ensure reliability and validity of abstracted medical record data, we will use our current methods for training and quality control, 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.

13.7.4 **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.

13.7.5 Blood Samples:

Following quality assurance testing of suitable mass (Nanodrop ND1000) and integrity (Agilent Bioanalyzer RNA Integrity Score), mRNA will be converted to cDNA (Illumina TruSeq), and >10 million sequence reads will be obtained on an Illumina HiSeq 4000 instrument in the UCLA Neuroscience Genomics Core. Reads will be mapped to the RefSeq human genome (hisat2/stringtie) to estimate gene transcript abundance counts per million mapped reads.

13.8 Safety and Compliance Monitoring

This is a small multisite clinical trial of a supportive care intervention that presents no more than minimal risk. 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).

13.8.1 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.

13.8.2 Data and Safety Monitoring Committee

Member Name (Title)	Discipline	Research Expertise
Chris Dvorak, MD (Chief, Division of Pediatric Allergy, Immunology, and Bone Marrow Transplantation, University of California at San Francisco)	Pediatric Hematology/Oncology and Hematopoietic Cell Transplantation	Hematopoietic Stem Cell Transplant, Cancer Control and Supportive Care
Kristina K. Hardy, PhD (Associate Professor, Depts. of Psychiatry and Behavioral Medicine and Pediatrics, George Washington University School of Medicine)	Pediatric Psychology and Behavioral Medicine	Psychosocial oncology and behavioral intervention development
John Salsman, PhD (Associate Professor and Director of Clinical Research in Adolescent and Young Adult Oncology, Dept. of Social Sciences and Health Policy, Wake Forrest University School of Medicine)	Adolescent and Young Adult Psychology	Adolescent and Young Adult health psychology, patient-reported outcomes research
Corinne Summers, MD (**Committee Chair,** Assistant Professor, Dept. of Pediatric Oncology, University of Washington School of Medicine)	Pediatric Hematology/Oncology and Hematopoietic Cell Transplantation	Hematopoietic Stem Cell Transplant

13.8.3 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 CRA 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 un-blinded 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.

13.8.4 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.

13.8.5 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 coordinate 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.

13.8.6 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.

13.8.7 Interim analysis plan.

An interim analysis to assess for safety and missingness will be lead 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 rules occurrence of serious events, including (but not limited to) stopping the study for efficacy if interim analysis is significant.

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 (non-completion of surveys without serious medical complications or death), staff will continue to request surveys until 2 months following the 6-month endpoint, as described above.

14.3 When and How to Withdraw Subject

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, as well as other difficult topics such as suicidal ideations, sexuality and substance abuse. During the coming together session and/or while completing surveys, parent(s)/caregiver(s)/spouse/significant other may be prompted to think about the threat to their child's/significant other's life by cancer. The topics to be covered may provoke sadness, anxiety, depression, fear or doubt for AYAs and/or their parent(s)/caregiver(s)/spouse/significant other. 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. Minimal physical risks are expected to arise from the study, primarily related to the optional blood sample component. All patients undergoing HCT will have a central line, and blood samples will be drawn from the central line as the default; peripheral IV blood draws will only be performed if the patient does not have a functional central line. There would not be an additional "poke" to draw research blood from a participant. Risks associated with blood draw include slightly prolonging the length of another planned blood draw, and rarely fainting or infection. The research blood samples will be drawn at the same time of clinical indicated blood draws so that these risks are not increased. Blood draws will be performed by trained personnel who are experienced in working with children and familiar with processes of lab draws from central lines, and the challenges of drawing blood from this population.

The particular type of genetic testing to be performed using the blood samples will not pose any additional risks to subjects. The CTRA analysis is not a traditional genetic test (it does not test for the presence or absence of certain genes or mutations that might confer any kind of risk to the patient). It is testing how "turned on" or "turned off" certain ubiquitous genes are in a particular subject, but does not provide information on the subject's underlying DNA makeup. The results of this analysis will not have any bearing on a participant's genetic risk factors for developing certain diseases.

The primary risk to participants will be concerns about confidentiality, and stress of discussing the topic of their or their child's/significant other's cancer 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 limited to authorized personnel. The Lead RA and other researchers involved in this project has 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 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-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:

17.1.1 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).

17.1.2 Pregnant women: There is a chance that a parent/caregiver/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 the following populations either because they do not meet inclusion/exclusion criteria of being physically or cognitively able to participate in in depth interviews, or because they are anticipated to have inconsistent presence at the bedside, suggesting inconsistent participation in said interviews.

17.2.1 Prisoners
17.2.2 Cognitively impaired adults
17.2.3 Wards of the state

18.0 Community-Based Participatory Research

N/A

19.0 Sharing of Results with Subjects

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

There are no plans to return results from the CTRA genetic analysis to participants, as this does not relate to their underlying genetic makeup or hereditary risk for disease.

20.0 Setting

1.6.1 Patients will be identified and recruited at either at SCCA or at SCH. See section 23 for specifics.

1.6.2 Study visits may be done in person at SCH in the inpatient room or in the outpatient clinical research center or at SCCA on the 6th floor pediatric transplant clinic, or via phone or other web based communication (i.e., zoom, WebEx, skype, blue jeans, go to meetings, WhatsApp, etc.).

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

20.4 No local research will be conducted outside of SCH or SCCA.

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; on outline of each section is listed in **Table 1.** All interventionists undergo at least 4hours of in person training including role-playing and progressive mastery of intervention materials. The fidelity of sessions 1-4 will be systematically assessed via audio-recording. The PI or supervising team member at

Seattle Children's will review the first of each 5 sessions for each interventionist, and score them for fidelity using a standardized tool (see appendix.). After the first 5 sessions are reviewed for each interventionist, one of each 5 subsequent sessions will be randomly selected to be monitored for fidelity. Interveners will receive feedback regarding adherence to protocol and approach will be refined with additional training, if needed.

21.2 Based on the estimated number of AYAs receiving allogeneic or autologous HCT for treatment at the study sites, there will be enough patients to meet study enrollment goals.

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

21.4 The PCAR team works closely with the Hematology/Oncology medical and social work teams if outside resources or needs arise.

21.5 **CTRA Gene Expression Profiling.** Transcriptome profiling and related bioinformatics analyses will be conducted by the UCLA Social Genomics Core (Directed by Dr. Steve Cole, study consultant). This Core will conduct global gene expression profiling using RNA sequencing and report results back to the coordinating institution.

22.0 Prior Approvals

NIH NCI/R01 CA225629-01 was reviewed by the designated NIH study section.

23.0 Participant Incentives

All active patient participants will receive three installment payments in the form of a $25 gift card during the 6-month duration of the study. Patients will be paid one installment of $25 for each RPCA survey (baseline, 3-months, and 6-months), for a total of up to $75 for participation.

Throughout their participation on the study, AYA participants will receive small, non-monetary items (i.e., a pen, lanyard, tote bag, etc.). Parent/guardian participants will also be offered non-monetary items (PRISM paraphernalia such as pens, bags, stress balls, mugs, etc.) but no gift-cards. AYA 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 after 10 participants have completed all study procedures. Each participant in the raffle will therefore have 10% 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

We anticipate enrolling 50-60 patients locally in the 3 year study duration (**Table** 3).

26.0 Provisions to Protect the Privacy Interests of Subjects

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. Emphasis will be made to ensure that subjects know that not participating will not impact patient care.

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.

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 wsill be HIPAA compliant and will protect all information received from subjects.

27.0 Compensation for Research-Related Injury

There is no compensation for research-related injury.

28.0 Economic Burden to Subjects

We strive to complete these visits with patients while they are already at the hospital. As above, if explicitly requested, intervention sessions may be conducted via phone or other web-based communication (e.g., zoom, WebEx, skype, blue jeans, go to meetings, WhatsApp, etc.) or via phone.

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.

No additional study visits will be scheduled for study conduction purposes alone (all visits will be conducted in conjunction with other medical visits). It should be noted, however, that one of our objectives is to determine economic burdens associated with the intervention and study participation.

29.0 Consent Process

29.1 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.

29.2 **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. For patients/families who are screened and provide verbal interest by phone, the written consent form may be mailed for receipt and review prior to enrollment. 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 held 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 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 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 the consent conference is conducted via 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 or mail 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 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 and 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 if requested. After the participant has completed the e-consent form, the RA will immediately complete a corresponding REDCap form that includes: a) the names of the patient and parent (if applicable); b) the name of the person obtaining consent; an attestation that the subject agreed to participate, that all risks and opportunities of the study were explained, and that the subject had adequate opportunity to have their questions answered; and c) the RAs electronic signature and corresponding date/time. If an interpreter is used, the name of the interpreter will also be documented.

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.

If participants request for a PDF of the consent forms to be emailed, participants may print/sign/scan the form and return to the RA; if mailed, a return envelope will be enclosed so participants can sign and return the form. Once forms are received, the RA will sign and date, as well as note the date which the phone consent conference took place.

In all cases, RAs will create a consent process note for 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.

A separate consent will be obtained from parents/guardians who choose to participate in the parent portion of the study, meaning they will be completing their own study questionnaires and will be disclosing their own financial and quality of life information in surveys. In addition, parents/caregivers/spouse/significant other may provide an addendum to the AYA consent/assent to acknowledge that they may participate in the ‘Coming Together’ portion of the study. Parents/guardians may elect to participate in either or both of these study components (i.e., still be involved in the ‘Coming Together’ portion of the study and not want to complete questionnaires and visa versa). If requested by the AYA, other individuals (i.e., other parents/caregivers/spouse/significant other) will also provide an addendum to the AYA consent/assent if they may participate in the ‘Coming Together’ portion of the study. There will be a separate addendum to the consent form for the optional HRV and blood sample (CTRA) measurement components of the study. Parent consents and both consent addendums will be presented to families following either the in-person or e-consent methods described above.

29.2.1 Non-English Speaking Subject:

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

29.2.2 For Spanish Speaking Parents:

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**.**

29.2.3 For patients 18 years and older:

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/caregiver/spouse/significant other to participate in session 5, "coming together," parents will be invited to sign a Spanish version of the consent. All discussions involving Spanish (non-English) speaking parents will occur with trained medical interpreters.

29.2.4 For all patients:

Session 5 ("coming together") will be offered in the presence of a Spanish interpreter. All other 1:1 sessions will still be conducted in English with English-speaking, trained interventionists.

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

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.

Everything pertaining to Spanish speaking parents would be the same for other non-English speaking parents except that discussions, conferences, and Session 5 would be in the native language of the parent.

29.3 If patient is still actively on study, however, patient 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 email/mail the consent to the participant and will call the participant (and parents if applicable) and go over study changes. If emailed, participants may e-sign the consent form via REDCap. If mailed, the 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. He/she 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 (i.e., zoom, WebEx, 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.

29.4 Waiver of HIPAA for Recruitment and Alteration of HIPAA

29.4.1 Provide protocol specific findings justifying this determination: The waiver of HIPAA Authorization 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. In addition, we are requesting an alteration 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 regarding instances when remote consenting is necessary. Site PIs will make the final determination as to when remote consenting is appropriate.

29.4.2 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 of HIPAA for screening 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 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 bone marrow transplant patients we are attempting to enroll are 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, without this alteration enrollment in this study is not feasible for the foreseeable future. Furthermore, the COVID-19 pandemic 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 this case, it is currently unclear when this pandemic will truly end and could take years for an acceptable measure of safety to be restored to our community; furthermore, even once the COVID-19 pandemic has resolved there are other potential circumstances that could similarly mitigate our ability to approach in-person (e.g., a bad flu season). Thus, this alteration is crucial to protect the health of potential research participants while still furthering this important research.

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.

29.4.3 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.

29.4.4 Waivers for participants who turn 18:

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 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.

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

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 a patient indicates that he or she does 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.

Since this is a minimal risk studies, 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.

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 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.

29.6 Cognitively Impaired Adults

N/A

29.7 Adults Unable to Consent

N/A

29.8 Consent for use of HUD

N/A

30.0 Process to Document Consent in Writing

Consent documents are attached in the appropriate section of the Click smart form, including identical REDCap consent forms for remote consenting. We are following the SOP as written.

We will obtain written assent/consent from participants whenever possible, as a wet ink or 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.

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.

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).

33.0 REFERENCES

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