Official Title:
Improving Symptom Management for Adolescents and Young Adults with Advanced Cancer: Development and Pilot Testing of a Novel Intervention

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Research Summary

State your primary study objectives

Estimates suggest >30,000 adolescents and young adults (AYAs) aged 15 to 29 are diagnosed with cancer in the United States each year.[13,14]The incidence of cancer in this age group has grown over the last four decades and is 2.7 times more frequent than among pediatric (aged<15) patients.[13] Improvements in morbidity and mortality outcomes for AYAs have lagged behind both younger pediatric and older adult cancer patients; in fact, AYAs are more likely to present with advanced disease, have more aggressive tumors, and have worse prognosis.[15-21] Consequently, AYAs often have high symptom (e.g., pain, fatigue, emotional distress) burden.[22,23] This has led reports from the Institute of Medicine[24] and others[25,26] to

recommend that AYAs with advanced cancer have routine access to palliative care services throughout their cancer trajectories to assist with symptom management and improving quality of life; however, AYAs are underserved in palliative care.[25,27]

At present, there is a paucity of developmentally appropriate psychosocial palliative care interventions to improve symptom management for AYAs with advanced cancer. Adult palliative care services often treat older cancer patients (mean age 60-65);[28] thus, the majority of psychosocial symptom management interventions have been tested among those with a mean age >40.[4,29,30] Pediatric palliative care also fails to meet the needs of AYA patients as services are often focused on patients aged <15, and providers may be less familiar and/or comfortable delivering services to AYAs.[26,31] AYAs are diagnosed during a critical developmental period when they are working to achieve complex, age-related goals such as completing their educations, achieving autonomy, building their careers, fostering successful peer and romantic relationships, and building their families.[32-35] The diagnosis of advanced cancer contributes to patients' loss of self, future goals, and relationships, which they must navigate as they cope with increased symptom burden. As an AYA's illness progresses, they may become increasingly reliant on a caregiver (e. g., parent, partner) for support[36] and assistance with symptom management[37,38] at a time when they are looking to become more independent. The combination of high symptom burden and challenges to achieving developmental milestones may exacerbate patient suffering;[31,39] yet, the unique, age-related needs of AYAs with advanced cancer often go unrecognized.

We propose to begin to fill this gap by developing and pilot testing a psychosocial symptom management intervention designed to meet the unique needs of AYAs with advanced cancer. Guided by the team's prior work developing symptom management interventions for older advanced cancer patients[7,10] and expertise in AYA Oncology, the proposed intervention will combine traditional behavioral symptom management strategies (e.g., activity pacing, relaxation training) commonly used in palliative care with important skills and concepts from Meaning-Centered Psychotherapy (MCP)[3-5] and Acceptance and Commitment Therapy (ACT).[40,41] Both MCP and ACT have been associated with decreased distress and symptom burden in oncology patients with advanced cancer.[5,40] We anticipate that the intervention will incorporate questions from MCP to help patients identify valued life areas impacted by symptoms; techniques from ACT will then be used to help patients obtain distance from psychological barriers (e.g., thoughts, emotional experiences) to enacting their values to allow for flexible, value-congruent behaviors. Skills from these approaches may be particularly relevant to AYAs with advanced cancer who experience significant disruption in life goals due to symptoms and may have greater difficulty understanding and finding meaning in their lives.[42]

Aim 1: Intervention Development. Preliminary intervention content has been outlined and will be further informed by focus groups with patients (AYAs with advanced cancer, aged 15-29; two groups, n=6/group), caregivers (one group, n=8), and a combined patient/caregiver group (one group; AYAs: n=4; caregivers: n=4) who will provide information about the symptom (e.g., pain, fatigue, emotional distress) experience of AYAs with advanced cancer, patients' symptom management needs and coping strategies, the unique developmental aspects of being an AYA or caring for an AYA with advanced cancer, and how patient and caregiver needs may interact to impact symptom management. Participant input will help to confirm whether the proposed intervention strategies (i.e., behavioral symptom management, ACT, MCP) may be of benefit for addressing the unique needs of AYAs with advanced cancer. User testing of the developed intervention will be conducted with an additional three AYAs with advanced cancer to further refine the intervention content and format, written study materials, and study procedures. H1: Information obtained will allow us to develop a novel intervention to improve symptom management and reduce symptom interference to increase value-congruent behavior. It is anticipated that the intervention will include four sessions spaced over 6-8 weeks and be delivered using videoconferencing. In the event that a participant is unable or prefers not to attend a group, an individual session will be scheduled.

Aim 2: Pilot Randomized Controlled Trial. AYAs with advanced cancer (N=40) will be randomized to the intervention or an education control arm using an allocation ratio of 1.5:1. Feasibility of study recruitment (N=40 in 12 months) and participant retention (>80% intervention completion) will be examined along with intervention acceptability. Patterns of change in symptom (i.e., pain, fatigue, distress) severity and interference, self-efficacy for symptom management, and targets of ACT and MCP (e.g., acceptance, experiential avoidance, congruency between values and actions) will be examined. H2: Study recruitment and retention will be feasible, and the intervention will be acceptable. H3: The intervention arm will evidence improvements in symptom severity and interference, self-efficacy, and targets of ACT and MCP not seen in the control arm.

This pilot trial will allow us to refine approaches to identify, recruit, and retain AYA participants and examine patterns of change in key outcome variables for the intervention and control arms. Information obtained will position the investigative team to examine the efficacy of the intervention in a larger randomized controlled trial.

State your secondary study objectives

Please select your research summary form:

Standard Research Summary Template

This is the regular (generic) research summary template which is required for all regular applications (unless your protocol fits under the other research summary templates in this category). Use of these instructions is helpful for ensuring that the research summary contains all necessary elements.

Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

Aim 1: Intervention Development. Preliminary intervention content has been outlined and will be further informed by focus groups with patients (AYAs with advanced cancer, or recurrent aged 15-29; two groups, n=6/group), caregivers (one group, n=8), and a combined patient/caregiver group (one group; AYAs: n=4; caregivers: n=4) who will provide information about the symptom (e.g., pain, fatigue, emotional distress) experience of AYAs with advanced cancer, patients' symptom management needs and coping strategies, the unique developmental aspects of being an AYA or caring for an AYA with advanced cancer, and how patient and caregiver needs may interact to impact symptom management. Participant input will help to confirm whether the proposed intervention strategies (i.e., behavioral symptom management, ACT, MCP) may be of benefit for addressing the unique needs of AYAs with advanced cancer. User testing of the developed intervention will be conducted with an additional three AYAs with advanced cancer to further refine the intervention content and format, written study materials, and study procedures. H1: Information obtained will allow us to develop a novel intervention to improve symptom management and reduce symptom interference to increase value-congruent behavior. It is anticipated that the intervention will include four sessions spaced over 6-8 weeks and be delivered using videoconferencing. In the event that a participant is unable or prefers not to attend a group, an individual session will be scheduled.

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Background & Significance

- Should support the scientific aims of the research

A. Significance. 1. Scope of the Problem. In the last four decades, the incidence of cancer among adolescents and young adults (AYAs; aged 15-29) has increased, and for some cancers (e.g., colorectal cancer, melanoma), has increased more rapidly than for any other age group.[43-45] Improvements in morbidity and mortality outcomes for AYAs have lagged behind both younger pediatric and older adult cancer patients; in fact, AYAs more often present with advanced disease, have more aggressive tumors, and have worse prognosis.[15-21] Cancer is currently the leading cause of disease-related death among AYAs.[46] The significant disparity in outcomes for AYAs may stem from a number of age-specific factors that result in decreased access to care and can contribute to delays in diagnosis.[47] For example, AYAs are more likely to be uninsured or underinsured when compared to younger or older cancer patients.[48-51] AYAs'

perceptions of invincibility may interfere with attending medical appointments even in the presence of symptoms,[52] and the relatively low frequency of cancer in this age group may lead medical professionals to attribute an AYA's symptoms to a condition other than cancer.[49]

2. AYAs with advanced cancer have high symptom (e.g., pain, fatigue, emotional distress) burden.[22,23,53,54] These symptoms are often interrelated and co-occur,[27,55,56] with patients reporting a median of 4 symptoms towards the end of life.[56] The Institute of Medicine[24] and others[25,26] have recommended that AYAs with advanced cancer have routine access to palliative care services throughout their cancer trajectories to assist with symptom management and improving quality of life. However, AYAs with advanced cancer are underserved in palliative care, and the integration of palliative care remains suboptimal.[25,27] Adult palliative care services primarily treat older cancer patients (mean age 60-65).[28] Thus, the majority of psychosocial symptom management interventions for advanced cancer patients have been tested among patients aged >40.[4,29,30] Pediatric palliative care services are often focused on patients aged <15.[25,22] Providers may be less familiar and/or comfortable delivering services to AYAs, and referral for AYA patients to palliative care specialists remains low.[26]

3. Pediatric and adult palliative care services are likely not appropriate to meet the unique needs of AYAs. AYAs are diagnosed in the early stages of their adult lives. This critical developmental period is when AYAs are working to achieve complex, age-related goals like completing their educations, building their careers, fostering successful peer and romantic relationships, and building their families.[32-35] AYAs may experience changes in their sense of identity and purpose in life as the goals towards which they had been working are now made more difficult, if not impossible, by their diagnosis, treatment, high symptom burden, and poor prognosis. The age-related challenges of AYAs may be more pronounced for those with advanced cancer. In an effort to prolong life, AYAs with advanced cancer often choose aggressive treatments that can result in additional side effects and lower quality of life.[1] They must learn to cope with high symptom burden and living with a life-limiting condition while their peers are establishing their autonomy and building their futures. AYAs with advanced cancer may instead experience a loss of independence as they must now rely on close others (e.g., parents, new romantic partners) for physical, emotional, and financial support[36] and assistance with symptom management.[37,38] The combination of high symptom burden and challenges to achieving developmental milestones may exacerbate suffering;[31,39] yet, the unique, age-related needs of AYAs with advanced cancer often go unrecognized. In line with NIH priority areas (PAR 19-153), we propose to begin to fill this gap by developing a psychosocial symptom management intervention for AYAs with advanced cancer.

B. Innovation. We seek to develop and provide a better understanding of the feasibility and acceptability of a novel, psychosocial symptom management intervention responsive to the high symptom burden and unique developmental needs of AYAs with advanced cancer. Despite the call for palliative care interventions, at present, studies of developmentally appropriate psychosocial interventions to improve symptom management for AYAs with advanced cancer are lacking. There is an urgent need to develop interventions to decrease symptom burden in this growing population of patients who have the potential to experience significant suffering as they face life-limiting illness. The proposed project will produce pilot data responsive to NIH's request for interventions to enhance palliative care services for AYAs with cancer (PAR 19-153) and is innovative for 3 main reasons.

1. The proposed intervention will combine traditional behavioral symptom management strategies commonly used in palliative care with skills and concepts from Meaning-Centered Psychotherapy (MCP)[3-5] and Acceptance and Commitment Therapy (ACT).[40,41] Developed for use with advanced cancer patients, MCP assists patients in reconnecting with, creating, and sustaining meaning in their lives. ACT promotes psychological flexibility by encouraging increased awareness of thoughts and their functions (rather than changing their content/frequency) and promotes active movement toward personal values.[40,41] Both MCP and ACT are associated with decreased distress and symptom burden in oncology patients.[5,40,41] The proposed intervention will incorporate questions from MCP to help patients identify valued life areas; techniques from ACT will help patients obtain distance from psychological barriers (e.g., thoughts, emotional experiences) to enacting their values to allow for flexible, value-congruent behaviors. Skills from ACT and MCP may be particularly relevant to AYAs with advanced cancer who experience significant disruption in life goals and may have greater difficulties finding meaning in their lives.[42]

2. The intervention will be developed using input from patient ***and*** caregiver stakeholders. To our knowledge, this is the first study to systematically develop a psychosocial symptom (i.e., pain, fatigue, emotional distress) management intervention for AYAs with advanced cancer. To ensure that the intervention addresses the developmental stage and unique needs and experiences of AYAs, intervention development will be guided in part by qualitative information obtained during focus groups held separately with AYAs with advanced cancer *and* their self-identified primary caregivers as well as a *combined* group of patients and caregivers. As an AYA's illness progresses, he or she may become increasingly reliant on a caregiver (e.g., parent, new or established romantic partner, friend) for support.[36] While caregivers play an important role in assisting patients with understanding, coping with, and adjusting to illness as well as symptom management,[37,38] caregivers face the challenge of providing assistance to an individual who is striving to achieve independence. AYA oncology patients describe independence as not only an indicator of adulthood but also as inherent to health.[57] The diagnosis of cancer and/or progression of disease may lead

to a new level of dependency, halting or even reversing progress towards autonomy.[57] Patients living independently may return to living with their families of origin, and those relying on friends or romantic partners may have concerns about placing demands on these newer, less established relationships. Caregivers of AYAs with advanced cancer can provide a unique understanding of the experiences of AYAs by sharing information about their experiences assisting patients with managing their illness. We will also gain a better understanding of how patient and caregiver needs interact to impact symptom management. By understanding and being responsive to the perspectives of both AYAs with advanced cancer *and* their caregivers, we will increase the potential for intervention uptake and engagement.
3. The intervention is being developed to be to highly implementable and optimize its potential for dissemination. The intervention is proposed to be brief (i.e., 4-session) and delivered via videoconferencing. This structure and format is responsive to the needs of AYAs, who have multiple competing demands and perceive in-person interventions to be burdensome,[58] and a good match for AYAs' current use of technology[59] for healthcare delivery.[60] Importantly, it is also a structure and format that can be widely implemented, as evidenced by the growth of telehealth during the COVID-19 pandemic[61] and value of brief interventions for patients with advanced disease.[62] Should intervention recruitment and retention be feasible, the intervention be acceptable, and there be signals that the intervention is promising, the investigative team is well positioned to rapidly disseminate the intervention within the Teen and Young Adult (TYA) Oncology Program at the Duke Cancer Institute. Following evaluation through a larger RCT, the investigative team is well positioned to more widely disseminate the intervention [e.g., Palliative Care Research Cooperative Group (PCRC)**; U24NR014637**].

Design & Procedures

- Describe the study, providing details regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue/specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

A. Study Design. We propose to develop a psychosocial symptom management intervention for AYAs with advanced or recurrent cancer and to examine feasibility, acceptability, and patterns of change in outcomes through a pilot RCT. Intervention development will be guided in part by qualitative data from focus groups with: 1) AYAs with advanced or recurrent cancer (n=6/group, 2 groups), 2) caregivers of AYAs with advanced or recurrent cancer (n=8, one group), and 3) a combined caregiver (n=4) and AYA (n=4) group. The intervention and study procedures will be further refined following review by a second group of patient user testers (N=3-5). User testers will review the patient intervention manual and provide feedback to better understand the experience of users and refine the intervention materials and study procedures. It is anticipated that the developed intervention will include traditional behavioral symptom management approaches commonly used in palliative care settings and techniques from MCP and ACT.

The intervention will then be pilot tested through a small RCT. A new group of AYAs with advanced or recurrent cancer (N=40) will be randomized with an allocation ratio of 1.5:1 to the intervention (n=24) or education control (n=16) arms. Participants will complete assessments at baseline (A1), post-treatment (A2; 6-8 weeks after A1), and 4-weeks post-treatment (A3). We will examine feasibility and acceptability, patterns of change in outcomes (i.e., symptoms, symptom interference) and intervention targets (e.g., self-efficacy, acceptance, experiential avoidance) for the intervention and control arms, and sustainability of effects over time.

B. Participants, Accrual, and Procedures. Patient participants (focus groups: N=16; user testers: N=3-5; RCT: N=40) will be AYAs, aged 15-29 with advanced or recurrent cancer. Briefly, patients will be recruited from the Duke Cancer Institute (DCI), a National Cancer Institute-designated Comprehensive Cancer Center, and Duke Children's Hospital and Health Center (Duke Children's). Eligibility criteria include: a) aged $\geq$15 and $\leq$29, b) diagnosis of advanced or recurrent cancer (i.e., diagnosis of incurable cancer or distant metastases, recurrent disease),[74] and c) able to speak/read English. Exclusion criteria include: a) active serious mental illness (e.g., schizophrenia) as indicated by medical records or b) visual, hearing, or cognitive impairment interfering with participation. Caregivers (N=12) will also participate in focus groups. Caregiver eligibility criteria include: a) aged $\geq$18, and b) able to speak/read English. Exclusion criteria include visual, hearing, or cognitive impairment or severe mental illness interfering with participation, as indicated by patient or caregiver self-report.

C. Intervention Development. Qualitative data will be obtained from AYA and caregiver stakeholders participating in intervention development focus groups. The focus groups will be held remotely via using videoconferencing technology (Zoom). Semi-structured interview guides will be used. The leader (Dorfman) will make field notes, and the interview guides will be modified following each group to

accommodate emergent themes. The goal is to better understand the needs and preferences of the target audience and to structure the intervention to address these needs. Participants will provide information about the symptom (i.e., pain, fatigue, distress) experience of AYAs with advanced or recurrent cancer, patients' symptom management needs, the unique developmental aspects of being an AYA or caring for an AYA with advanced or recurrent cancer, and how patient and caregiver needs may interact to impact symptom management. Participants will also provide information on coping strategies used to manage the AYA's diagnosis and symptoms. Information obtained will allow us to confirm the utility of and, if necessary, adapt the proposed intervention strategies (i.e., from behavioral symptom management, ACT, MCP) to meet the needs of this population and develop additional intervention content. AYAs will also be asked about their preferences for intervention format (e.g., session number, videoconferencing) and their attitudes towards proposed intervention content, which will help guide the structure and format of the intervention. Groups will be 60 minutes long and audio recorded. Participants will be reimbursed for participation. Our team has extensive experience conducting focus groups and using focus groups to inform intervention development.[9,75-77]

Patient participants will also complete a one-time assessment in REDCap. Participants will complete a sociodemographic survey (e.g., age, sex, race/ethnicity, education) and a survey about their cancer treatments. AYAs will complete other self-report measures. Symptom burden will be assessed using the Brief Pain Inventory[94] as well as the PROMIS Computer Adaptive Tests for Fatigue, Depression, and Anxiety. The Self-Efficacy for Managing Chronic Disease Scale,[95] Acceptance and Action Questionnaire-II (AAQ-II),[88] modified Bulls Eye Values Survey,[92] and FACIT-SP-12 will also be administered. The Self-Efficacy for Managing Chronic Disease Scale[95] assesses symptom self-efficacy. The AAQ-II assesses acceptance, experiential avoidance and psychological flexibility.[88] The modified Bulls Eye Values Survey[92] examines personal values, values attainment, and persistence towards values in the face of barriers. The FACIT-SP-12 will be used to examine meaning.

Caregivers will also complete at one-time assessment in REDCap. Caregivers will complete a sociodemographic survey (e.g., age, sex, race/ethnicity, education) and a survey about their loved one's cancer treatments. They will also respond to questions asking about their perception of their loved one's self-efficacy for managing symptoms (i.e., modified Self-efficacy for managing chronic disease scale) as well as their own self-efficacy for helping their loved one manage symptoms (i.e., modified self-efficacy for managing chronic disease scale).

The developed intervention will then be reviewed to N=3-5 AYAs with advanced or recurrent cancer to assist with refining intervention content and study procedures. As with focus group/interview participants, user testers will also complete a one-time assessment. Information obtained from user testers will be used to refine the intervention.

D. Aim 2: Pilot RCT. AYAs with advanced or recurrent cancer (aged 15-29) will complete the baseline assessment electronically via Research Electronic Data Capture (REDCap) prior to randomization. The clinical research coordinator will be present at the baseline assessment to assist participants with using REDCap. Participants will then be randomized by the coordinator to the intervention or education control arm using an allocation ratio of 1.5:1. Randomization will be stratified by age (15-19 vs. 20-29). Age categories were chosen to match contemporary definitions of the developmental periods of older adolescence (15-19) and young adulthood (20-29) and echo the definitions of adolescents and young adults adopted by the National Cancer Institute Surveillance, Epidemiology, and End Results Programs.[13,14] Follow-up assessments will be completed remotely using REDCap on the participant's own or a study-specific device (iPad). Self-report measures have been formatted for use in REDCap. The coordinator will be available via phone in the event of questions or issues.

Intervention Content and Format. Content from the team's prior symptom management interventions for advanced or recurrent cancer patients and AYA cancer survivors as well as the team's expertise in palliative care , AYA Oncology, ACT , MCP, and adolescence has assisted with outlining potential strategies /skills to be included in the intervention (Table 2) that we believe will address patients' symptom management needs while also being responsive to their developmental stage. We propose four, 60-minute sessions delivered over 6-8 weeks to patients in their homes using videoconferencing. The team has a strong history of using videoconferencing to deliver symptom management interventions. Participants will receive an iPad equipped with data plan and videoconferencing software to use during the intervention sessions. It is anticipated that the intervention will provide training in behavioral symptom management skills (e.g., relaxation training, activity-rest cycling) and include skills from ACT and MCP targeting avoidance of uncomfortable experiences (e.g., thoughts, emotions) and promoting engagement in value-directed activity. Participants will receive a written intervention manual. Skills acquisition will be promoted through homework, and homework will be reviewed at each session.

The intervention outlined in Table 2 is flexible. Based on data obtained during Aim 1, the intervention may be modified in the following ways: format (video vs. telephone vs. in-person), session number, spacing, and length, and content (e.g., skill order, examples, symptom management skills). There may be age-related variability in patients' experiences. If indicated during Aim 1, intervention topics will be tailored to

address age-specific needs (e.g., discussion of loss of meaning associated with education and/or employment goals depending on life stage). The goal is to develop a patient-centered intervention; if indicated during Aim 1, caregivers may be included to assist AYAs with symptom management (e.g., one session).

Education Control Arm. The control arm will receive the NCI booklet, "Coping with Advanced Cancer,"[79] which provides basic strategies for symptom (e.g., pain, fatigue) management, coping with negative emotions, and communication and will continue their usual medical care of advanced cancer.

Study Measures. Participants will complete three assessments in REDCap. At baseline, participants will complete a sociodemographic survey (e.g., age, sex, race/ethnicity, education) and a survey about their cancer treatments. Feasibility will be assessed by examining study enrollment (N=40 AYAs in 12 months), attrition (>80% completing all 4 sessions), and participants' use of intervention strategies. Acceptability will be assessed using the Treatment Acceptability Questionnaire (TAQ).[81] Intervention arm participants will complete the TAQ at post-treatment. The intervention will be deemed acceptable if >80% of participants rate the intervention as >5 out of 7 on the TAQ. At post-treatment, the intervention arm will also provide open-ended feedback on the study materials, intervention format, and appropriateness of the intervention for the population. Lastly, intervention arm participants will complete the satisfaction with therapy and therapist scale, revised to assess their satisfaction with the intervention and interventionist.

AYAs will complete other self-report measures at each assessment to examine change in treatment targets. Most of the assessment tools have been used with the full age range of the proposed study sample (age 15-29),[82-86] and all tools have been validated for use with those aged >18.[87-93] Symptom severity will be assessed using the Brief Pain Inventory[94] as well as the PROMIS Computer Adaptive Tests for Depression, Anxiety, and Fatigue. Other intervention targets. The Self-Efficacy for Managing Chronic Disease Scale,[95] Acceptance and Action Questionnaire-II (AAQ-II),[88] modified Bulls Eye Values Survey[92] and FACIT-SP-12 will be administered at each assessment; changes in scores will serve as a validity check to ensure the intervention targeted patients' confidence in their abilities to manage symptoms and important concepts from ACT and MCP. The Self-Efficacy for Managing Chronic Disease Scale[95] assesses symptom self-efficacy. The AAQ-II assesses acceptance, experiential avoidance and psychological flexibility.[88] The modified Bulls Eye Values Survey[92] examines personal values, values attainment, and persistence towards values in the face of barriers. The valuing questionnaire will also be used to assess patient values. The FACIT-SP will be used to assess meaning. Use of intervention strategies. At the post-treatment and follow-up assessment, intervention arm participants will also provide information about the use of strategies presented during the intervention over the last week.

The timeline of study assessments is included, below:

Timing of Study Questionnaires SMILE RCT

	Assessment 1	Assessment 2	Assessment 3
Sociodemographics	X		
Medical/Cancer treatment information	X		
PROMIS Depression CAT	X	X	X
PROMIS Anxiety CAT	X	X	X
PROMIS Fatigue CAT	X	X	X
Brief Pain Inventory	X	X	X
Self-Efficacy for Managing Chronic Disease (6-item)	X	X	X
Acceptance and Action Questionnaire-II (7-item)	X	X	X

Bulls Eye Values Scale	X	X	X
Valuing Questionnaire	X	X	X
Treatment Acceptability Scale (Intervention Only)		X	
STTS-R (Intervention Only)		X	
Open Ended Questions about Intervention (Intervention Only)		X	
Use of Intervention Strategies (Intervention Only)		X	X

USE OF PSYCHSOCIAL RESOURCES: Participants will be asked about their use of psychosocial services. After completing the study, participants will be contacted via phone and asked to complete 1-4 items (depending on pattern of responding) about their use of psychosocial services in the last 6 months. Prior to completing these items, participants and/or their parents/guardians (if aged <18) will complete a consent addendum. Items may be answered over the phone or online via redcap. Participants will be compensated an additional $5 for completing the items.

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

Patient Eligibility Criteria : a) aged >15 and <29, b) diagnosis of advanced or recurrent cancer (i.e., diagnosis of incurable cancer or distant metastases recurrent disease),[74] and c) able to speak/read English. Exclusion criteria include: a) active serious mental illness (e.g., schizophrenia) as indicated by medical records or b) visual, hearing, or cognitive impairment interfering with participation.

Caregiver Eligibility Criteria: a) aged >18, and b) able to speak/read English. Exclusion criteria include visual, hearing, or cognitive impairment or severe mental illness interfering with participation, as indicated by patient or caregiver self-report.

Patient participants will be recruited from the DCI, an NCI-designated comprehensive cancer center, as well as Duke Children's.

Potential patient participants will be identified via the following avenues:

a) Duke Teen and Young Adult (TYA) Oncology Database. Supported by a grant from the St. Baldrick's Foundation (PI: Dr. David Van Mater, Co-Medical Director of the Duke TYA Oncology Program), the Duke TYA Oncology Program has established a database of AYA cancer patients (aged 15-29) treated at the DCI or Duke Children's. Individuals providing consent/assent to be included in the database are asked if they would be willing to participate in future research studies. Those interested, will be approached to participate in the proposed study. We anticipate that at least 40% of participants will be identified through this avenue.

b) Electronic Health Records under a HIPPA Waiver. Since the TYA database recruits patients upon diagnosis, it is possible that some patients with advanced or recurrent cancer were not captured by or recruited to participate in the database. Thus, we will use additional approaches to recruit AYAs. Using procedures implemented in our prior studies, patients will be identified through electronic health records under a HIPPA waiver. We anticipate that the remaining 60% of patients will be identified using this strategy.

When identifying patients, study staff will check against the "banner" in MaestroCare to verify whether or not the patient has opted out for being contacted.

Caregiver participants will be identified by a participating patient. Patients will provide permission for the study team to contact their identified caregiver.

Subject Recruitment and Compensation

- Describe recruitment procedures, including what method(s) will be used, when the study will be introduced to potential participants and by whom. If any follow-up contact is planned, describe the proposed method and timing. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about how many DUHS participants will be recruited. If participants are to be compensated and/or reimbursed, provide specific prorated amounts to be provided for expenses such as travel and /or lost wages, and/or for inducement to participate.

Potential participants will be recruited in the following ways:

AYAs with Advanced or recurrent Cancer

a) Patients may be referred to the study by their providers. The medical team will introduce the study, provide potential participants and their parents/guardians (if aged <18) with the study brochure, and, if interested, the PI or study staff member will contact them to assess eligibility, further describe the study, and discuss questions and concerns.

b) A letter and study brochure or flyer including a description of the study will be mailed and/or sent via mychart informing potentially eligible patients and their parents/guardians (if aged<18) of the study. The letter will state that the PI or member of the study staff may approach them in clinic at their next appointment or via phone. Patients or parents/guardians (if aged <18) wishing to be approached will be provided with a phone number to call to initiate participation in the study. The letter will also state that they will be called via phone in the event that we are unable to make contact during a clinic appointment.

If a patient and/or parent/guardian (if aged <18) expresses interest and is eligible to participate, he or she will be scheduled for an in-person appointment during which informed consent/assent will be conducted. The patient's legal guardian will complete informed consent for adolescent patients aged <18. Adolescents will be asked to complete assent documentation if they are interested in participating. In the event that the PI or study staff member is unable to make contact with the patient during a clinic appointment (e.g., due to time constraints), the patient and parent/guardian (if aged<18) will be informed that the PI would like to contact him/her by telephone. In these cases, informed consent/assent will occur at the time of the first scheduled in-person contact (e.g., focus group, baseline assessment).

Caregivers

Patients recruited for the focus groups will be asked for permission to approach their self-identified primary caregiver and to provide the contact information (e.g., phone number) for this individual. Patients will also be asked to confirm caregiver eligibility (i.e., whether the caregiver has any illness, visual, hearing, or cognitive impairment that would prohibit their participation in focus groups). Patients can refuse for their caregiver to be approached for the study. Caregivers will be provided with additional information about the study and eligibility will be confirmed. Caregivers may also directly contact study staff. Informed consent procedures for caregivers will occur via phone; eligible and interested caregivers will be asked to provide verbal consent. Caregivers consenting via phone will be mailed two written consent forms (one for the caregiver and one to be returned to study staff). Caregivers will be asked to return signed consent forms to a study staff member at the first face-to-face contact (i.e., focus group).

Compensation: In appreciation for their time, participants will be compensated as follows.

Focus group participants: $20/participant
User testers: $20
RCT participants: $20/assessment for a possibility of $60
RCT participants completing the psychosocial services items: $5

Consent Process

- Complete the consent section in the iRIS Submission Form.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

Only individuals without evidence of cognitive impairment that would preclude informed consent will be consented.

Study Interventions

- If not already presented in the Design & Procedures section, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i. e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

Intervention Content and Format. Content from the team's prior symptom management interventions for advanced cancer patients and AYA cancer survivors as well as the team's expertise in palliative care , AYA Oncology, ACT , MCP, and adolescence has assisted with outlining potential strategies/skills to be included in the intervention (see Table 2, below) that we believe will address patients' symptom management needs while also being responsive to their developmental stage. We propose four, 60-minute sessions delivered over 6-8 weeks to patients in their homes using videoconferencing. The team has a strong history of using videoconferencing to deliver symptom management interventions. Participants will receive an iPad equipped with data plan and videoconferencing software to use during the intervention sessions. It is anticipated that the intervention will provide training in behavioral symptom management skills (e.g., relaxation training, activity-rest cycling) and include skills from ACT and MCP targeting avoidance of uncomfortable experiences (e.g., thoughts, emotions) and promoting engagement in value-directed activity. Participants will receive a written intervention manual. Skills acquisition will be promoted through homework, and homework will be reviewed at each session.

The intervention outlined in Table 2 is flexible. Based on data obtained during Aim 1, the intervention may be modified in the following ways: format (video vs. telephone vs. in-person), session number, spacing, and length, and content (e.g., skill order, examples, symptom management skills). There may be age-related variability in patients' experiences. If indicated during Aim 1, intervention topics will be tailored to address age-specific needs (e.g., discussion of loss of meaning associated with education and/or employment goals depending on life stage). The goal is to develop a patient-centered intervention; if indicated during Aim 1, caregivers may be included to assist AYAs with symptom management (e.g., one session).

Table 2. Potential strategies/skills to be included in the intervention

A. Behavioral Symptom Management	
Skills	*Description of and Rationale for Inclusion of Skills*
Progressive Muscle Relaxation and Paced Breathing	Provide instruction in relaxation training to assist with reducing muscle tension in the service of decreasing pain, fatigue, and stress/distress.
Activity-Rest Cycling	Help participants adjust expectations and pace themselves when engaging in/initiating developmentally appropriate activities. Promote acceptance of symptoms while promoting movement towards goals rather than experiential avoidance.
B. Acceptance and Commitment Therapy	
Skills	*Description of and Rationale for Inclusion of Skills*
Doing what matters based on guiding principles/values	Assist patients with identifying and working towards personal valued life areas while reducing thoughts about what they "should" value or what others would "expect" them to value given their age/life stage, cancer diagnosis, advanced stage of disease, and symptom experience. Promote committed action by assisting patients with taking small steps to engage in activities in the short- and long-term that are important and meaningful in the service of increasing emotional wellbeing. Help patients create actionable plans to achieve goals.
Body and Cognitive Awareness Trainings	Learn to be with what one is feeling (physically/emotionally) and thinking rather than trying to change feelings or thoughts. Promote cognitive defusion (decrease attachment to thoughts) with the goal of preventing negative thoughts, emotions, and symptoms from interfering with guiding principles/values and associated goals.
Education about acceptance as an alternative to experiential avoidance	Promote acceptance of current experiences (thoughts, emotions, physical sensations). Reduce motivation to avoid situations, help to promote value-based action, and promote taking a non-judgmental stance.
C. Meaning Centered Psychotherapy	
Skills	*Description of and Rationale for Inclusion of Skills*
Ask patients to: 1) Identify meaningful times in life 2) Understand self before and after cancer 3) Understand sources of meaning in life	Identify guiding principles/values and how the prioritization of these principles/values may have changed since the diagnosis of cancer. Increase awareness of attitudes, ability to engage with life, and build a legacy for the future. Help patients understand sources of meaning and use them in their daily life with the goal of helping to increase wellbeing.

Education Control Arm. The control arm will receive the NCI booklet, "Coping with Advanced Cancer,"[79] which provides basic strategies for symptom (e.g., pain, fatigue) management, coping with negative emotions, and communication and will continue their usual medical care of advanced cancer.

Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant individuals, imprisoned persons or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

Potential Risks. No adverse events are anticipated. Participation in all portions of the study is voluntary and participants can withdraw at any time. The risks associated with all portions of this study are minimal and rare. Participation in focus groups or a psychosocial symptom management intervention are associated with few negative side effects. The focus groups, intervention sessions, and assessments will cover topics including physical health (e.g., cancer diagnosis and treatments), physical symptoms (e.g., pain, fatigue), psychological distress, symptom interference, self-efficacy for symptom management, personal values, and experiential avoidance, all of which may request participants to provide sensitive and personal information. Participants may feel embarrassed or uncomfortable with disclosing this information. There is also the possibility of breach of confidentiality. For example, in a group setting, such as a focus group, there is risk of disclosure of personal information by another participant. Additionally, there is some risk of loss of confidentiality inherent to the use of videoconferencing to conduct the study intervention sessions. All efforts will be made to remain sensitive to participant's needs, HIPAA requirements, and confidentiality procedures (see below). To ensure that there are no changes in potential risk during the course of the study and that confidentiality is maintained, the study team will implement a Data and Safety Monitoring Plan.

Protection Against Risk. First, if a participant (i.e., AYA with advanced or recurrent cancer or caregiver) endorses psychological distress due to study participation, the PI (Caroline Dorfman, PhD) will consult with study Co-Is, Drs. Tamara Somers, Jennifer Plumb Vilardaga, Cheyenne Corbett, and Gary Maslow. Drs. Somers and Plumb Vilardaga are licensed clinical psychologists. Dr. Somers co-directs and Dr. Plumb Vilardaga is a member of The Cancer Symptom Management and Support Program, which focuses on conducting clinical research and providing behavioral medicine services to address the psychological,

social, behavioral, and symptom management needs of cancer patients and their families. Additional clinical services provided include psychotherapy, psychological assessment, brief memory and cognitive testing, behavioral weight management, treatment of sleep difficulties, coping skills training for symptom management, treatment of sexual difficulties, and stress management. Dr. Plumb Vilardaga also holds a position within the Duke Department of Psychiatry and Behavioral Sciences. In addition to conducting funded research within the department, she has a clinical practice within the Duke Faculty Practice in Psychiatry. Dr. Maslow is a general pediatrician and child and adolescent psychiatrist, Co-Chief of the Division of Child and Family Mental Health and Developmental Neurosciences within the Department of Psychiatry and Behavioral Sciences, and Medical Director of Psychiatry Services for the Duke Cancer Institute. In addition to conducting research to better understand the developmental challenges facing youth with childhood-onset chronic conditions as they grow-up, Dr. Maslow has an active clinical practice at DUMC. Dr. Corbett is the Director of the Duke Cancer Patient Support Program, an established psychosocial support program that provides no-cost services and resources to patients and their families throughout their experience with cancer. Drs. Somers, Plumb Vilardaga, Maslow, and Corbett will provide guidance regarding the appropriate course of action in the event that a participant endorses distress associated with study participation.

The PI is also a licensed clinical psychologist in the Department of Psychiatry and Behavioral Sciences at Duke and a member of the Duke Teen and Young Adult Oncology Program, Duke Cancer Patient Support Program, and Cancer Symptom Management and Support Program. Her involvement in these programs will allow her to readily facilitate appropriate referrals for psychosocial services offered through the DCI (e. g., clinical psychologists and medical family therapists affiliated with the Duke Cancer Patient Support and Cancer Symptom Management and Support Programs) and Duke Department of Psychiatry and Behavioral Sciences. Contact information for the PI will be provided should participants have any questions or concerns. Additionally, the clinical research coordinator will be trained to monitor participants' psychological status and report to the PI if a participant shows signs of experiencing high levels of physical and/or emotional distress that need to be addressed outside the context of the trial. If this is determined to be the case, the clinical research coordinator will work directly with the PI and the participant to move forward in a way that is in the best interest of the participant. No participant will be kept in the trial if he or she is experiencing increased or extreme distress. While the PI, Co-Is, and other study staff members have conducted research in the proposed area and have not encountered participants who experience significant psychological distress as a result of study procedures, we are confident that we have sufficient resources (e.g., access to no-cost psychosocial services through the Duke Cancer Patient Support Program, access to psychiatric care through the Department of Psychiatry and Behavioral Sciences) to assist participants in the event that a participant experiences study-related distress. Our prior research has instead found participation in behavioral symptom management interventions to be associated with benefits to physical health, mood, and quality of life; we believe that the possible significance of study findings outweighs the risk.

Second, the intervention will be delivered by a study therapist under the supervision of the PI (Dorfman) and Dr. Plumb Vilardaga. The study therapist will receive training from the PI and Co-Is in behavioral symptom management strategies (Somers), ACT (Plumb Vilardaga), MCP, and AYA Oncology (Dorfman, Wagner, Maslow, Corbett). Drs. Dorfman and Somers will provide the therapist with additional training to address the nuances of this delivery method (e.g., strategies for assisting patients with using the videoconferencing technology, strategies to engage patients and promote retention). A written study manual will be created to ensure consistency of intervention delivery. Intervention sessions will also be audio recorded and discussed during weekly supervision sessions between the PI, Dr. Plumb Vilardaga, and the study therapist. Additionally, Dr. Somers will review the audio recordings for approximately 20% of the intervention sessions. A fidelity checklist will be developed for the proposed study to assess adherence to and competency in delivery of the core components of the intervention. Dr. Somers will use this checklist when reviewing recordings of intervention sessions, and this information will be discussed with the study interventionists.

Third, there is the possibility of a breach of confidentiality, which will be addressed in the consent form and expressed to participants upon accrual. All efforts will be made to maintain confidentiality. For example, in a group setting, such as in a focus group, there is risk of disclosure of personal information by another participant. Individuals participating in focus groups will be instructed to maintain participants' confidentiality at the onset of the group, and participants will be asked not talk about other participants' comments outside of the group.

Additional efforts will be employed to maintain confidentiality. Two password-protected databases will be used to ensure confidentiality of participant information and data by keeping identifying information separate from research records. A tracking database will be used for recruitment and follow-up. This database will house information related to the participants in the study, such as phone numbers and addresses. No medically sensitive or outcome data will be stored in this database. This database will also track nonparticipants (i.e., those who have declined participation), only to the barest minimum, to ensure that they are not contacted again about participation. At the end of the study, all identifiable data of non-participants such as their names will be deleted. All study data (self-report, data abstracted from medical records, session record) will be stored in a separate, password-protected database without any personal identifiers.

The databases will be created in Research Electronic Data Capture (REDCap). Developed by Vanderbilt's Clinical and Translational Science Award and currently used and supported by more than 1,000 consortium partners, REDCap is a secure, web-based application designed to support data capture. Data stored in REDCap is HIPAA-compliant and secure and stored on the Duke Heath Technology Services' servers behind the Duke Firewall. The Duke Office of Clinical Research (DOCR), located within the Duke School of Medicine, provides navigation, tools, and training to support the conduct of clinical research at Duke. DOCR is a consolidated group of research support professionals who are skilled in all aspects of clinical research, including study startup, database development, and project coordination. DOCR manages and supports REDCap. The PI will have access to the DOCR Research Management Team who provide research management and support to investigators at Duke.

Electronic files (e.g., audio files and deidentified transcripts of focus groups) will be stored in separate password protected files on an Office of Information Technology (OIT) secured DUMC network drive. This drive will be backed to tape and secured by the OIT department on a daily basis. Access to the DUMC network requires a password protected, 128-bit encrypted virtual private network connection provided by Cisco systems. Only the PI, Co-Is, and research staff members affiliated with the project will have access to these records. Self-report data collected during assessments will be entered in real time into REDCap. In the event that a participant would prefer to complete self-report assessment using paper and pencil, paper copies of assessment packets will be filed by subject number and housed in a locked cabinet in the offices of the Pain Prevention and Treatment Research Program (PPTRP).

There is some risk of loss of confidentiality inherent to the use of videoconferencing to conduct the study intervention sessions. To protect patient privacy, we will use the Zoom (https://duke.zoom.us/) videoconferencing program, which has standard internationally recognized and accepted encryption algorithms. Encryption is the process of encoding a message (i.e., videoconferencing) using the principles of mathematics, in such a way that it is readable only by the intended recipient. An encryption of 128 bit is the minimum size recommended for video communication; Zoom's encryption is 256 bit. The Duke-Zoom contract has provisions that protect privacy and implement security protections which supersede the standard EULA (End User License Agreement) that an individual sees when signing up for a free or consumer account with Zoom. Specifically, Zoom does not have ownership of content or data originated from Duke that is stored or transmitted using Zoom. Further, Zoom maintains physical and technical safeguards to prevent unauthorized disclosure of or access to Duke Data and complies with Duke's Data Security requirements. Zoom has also agreed to further protect data under strict security and privacy protections and does not share data with any other party without the prior written agreement of Duke.

Members of the study team (Dorfman, Somers, Plumb Vilardaga, Maslow) are clinically active therapists at Duke. They have been using Zoom to conduct therapy sessions since the start of the COVID-19 pandemic (March 2020). They are familiar with procedures to ensure security while using Zoom. Specifically, the following recommended steps will be taken: 1) generate meeting ID automatically; 2) require a meeting password; 3) enable a waiting room; and 4) require authenticated users. At the initial study visit, each participant will be set up with a Zoom account. Participants will be required to log in to Zoom with their Zoom account to access the meeting. Generating the meeting ID automatically provides protection if a meeting ID is accidentally shared. By enabling the waiting room, we will be able to view attendees before admitting them to the meeting. We will also have the ability to remove a participant from the meeting in the event that someone other than the participant attempts to join. Once the meeting is in progress, lock meeting will be used to prevent additional participants from joining. Prior to starting the meeting recording, 'display participants' names will be unchecked so that the participant's name is not included in the recording. Only the meeting host (the study interventionist) will have permission to record the session, and participants will be advised that they are being recorded. Sessions will be recorded locally on a Duke owned computer rather than to the cloud and moved to the Department of Psychiatry and Behavioral Sciences protected folder immediately following the session. In the event that a participant uses a study tablet (iPad), all history on the tablet (e.g., web searches, documents created), will be wiped clean after the participant returns the tablet prior to its re-distribution.

The PI has completed the Duke University Health System IRB's online training course: Protecting Research Subjects, as well as human research subjects protection training and certification through the Collaborative Institutional Training Initiative (CITI) program, both of which address confidentiality. All other individuals involved in this study will be required to complete these courses and ongoing training.

Finally, all participants will continue their usual medical care during the course of the study and be informed that choosing to participate in the study will in no way impact the treatment they receive at DUMC. All patients will continue to be monitored by their physicians at DCI or Duke Children's throughout the course of the study; thus participants' doctors will provide monitoring of their overall medical status. If a health concern is identified during contact with study staff, the patient's treating oncologist will be contacted, and appropriate referrals for medical treatment will be provided. All research personnel who have direct contact with patients will be trained to observe and report any adverse events. The PI will report any adverse event to Duke's Institutional Review Board (IRB) in real time.

Vulnerable Subjects. This study focuses on developing and pilot testing a novel psychosocial symptom management intervention for AYAs with advanced or recurrent cancer, aged 15-29; thus, individuals aged >15 and <18 will be included in the proposed study. The age range selected for inclusion in the proposed study is consistent with the definition of an AYA as adopted by the National Cancer Institute Surveillance, Epidemiology, and End Results Programs as well as internationally by the Canadian Partnership against Cancer. AYA cancer patients are diagnosed during a critical developmental period (e.g., working to complete education, start a career, achieve independence, build peer and romantic relationships, build a family), and as such, their needs differ from those of many older cancer patients and those younger than age 15. Patients aged >15 and <18 and their parents/guardians will be provided with information about the study; parents/guardians will be asked to provide consent, and patients aged >15 and <18 will complete assent documentation if they are interested in participating. As with all participants, patients aged >15 and <18 and their parents/guardians will be reminded that participation in the study is voluntary and that they can withdraw from the study at any time without penalty. They will also be informed that their decision whether or not to participate in the proposed study will in no way impact their continued treatment at DCI, Duke Children's, or Duke University Medical Center.

Pregnant women will not be excluded from this study; thus, it is possible that an AYA patient or their caregiver participating in this study may be pregnant as the majority of female participants will be of childbearing age. The risk to pregnant women of participating in a focus group or psychosocial symptom management intervention is extremely low. No study activities will directly impact the health of the pregnant woman or her fetus. Pregnant women providing consent/assent will be fully informed regarding the minimal foreseeable impact of the research on the fetus. The primary risks of participation in the proposed study are the potential for increased distress and loss of confidentiality, and significant steps will be taken to minimize these risks (see above). Dr. Lars Wagner (Co-I) is a pediatric oncologist. He will review the chart of any pregnant participant, consult with the participants' OB/GYN as necessary to confirm the appropriateness of her participation in the proposed study, and ensure that there are no contraindications for participation in all parts of this study. The anticipated benefits to the overall wellbeing of the participant (see below) and minimal risk to the woman and her fetus are reasonable to warrant participation in the proposed study.

Use of Zoom during Focus Groups:
To ensure security while using Zoom, the following recommended steps will be taken:

Prior to Meetings:
Generate meeting ID automatically – Unique meeting IDs expire 30 days after the meeting has occurred, and provide protection if a meeting ID was shared accidentally to a public audience.
Require meeting password – Don't share your meeting password.
Enable waiting room – Review attendees before admitting them to the meeting.

During Meetings:
Lock meeting – Prevents any additional participants from joining.
Screen sharing is host only – By default, only hosts can share their screens. Hosts can grant individuals the ability to share in the participant panel.
Remove unwanted participants - Beside the participants name (in the Participant pane) select M ore, and then select Remove.
Report participant - If a user made attempts to disrupt your meeting either by speaking, chatting, or showing offensive video, select the option Report which is available under the Security icon or on each participant's name. This will alert Zoom Support.

Recording Meetings:
Attendees will be advised that they are being recorded.
'Display participants' names will be unchecked so that their name is not included in the recording.
Only the meeting host will have permission to record the session.

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

There are no costs to the subjects.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

E. Statistical Considerations. This study aims to develop and pilot a novel psychosocial symptom management intervention for AYA's with advanced or recurrent cancer and is not designed to make conclusions about efficacy without further study.[96] Sample size estimates are based on pragmatics of recruitment over the study timeframe as well as our ability to obtain sufficient data to understand the experiences of the target population and examine intervention feasibility and acceptability. Information gathered will inform the design of future trials. Based on our past published work[9,76] using focus groups to develop symptom management interventions, a sample size of N=28 (n=16 AYAs, n=12 caregivers) is sufficient to obtain information to confirm, and, when necessary, adapt proposed intervention content to meet the needs of AYAs with advanced or recurrent cancer. N=40 AYAs will participate in the pilot RCT. The sample size accounts for 20% attrition, which was derived from our prior work (10-15%)[7,9,10] and attrition rates for AYAs with cancer receiving mHealth interventions (12-21%).[97-99] The RCT sample size (intervention: n=24, control: n=16) was derived from published recommendations[100] and our past preparatory work.[7,11] While Aim 2 focuses on examining distributions of change in outcomes and intervention targets rather than testing statistical significance, a priori power calculations using G-Power[101] based on intervention effects seen in our prior work[7] suggest, after accounting for attrition, we will have ~80% power to detect medium effect sizes (d=0.5; α=0.05, two-tailed) with an intervention sample of n=19.

Aim 1. Focus groups will be transcribed verbatim. Qualitative Description[102-104] using thematic analysis[105-108] as the methodological approach will be used to identify, analyze and report themes and trends across data. A preliminary code book derived from the focus group interview guides will be developed prior to analysis. Codes will be applied to transcripts using NVivo[109] by two individuals to ensure similar understanding of codes and consistency in judgment.[107] Discrepancies in interpretation of the data or application of codes will be resolved. Codebooks will be updated to add data-driven codes; emerging codes will be applied to previously coded text.[108] Codes will then be sorted into themes/subthemes using an iterative process.[108] A descriptive summary will be produced and used to inform the intervention.[104] Intervention user testers (N=3) will provide oral and written feedback related to intervention content, content presentation, and study procedures to better understand the experience of intervention users; materials and procedures will be refined from this feedback.

Aim 2. Descriptive statistics (e.g., mean, percent) will be used to examine feasibility and acceptability data. Change in outcomes (i.e., symptoms, symptom interference) and intervention targets (e.g., self-efficacy, experiential avoidance) from baseline to post-treatment and post-treatment to 4-week follow-up will be examined using paired t-tests. Effect sizes will be computed for the intervention and control arms using Hedges' g_{av};[110] associated confidence intervals will be examined. Other analyses. Feasibility, acceptability, and patterns of change in outcomes and intervention targets will be examined by sex using descriptive statistics to examine differences that may be obscured when the data is pooled.[111] We will also examine session completion rates and account for this as necessary in analyses. Our prior work testing videoconferencing symptom management interventions suggests participants will complete 3.4-3.7 of 4 sessions, with 83-90% completing all sessions.[6,8,9]

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

The proposed study carries minimal risk. Data obtained from participants will include information from medical chart review, patient and caregiver interviews, and self-report inventories. The PI, Co-Is, and key personnel consider the management of participant information and data as a key priority. Best practices for confidentiality and data management will be observed.

All participants will continue their usual medical care over the course of their participation in the study and be informed that choosing to participate in the study will in no way impact the treatment they receive at Duke University Medical Center (DUMC). All patient participants will continue to be monitored by their physicians at the Duke Cancer Institute (DCI) and Duke Children's Hospital and Health Center (Duke Children's) throughout the course of the study; thus patients' doctors will provide monitoring of their overall medical status. If a health concern is identified during contact with study staff, the patient's treating oncologist will be contacted, and appropriate referrals for medical treatment will be provided to patients. All research personnel who have direct contact with patients will be trained to observe and report any adverse events. The PI will report any adverse event to Duke's Institutional Review Board (IRB) in real time. An adverse event is defined as any untoward medical event occurring during the clinical evaluation, which is causally related to the study protocol. A serious adverse event is defined as any event which results in death, is immediately life threatening, results in persistent or significant disability/incapacity, results in patient hospitalization, or is serious for any other reason representing significant hazard. We will appoint two data safety officers. One data safety officer will be a physician who is not associated with this study. The appointed physician officer will have experience with clinical research and trials and have a thorough understanding of adverse events. The other data safety officer will be a senior investigator who has expertise in psychosocial symptom management and will have an annual responsibility to evaluate our current methods of assessment and intervention and identify any problems. All adverse events will be reported to Duke's IRB and the data safety officers in real time.

All data will be stored on a secure server with multiple backups created regularly. All interactions with study participants will be under the direction of three licensed clinical psychologists (Dr. Caroline Dorfman, PI; Dr. Tamara Somers, Co-I; Dr. Dr. Jennifer Plumb Vilardaga, Co-I), a pediatrician and child and adolescent psychiatrist (Dr. Gary Maslow, Co-I), a medical family therapist (Dr. Cheyenne Corbett, Co-I), and an oncologist (Dr. Lars Wagner, Co-I). Audio recordings of sessions will also be obtained and reviewed by Dr. Somers to ensure fidelity of intervention delivery and that the study therapist is providing effective, ethical treatment. As a practicing clinical psychologist, the PI has experience with distressed patients with chronic disease. If a participant shows signs of experiencing high levels of physical or emotional distress that need to be addressed outside the context of this trial, the PI will work directly with the participant to move forward in a way that is in the participant's best interest. No participant will be kept in the trial if they are experiencing increased extreme distress. Study staff will be carefully trained to monitor participants' psychological status and report to Dr. Dorfman when emotional distress is identified in a participant. Dr. Dorfman as well as Dr. Somers work directly with the Duke Cancer Patient Support Program, which is directed by Dr. Corbett (Co-I). Dr. Plumb Vilardaga is also a practicing licensed clinical psychologist and Dr. Maslow is a practicing child and adolescent psychiatrist within the Department of Psychiatry and Behavioral Sciences at Duke. As such, members of the investigative team are integrated into the psychosocial care programs at DCI and within Duke; they have experience referring cancer patients who are distressed to appropriate psychosocial or psychiatric care. They will use the same resources when making referrals for distressed participants in this study.

The sponsor-investigator or principal investigator (PI), and Duke Cancer Institute (DCI), through the PRMS and PRMC, will monitor this clinical research study. For internal review, the sponsor-investigator or PI will continuously monitor and tabulate adverse events. The study team will make reports to the Duke University Hospital System (DUHS) Institutional Review Board (IRB). If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events (AE) will be taken. This may require a protocol amendment, dose de-escalation, or potentially study closure. The study sponsor-investigator or PI will also continuously monitor study conduct, data, and safety to ensure:

- Interim analyses occur as scheduled.
- Stopping rules for toxicity and/or response are met.
- Risk/benefit ratio is not altered to subject detriment.
- Appropriate internal AE and outcomes monitoring is performed.
- Over-accrual does not occur.
- Under-accrual is addressed with appropriate amendments or actions.
- Data are being appropriately collected in a reasonably timely manner.

PRMS protocol review begins with the PRMC. PRMC new protocol reviews focus on scientific relevance, study design, biostatistical input adequacy, protocol prioritization, feasibility of study completion within a reasonable time frame and trial risk assessment. The sponsor-investigator or PI will abide by PRMC risk level assessment. PRMC also conducts annual scientific progress reviews on protocols open to enrollment and focuses on protocol prioritization, accrual, and scientific progress. The PRMC conducts reviews at the time of IRB annual renewals and maintains documentation in eIRB/iRIS.

During the initial PRMC approval, the PRMC determines the monitoring risk level and frequency which will be commensurate with the type and level of intervention, phase, endpoints, degree of risk, size, and

protocol complexity. The DCI monitoring team will conduct formal, independent monitoring according to the risk level and the PRMC monitoring plan until the study is closed to enrollment or subjects are no longer receiving study drug or other interventions that are more than minimal risk.

Findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns may prompt additional monitoring. DUHS and DCI Leadership, PRMC, DCI Safety Oversight Committee (SOC), a sponsor, an investigator, or the IRB may also request additional monitoring visits.