DF/HCC Social-Behavioral Research Protocol

Bounce Back: A Stress Management and Resiliency Program for Adolescent and Young Adult Survivors

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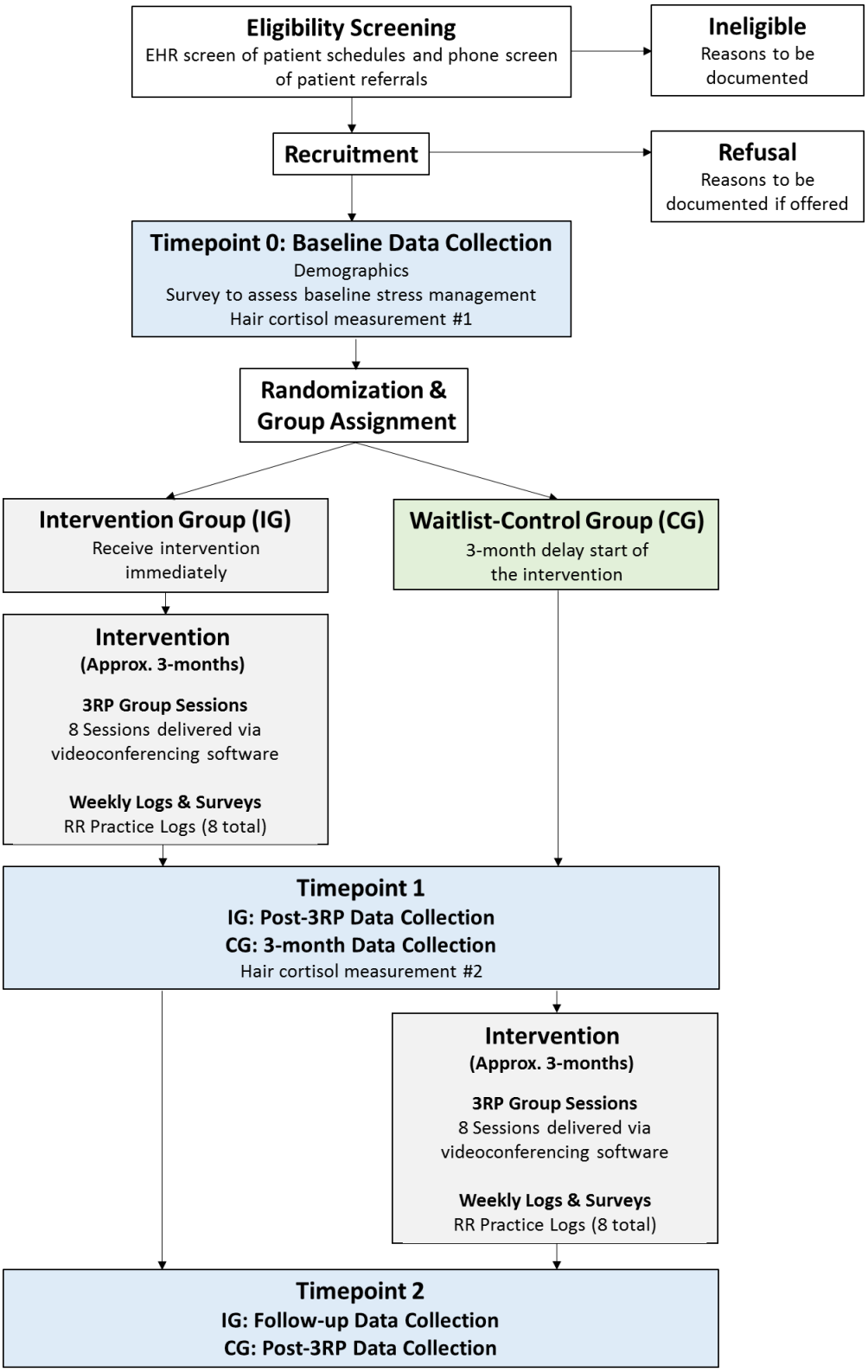
Protocol Schema



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1.0 INTRODUCTION

1.1 Overview. Survivors of cancers diagnosed during the adolescent and young adult (AYA) period (ages 15-39) are a largely understudied and underserved population.[1] Although cancer-related mortality rates are declining among survivors diagnosed during childhood and later adulthood, the biologically and genetically distinct characteristics of cancers diagnosed during the AYA period places survivors of AYA cancers at increased risk for poorer treatment outcomes and chronic late effects.[1-3] A cancer diagnosis during the AYA period, a life stage marked by formative changes, significantly disrupts a number of key life domains during a time of peak physical, psychological, and socioemotional development.[1] These disruptions have the potential to exacerbate the post-treatment transition process, contributing to adjustment difficulties. As such, rates of distress are high in this age group and are compounded by feelings of isolation.[1-3] Stress associated with negative psychosocial experiences can contribute to long-term maladaptive health behaviors, stress-related decrements in immune functioning, and overall lower quality of life.[5-9] This represents an important unaddressed cause of cancer-related morbidity for this already vulnerable population. There are currently no evidence-based interventions in the years following treatment that tackle the key transitional issues commonly associated with the AYA developmental period. As such, this study proposes to test the effects of a highly scalable videoconferencing-delivered group program (Relaxation Response Resiliency Program; 3RP)[4] aimed at mitigating the deleterious effects of stress by promoting stress management and coping among survivors of AYA cancers. Specifically, we propose to test the preliminary effect of an adapted 3RP[4] (called 3RP-AYA) that dually supports stress management and addresses the unique needs of survivors diagnosed during the AYA period who are within 0-5 years from having completed cancer treatment.

Importantly, the original 3RP is an established program developed at the Benson-Henry Institute for Mind Body Medicine (BHI) that has been tested with a variety of patient and provider populations (see 1.3); however, it has yet to be tested with survivors of cancers diagnosed during the AYA period. To tailor and adapt the original 3RP, we conducted qualitative interviews with AYA survivors (protocol DF/HCC 17-315) to understand some of the 1) the psychosocial and transitional challenges AYAs face with early survivorship, 2) existing coping strategies, 3) their perceptions of the existing 3RP, 4) preferences for program content, structure, delivery modality (in-person, vs. phone vs. videoconference) and intervention schedule (e.g., program timing, session length, number), and 4) barriers to participation. Emerging findings from these interviews guided the adaptations to the program. Specifically, themes included the following: 1) the desire to have the program available as soon as AYAs complete cancer treatment; 2) an interest in learning a variety of mind-body tools with a preference for more active strategies (e.g., yoga); 3) inclusion of topics related to talking to others about their cancer experience; 4) inclusion of topics related to academic transitions; and 5) cognitive strategies to break patterns of rumination and manage uncertainty about the future. Based on some of these findings, we adapted the contents of the original 3RP to develop the 3RP-AYA. Moving forward in this protocol we will refer to this adapted program as the 3RP-AYA. As such, for this protocol, participants will be offered 8 weekly, virtually-delivered group 3RP-AYA sessions to test the feasibility, acceptability and preliminary effects of the 3RP-AYA (via self-report surveys). We will also examine the feasibility, acceptability and preliminary effects of collecting and analyzing objective physiologic data (hair cortisol; detailed in section 5.2.3a).

1.2 Background and Rationale. Survivors of cancers diagnosed during adolescence and young adulthood (AYAs) have poorer health outcomes. Approximately 70,000 AYAs (ages 15-39) are diagnosed with cancer yearly; cancer is the leading cause of disease related-deaths for AYAs.[1] Due to the biological and genetic features of their cancer, and the timing of their diagnosis (i.e., a developmental period marked by physical and socioemotional changes), AYAs face poorer treatment outcomes and higher mortality rates.[1-3] Survival rates for younger and older survivors have improved over the past 20 years, but mortality rates for AYAs remain unchanged.[2]

AYAs are at increased risk for experiencing negative psychosocial and physical challenges associated with cancer treatment. The consequences of cancer and cancer treatment engenders challenges that are developmentally incompatible with the expectations associated with the AYA life stage.[1,10] A cancer diagnosis during the AYA period significantly disrupts a number of key life domains during a time of peak physical and socioemotional development.[1,11] Physical after-effects of treatment, such as chronic pain and fatigue, lead to functional impairments. As AYAs strive to rejoin their same aged-peers, they may have difficulty separating themselves from their cancer-identity, feeling isolated and "stuck" in their experiences.[12,13]

Distress is prevalent in AYAs. The challenges of normative development coupled with the sequelae of cancer treatment can be overwhelming, triggering anxiety and depressed mood. Distress occurs when these stressors are not dealt with in an adaptive manner. As such, rates of distress are higher in this cohort compared to individuals diagnosed in early childhood and later adulthood.[1-3] While acute symptoms persist for several years after treatment, peak levels of distress coincide with the first few years of completion.[12,13]

Chronic, unmanaged stress can provoke widespread neuroendocrine and immune dysregulation. There is a well-established link between stress and health.[14-16] Chronic stress stimulates activation of the sympathetic nervous system (SNS) and Hypothalamic-Pituitary-Adrenal (HPA) axis; chronic stimulation of these major stress systems can lead to decrements in immune functioning and poorer health states. [15,16] However, the significance of these alterations has not been examined among AYAs, particularly those completing cancer treatment. Further, little is known how prolonged stress exposure during a sensitive period of development can impact physical and socioemotional well-being. In the unaffected population and adult survivors, stress is linked with increased risk for physical disease and poorer response to treatment.[16-18]

Stress can also contribute to maladaptive health behaviors and quality of life impairments. Among AYAs, stress has been linked to physical inactivity, excess drinking, smoking, and substance use.[19,20] Stress has also been shown to exacerbate the post-treatment symptoms AYAs experience, including pain, fatigue, and insomnia.[21] These consequences increase AYAs risk for cancer-related morbidity and early mortality.

Despite their multiple vulnerabilities, there are a lack of targeted psychosocial programs that target their needs. Historically low research participation and their wide geographic distribution have made it difficult to identify AYAs and provide targeted treatment.[1-3]The NCI and Livestrong Foundation have thus identified AYAs as a high priority population.[1-3] The AYA-HOPE was the first to document high unmet needs among AYAs despite reported rates of distress, with 41% identifying psychosocial support as an unmet need.[1]

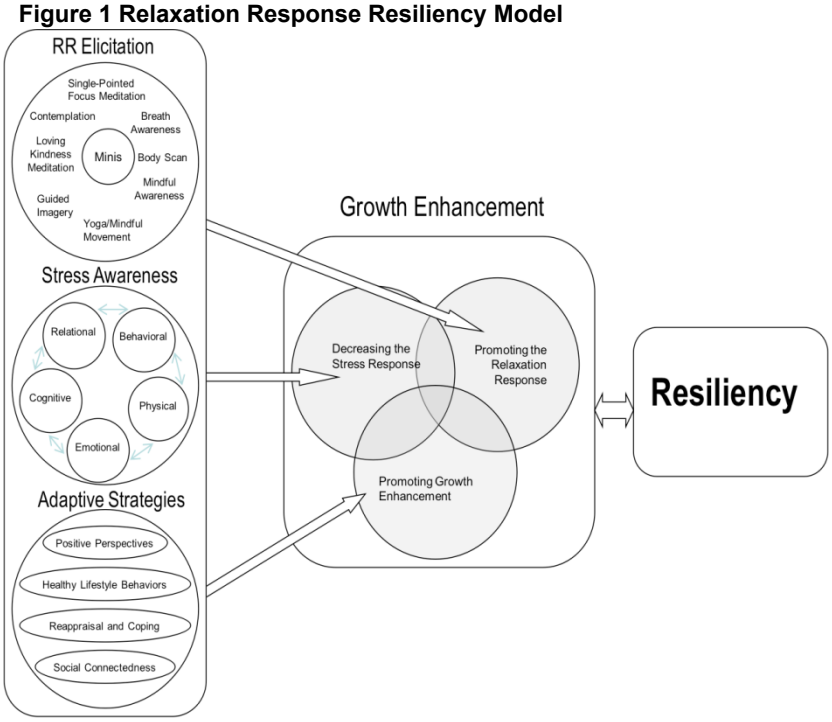
Mind-body programs centered on the relaxation response (RR) may help mitigate the negative physiological effects of stress on AYAs. The RR is a physiological state characterized by decreased SNS arousal.[22,23] Physiological changes associated with the RR[22-25] are counter to the stress response. RCTs have found that RR elicitation may reduce adrenergic end-organ responsivity, suggesting that it may enable people to remain relaxed under stressful conditions.[22,23,26] RR practice has been shown to relieve stress-related conditions, such as migraines, chronic pain, and anxiety.[26-31] The Relaxation Response Resiliency Program (3RP)[4] is a mind-body program that was designed to promote stress adaptation and resiliency.

Mind-body strategies may also ameliorate the negative psychological and emotional effects of stress while assisting AYAs with managing the psychosocial challenges of early survivorship; however, efficacy remains unexplored. AYAs have shown interest in using complementary and alternative medicine (CAM), which encompasses mind-body approaches, to cope with stress and improve overall well-being;[32-34] yet, there are no established interventions demonstrating the utility of these approaches for AYAs. Given their interests and the potential for mind-body approaches, research is needed to demonstrate the benefits of these approaches for AYAs. Currently, there are no known established interventions that aim to increase AYAs' ability to cope and manage the specific psychosocial and developmental issues they face during the early post-treatment period.

This study thus attempts to address important gaps in the support of AYAs. It proposes to test the effects of a highly scalable, tailored, virtual program, the 3RP-AYA, for a group who is at highest risk for adverse physical and mental health outcomes yet who lacks access to targeted psychosocial resources. The program aims to reduce the harmful, whole-body effects of stress by integrating mind-body, positive psychology, and cognitive behavioral strategies to improve stress management among AYA survivors. These strategies have individually been shown to appeal to AYAs and improve the aftereffects of survivorship;[35,36] however, no study has tested the combined effects of these approaches, as we propose to do.

1.3 Intervention Schematic: The original 3RP framework (see Figure 1). Dr. Park (primary mentor) and colleagues at the Benson-Henry Institute for Mind Body Medicine (BHI) developed the *3RP Model* to explain how we can improve our ability to adapt to significant stress and life events, which we define as *resiliency.* The model asserts that resiliency is achieved by (1) promoting the relaxation response; (2) decreasing the stress response; and (3) promoting growth enhancement. Its corresponding program, the original 3RP,[4] uses a blending of stress coping and cognitive behavioral treatment to achieve these goals. *Promoting the relaxation response* involves adopting strategies (e.g., guided imagery) to reduce heart rate, muscle tension, and breathing rate, in order to reduce our physiological response to stress. *Decreasing the stress response* entails increasing one's awareness of being in the stress response (negative thoughts, emotions, and behaviors) and learning skills to change/alter these components (e.g., cognitive restructuring and acceptance). *Promoting growth enhancement* involves learning adaptive strategies to increase self-acceptance, self-efficacy, healthy lifestyle behaviors, and social connectedness. This same model and key components underlie the 3RP-AYA.

Figure 1 Relaxation Response Resiliency Model



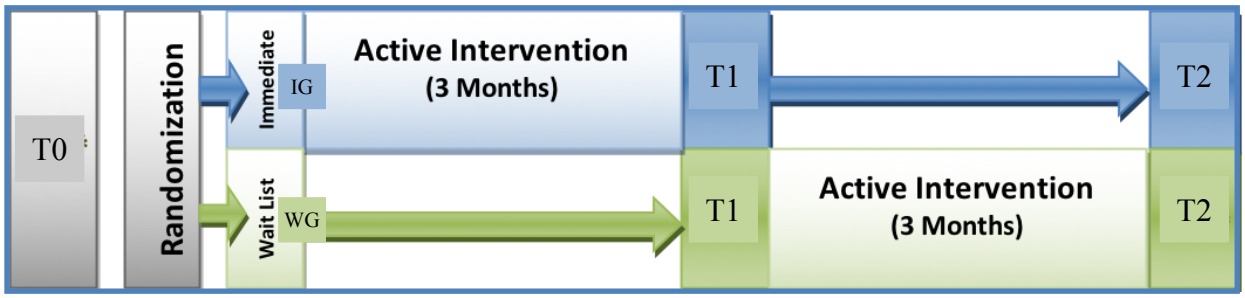
Preliminary studies: BHI investigators have demonstrated the efficacy of the 3RP in decreasing stress and improving psychological and physical health symptoms among patients with chronic pain,28 insomnia,37 infertility,[38] and other medical symptoms.[39] Recently, Drs. Park and Perez adapted the 3RP and conducted an NCI-funded pilot with 28 cancer interpreters.[40] Post-treatment follow-up results indicated improvements in job satisfaction (p=0.02; Cohen's d=.41) and stress reactivity (MOCS-A; p=0.13; Cohen's d=.33). Dr. Perez has also led a 3RP group treatment for a randomized trial (PI: John Denninger, M.D., Ph.D., DF/HCC 13-266) examining the efficacy of this treatment among patients diagnosed with the precursors of multiple myeloma. Currently, the feasibility of delivering a group 3RP virtually via Partners Health Care Telehealth videoconferencing software is being tested with parents of children with special needs (PI: Elyse R. Park, funded by the Dan Marino Foundation, Partners IRB Protocol #: 2016P001622). Dr. Perez is also currently conducting a study to assess the acceptability and feasibility of delivering the 3RP virtually for lymphoma survivors within 2 years of completing cancer treatment (DF/HCC 16-396 and DF/HCC 17-063).

2.0 OBJECTIVES

2.1. Primary Aim: To examine, in a pilot RCT (total n=72, goal of having approximately n=60 completers), the feasibility and acceptability of an 8-session stress-management and resiliency group program (3RP-AYA)

delivered via videoconference technology for survivors of AYA cancer between the ages of 16-29 at study enrollment, but who were diagnosed between ages 14 and 29 and who are within 5 years of treatment completion. *Hypothesis 1*: The program will be **feasible** (defined by enrollment rate, session attendance and reported relaxation response elicitation practice) and **acceptable** (defined by program satisfaction, ease, and utility).

2.2. Exploratory Aims:
a) Using a randomized, waitlist controlled design, we will examine the preliminary effects of the 3RP-AYA on stress and stress management among AYAs. Specifically, we will examine the preliminary effects of the 3RP-AYA on psychosocial measures of mindfulness, depressed mood, anxiety and stress collected at three timepoints, as detailed below: T0 (baseline), T1 (IG: posttreatment, WG: baseline2), T2 (IG: 3 month follow-up, WG: posttreatment).



Exploratory *Hypothesis 2.2a*: Compared to the waitlist-controlled group (WG), the immediate start intervention group (IG) will demonstrate greater mindfulness, lower depressed mood, anxiety and perceived stress at post-treatment. Additionally, the immediate start intervention group (IG) and waitlist control group (WG) combined will demonstrate greater mindfulness, less depressed mood, anxiety and perceived stress at treatment completion (T0-T1 for IG; T1-T2 for WG).

b) We will explore the feasibility and acceptability of collecting hair samples to examine intervention-related changes in cortisol, a stress biomarker. *Exploratory Hypothesis 2.2b2b*: The 3RP-AYA group will demonstrate lower stress reactivity (as manifested by hair cortisol) at timepointt 1 (post-treatment for IG; baseline/waitlist period for WG).

c) In efforts to inform the literature and guide future studies on engaging AYA in psychosocial treatment, we, we will examine AYA reasons for deciding not to participate in this behavioral trial. *Exploratory Hypothesis 2.2c:* Participants approached about the study who choose not to participate will do so for a variety of reasons, such as time constraints.

3.0 RESEARCH SUBJECT SELECTION

Eligible participants include individuals who:
1) were diagnosed with cancer between ages 14 and 29;
2) completed cancer treatment within the past 5 years;
3) are between 16-29 years old at time of study enrollment.

Exclusion criteria: Patients will not be eligible if they are unable to speak or read English, are unwilling or unable to participate in the study, or are considered medically or otherwise unable to

participate by their oncology provider or study PI. Additionally, participants will be ineligible if they are unwilling or unable to participate in the 3RP-AYA session delivered online via Partners Health Care Telehealth Services videoconferencing software and if a patient has previously participated in sister-protocol DF/HCC #17-063.

Rationale for eligibility criteria: Although the accepted age range for AYAs (as defined by the IOM) is 15-39[1], our age range of 14- 29 for time of diagnosis was chosen in our efforts to target an adolescent and young adult population who was diagnosed during a time of great developmental change and important but stressful life transitions, including moving from childhood to older adolescence or young adulthood, graduating from high school or college, and entering financial independence (including no longer being eligible for parental insurance). Our range of 14-29 for age of diagnosis is also within the focal age-range identified by the NCTN-affiliated Children Oncology Group (COG) scientific committees that focus on AYA cancer.[42] We believe this group may be particular susceptible to having difficulty accessing psychosocial care in the context of changes in insurance that happen around this time period). This was also a group, based on findings from our sister protocol (DF/HCC #17-063) that identified wanting a program such as the one described within. Our window for treatment completion (0-5 years) is consistent with the "early survivorship" period.[1,2,43] These criteria will allow us to target a group who is most likely to experience increased psychosocial vulnerability and who demonstrates a high level of unmet needs. Patients who are within 5 years of completing cancer treatment and do not have evidence of residual disease, but who are receiving maintenance treatment (e.g. Rituxumab), may still be considered eligible for the study. Also, given our intentions to deliver this focus group via videoconference technology (i.e., Partners Telehealth), patients who are unwilling or unable to participate in the intervention delivered via Partners Telehealth software (due to lack of access to a mobile device, such as a laptop, computer, or mobile phone) will be ineligible. Importantly, we will closely document and monitor the numbers of individuals who are unable to participate given this criterion, as it will further inform the feasibility of this type of treatment modality. Lastly, though future work may examine the utility of this program among Spanish-speaking survivors and survivors of AYA cancers who speak other primary languages, we have chosen to include patients who speak English due to the breadth and exploratory nature of this pilot.

Inclusion Criteria	Exclusion Criteria
Diagnosed with any cancer between ages 14 and 29	Unwilling or unable to participate in the study
Completed cancer treatment within the past 5 years	Unable to speak or read English
Between 16-29 years of age at time of enrollment	Is medically or otherwise unable to participate (as determined by a physician or study PI)
	Unwilling or unable to participate in study sessions delivered via the Partners Telehealth videoconferencing software
	Participation in a focus group during Phase 1 (DF/HCC 17-315) or the sister-protocol (DF/HCC 17-063)

4.0 RESEARCH SUBJECT ENTRY

4.1 Recruitment

As done in our sister-protocols, DF/HCC 17-315 and DF/HCC 17-063, we will use a multi-modal approach to identify and recruit patients for this study. Lessons learned from our work with protocols DF/HCC 17-315 and DF/HCC 17-063 and also strategies gleaned from studies conducted with AYAs emphasize the need to access this hard-to-reach group using proactive vs. reactive recruitment approaches.

Proactive recruitment is defined in this protocol as any recruitment outreach in which the study team actively contacts or approaches the patient regarding interest in study participation.

Reactive recruitment is defined in this protocol as any passive recruitment outreach in which potential participants will see or receive study recruitment material (e.g. study flyers, recruitment letter), but the study team will not actively follow-up unless the participant initiates contact and expresses interest to the study team.

Studies have shown that reactive recruitment approaches are most effective in accessing and engaging this hard-to-reach population, and experience from our sister protocols (DF/HCC 17-315 and DF/HCC 17-063) corroborate existing research. Our multi-modal proactive and/or reactive approaches detailed below are strategically designed to ensure successful reach, engagement, and retention of this population while at the same time maintaining patient safety and research compliance. Patient safety is largely upheld through our emphasis of engaging providers and ensuring provider agreement with referring patients to our study. Given this, participants may learn about the study through a variety of recruitment methods.

4.1a Recruitment Flyers (Appendices 8.1 and 8.2). Patients will have the opportunity to learn about this study via study flyers. Flyers will be distributed to through social media (see 4.1e) and through providers at external, interested healthcare institutions and clinics, including the CONNECCs network. Eastern Maine Medical Center has requested specific language be modified in order to refer patients from their site. The version of this study recruitment flyer can be found in Appendix 8.2. Providers may hang study flyers in clinic spaces, and they may choose to give flyers directly to patients during a clinic visit. Patients will thus have the opportunity to reach out directly to the study team via email or phone upon learning about the study via the recruitment flyers. If a patient learns about the study via a flyer during a clinic visit at an external institution, they may also give their provider permission to email their name and an email/phone number to study staff at MGH to facilitate proactive outreach. In addition to distributing flyers at external institutions, the study team may also distribute flyers at cancer and survivor-related conferences and organizations (e.g., DFCI Young Adult Program Conference, Stupid Cancer, etc). This will enable patients to reach out directly to study staff if they are interested in learning more about the study.

4.1b Proactive Patient Screening and Recruitment: Study staff will also proactively identify and recruit AYAs from the MGH Cancer Center and Dana Farber Cancer Institute (DFCI). Specifically, study staff will screen cancer survivors' electronic health records (EHR) for demographic and clinical eligibility criteria (i.e., cancer diagnosis, age at cancer diagnosis, and completion status of cancer treatment) (HIPAA waiver detailing medical records access submitted to DF/HCC IRB). Upon identification of potentially eligible AYAs, study staff will email the cancer care team (i.e. oncologist, nurse practitioner) to provide eligible participants' name and medical record number and to request review of the patient for study participation. If a provider does not respond to the permission email, it will be assumed that they give permission for the study team to approach the patient in person or pursue outreach (Appendix 8.3). A study staff member will commence outreach efforts utilizing our study script (Appendix 8.4) and one of two methods: by approaching patients at an upcoming clinic visit and/or by mailing a study flyer and proactive recruitment letter signed by the study or site PI for those without upcoming clinic visits (Appendi8.5). Because these patients are often busy, may not have access to their mail (either because they are away at school or their parents collect mail from home), and respond differently to different modes of communication, study staff will attempt to connect with the prospective patient by email and/or phone for those who are mailed letters. Specifically, as we have successfully done in protocol DF/HCC 17-315, if the patient does not respond to the mailed letter

within approximately one week, study staff may contact the patient via email or phone to go through the letter and study flyer with the patient and to ask if they are interested in participating in the study (Appendix 8.4). If study staff are unable to get in contact with a potential participant, as characterized by speaking with the patient over the phone, study staff may leave a voicemail (Appendix 8.7). Study staff will leave a maximum of 3 voicemails or emails. Attempts will be discontinued to contact the patient after all 3 voicemail or email attempts have been made, and the patient will be considered a passive opt-out. Of note: the role of the DFCI as a study site is for screening and recruitment purposes only. Study staff at the DFCI are not responsible for any aspect of participant consent, enrollment, or intervention delivery within the scope of this study. Study staff at MGH Boston assume responsibility for participants from the time of consent through the completion of study procedures and follow-up.

4.1c Reactive Recruitment Letters (Appendix 8.9): Pediatric clinicians at healthcare institutions external to Partners may choose to send reactive recruitment letters to potential participants, detailing the study and offering their recommendation to reach out to study staff to learn about the study. Reactive recruitment letters will be tailored to fit the letterhead and contact information of providers at each institution who would like to send them to their patients (Appendix 8.9). A provider may send up to three reactive recruitment letters total. Reactive recruitment letters allow providers to inform potentially eligible patients who do not have upcoming in-clinic visits about this study, ensuring they have the same opportunity to decide to participate as those patients who have more regular visits and would receive study information or materials in-person. This is particularly important in light of the fact that survivors have fewer clinic visits as they move further from completion of treatment. As indicated in 4.1a, if a provider receives permission from an interested patient at an external institution during a clinic visit (e.g., if a patient has a clinic visit after receipt of this letter), the provider may pass along the name of the patient and an email/phone number to study staff via email to facilitate outreach. If an interested individual reaches out to the study staff as a result of reactive recruitment letters, study staff will follow the study script for appropriate screening of eligibility and informed consenting procedures (Appendix 8.4).

4.1d DFCI Transfer of Information (Appendix 8.8): As done in sister protocol DF/HCC #17-315, the DFCI will be open as a site under this protocol (Site-PI: Kenney). As outlined in 4.1b, study staff at DFCI will screen patient cancer survivors' electronic health records (EHR) for demographic and clinical eligibility criteria (i.e., cancer diagnosis, age at cancer diagnosis, and completion status of cancer treatment) (HIPAA waiver detailing medical records access submitted to DF/HCC IRB). Upon, identification of potentially eligible AYAs, DFCI study staff will seek permission to approach from the cancer care team and will either 1) approach patients at an upcoming clinic visit and/or 2) mail a study flyer and proactive recruitment letter signed by the site PI (Lisa Kenney, MD) for those without upcoming clinic visits (Appendix 5). However, if the patient does not respond to the mailed letter within approximately one week, DFCI study staff (Lisa Kenney, MD) may transfer the potentially eligible participants' contact information to MGH using the secure study REDCap Database (database framework outlined in Appendix 8.8). The study team at MGH will proceed to contact these potentially eligible participants by phone to follow-up the recruitment letters and invite the AYA to participate. MGH study staff may leave up to three voice mail messages for potential participants. If study staff encounter an interested, potentially eligible participant, they will follow the study eligibility screening script to determine eligibility and commence informed consent procedures (Appendix 8.4). Please see section 4.1b for further information regarding the role of the DFCI as a study site.

4.1e Social Media Recruitment (Appendix 8.10): Based on emerging findings from our focus groups (**DF/HCC 17-315)**, AYAs identified an interest in learning about studies, such as the one proposed, via social media. Accordingly, social media advertisements will be used to disseminate

information about the study for AYAs to directly contact study staff for more information or to express interest in participation. Specifically, information about the proposed study will be posted on a variety of social media outlets and/or forums including, but not limited to the following: Facebook, Instagram, and Twitter. The social media advertisement will additionally be sent to external healthcare institutions to capture a diverse audience of adolescent and young adult cancer survivors. The social media advertisement will only be posted to accounts, forums, groups, or websites with proper permission of the account holder or organizer. Any feedback related to social media advertisements will be recorded in the study regulatory binder and reported during annual study reviews to the study team and IRB. If an interested individual reaches out to the study staff as a result of social media advertising, study staff will follow the study script for appropriate screening and informed consenting procedures (Appendix 8.4).

4.1f Study Website and Research Portals (Appendices 8.2 and 8.25): In addition to posting information on the study to various social media venues, the study team will also maintain a study website. Content of this website can be found in Appendix 8.25. The website will also be added to other study materials to facilitate potential participants to visit and learn more about the study. Study staff contact information will be posted on the website for any questions related to the study. Additionally, study staff may use research portals, as outlined in Appendix 8.2, to post about the study for potentially interested participants. Among these, ResearchMatch.org will be utilized as a recruitment tool. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository (see IRB #090207).

Minor Recruitment: Special protections will be enacted during recruitment and enrollment for participants under the age of 18. For recruitment of participants under the age of 18, whenever possible, study staff will explain the study procedures to both the patient and their parent or legal guardian concurrently in person, via secure videoconferencing, or via phone. Assent will be obtained by the minor participant in person or by phone, and written consent by the parent or legal guardian and written assent of minor participants will also be obtained in person, electronically, or via email (methods 4.2a, 4.2b, 4.2c). If a participant turns 18 during active study procedures (as defined by time of minor assent to Timepoint 2),), study staff will reconsent the participant. If a participant turns 18 after completion of all study procedures, original minor assent and consent will be maintained for the participant.

Outreach and the Informed Consent Process: If given the opportunity, study staff may attend related conferences, symposia, or other events in order to share study-related information and recruit participants for the study (detailed in section 4.1a: recruitment flyers). Study staff may bring blank copies of the consent form and prepaid envelopes to such events in order to provide potentially interested participants with these forms to review in detail at their leisure. The blank informed consent document will not include any specific patient information but will provide patients with the opportunity to take additional time to review the components of the study to make a more informed decision about participating. A contact phone number or email will be collected from interested participants in order for study staff to follow-up and complete the full informed consent process electronically (4.2b) or over the phone/mail (4.2c).

4.2 The Informed Consent Process & Enrollment

A member of the study staff will determine patients' eligibility status, explain the purpose of the study and study procedures, and answer any questions prior to completing informed consent. During the informed consent discussion, study staff will carefully review the informed consent document with the patient.

All patients will be provided with study staff contact information if any questions or concerns regarding the research arise. In addition, all patients will be explicitly informed that Partners Telehealth services provides

secure HIPAA-compliant videoconferencing software. We will explain that although we will do our best to ensure confidentiality on our end, we cannot guarantee 100% that other group members will not share the content of the group. Patients will also be advised to wear headphones and sit in a quiet place during the virtual study visits to protect their own, and other group members', privacy. Participants will also be informed that after signing the informed consent, they will complete a brief test call with a study staff member using the videoconferencing software in order to ensure proficiency with the software. If a participant completes a study questionnaire and is later deemed ineligible, their responses will be exempt from data analysis. Subjects who are found to be unable to use the videoconferencing software during the brief test call will be considered ineligible for the study.

For eligible patients, a trained member of study staff with a bachelor's-level training or greater will obtain informed consent in one of three ways: 1) in-person, 2) electronically, or 3) via phone and mail correspondence, in accordance with patient preferences and availability, prior to participating.

4.2a In-person Informed Consent Process: Study staff will go through the informed consent discussion detailed above in a private room to protect patient confidentiality and answer any questions. Upon consent, study staff will maintain one copy of the informed consent form for study records, and participants will be instructed to maintain one copy for personal reference. Patients who would like more time to consider participation during in-clinic approach are able to take the forms home with them to review, and if interested, they may complete the consent process electronically (4.2b) or proceed to mail back the consent forms (see 4.2c).

4.2b Electronic Informed Consent Process (EIC): In the event that a potentially eligible participant expresses interest in participation but is unable or unwilling to complete the informed consent process in-person, study staff will begin the EIC process. This process begins with study staff collecting the best email address to contact the patient and sending the patient the informed consent portal via REDCap (Appendix 8.11). The REDCap link will direct patients to an encrypted REDCap portal; the Electronic/Paperless Consent Template Project will be used. Once the patient confirms receipt of the EIC form link, they will be prompted to enter in their full name and birthday to access the informed consent form and verify their identify. This portal will have the electronic (paperless) consent form, exactly identical in content to the paper version, to guide the patient through the consent discussion with study staff over the phone or secure videoconferencing technology. The patient will be given ample opportunity to ask questions and take their time to consider their participation. If a patient would prefer, they may return to the EIC portal as many times as they would like to review the consent form on their own time. When ready to sign consent, patients will indicate who they are signing the EIC form for (e.g. self, minor), and will digitally sign and date/time the consent form (see section 4.21 for the detailed minor electronic assent process). Additionally, patients will be prompted after signing to indicate the method through which they would like to receive a copy of the consent form for their record: digitally or through hard copy. If a patient would like to receive a copy of the consent form digitally, they will be asked of their preference to receive the email as encrypted, the default, or opt-out and receive the email unencrypted. These options allow participants to be informed of what an encrypted (Send Secure) email would appear as in their inbox and the steps to get into the email, or alternatively, to give permission receive the email without this extra layer of security but in a more accessible format. Partner's Healthcare language concerning the Send Secure feature is included to assist in this decision. Study staff will confirm receipt of the digital signature and will sign and date the consent form as the consenting study staff member. At any point, if a patient would prefer to receive a hard copy of the consent form, the EIC process will stop, and study staff will commence the phone and mail correspondence process for informed consent.

4.2c Phone and Mail Correspondence Process: If a potential participant would prefer to complete the informed consent process via mail correspondence instead of electronically, study staff will start by facilitating the informed consent discussion either in-person or over the phone. Once all questions are answered to patient satisfaction, study staff will mail 2 signed copies of the informed

consent form for the participant to review, sign and mail back at their convenience. Patients will be provided with a pre-stamped, pre-addressed envelope for their return. Study staff will maintain one copy of the informed consent form for study records, and participants will be instructed to maintain one copy for personal reference. The envelope may additionally include relevant study questionnaires or the remuneration form for the participant to fill out and return to study staff, if applicable.

Once informed assent and/or consent has been obtained from a participant and they have completed the baseline assessment (Timepoint 0), study staff will enroll the participant on-study (Registration procedures detailed in Section 4.4).

4.3 Participant Communication Methods

Recruiting AYAs for research studies is historically difficult, as shown in previous literature. Accordingly, it is important to access and maintain contact with participants through communication methods they are most comfortable with, including phone, secure videoconferencing, email, and SMS texting. During the informed consent process, study staff will elicit patient preferences about methods of study contact to facilitate participation (e.g., scheduling study visits, sending reminders, etc). The limitations of each method will be described in detail. Specifically, patients may opt to pursue communication with study staff using email or text messaging in addition to the phone.

4.3a SMS Messaging: As successfully done in our sister protocol, DF/HCC 17-315, to encourage and provide ease of scheduling and communicating with the study team, at time of consent, participants may elect to provide a personal mobile phone number and provide permission to receive SMS messages via an online service (GoogleVoice) regarding the study that the study staff will monitor. Before doing so, participants will be informed of the limitations of using GoogleVoice, particularly emphasizing that it is not HIPAA-compliant and thus does not offer protection over their personal health information. In the event participants still prefer the use of text messaging, study staff will send brief messages containing limited information regarding scheduling, reminders, and follow-up. Participants will be provided with the number (617)-982-3972 for SMS study-related communications. Study staff will follow the templates as outlined in Appendix 8.12 for SMS communication. Under the discretion of trained study staff and extenuating circumstances, study staff may stray from the following templates to address scheduling/reminder situations not covered by the following. Under no circumstances will study staff ever screen or discuss personal medical history, exchange personal health information, or other sensitive information via SMS message. If a participant introduces sensitive information, including but not limited to the examples just listed, into a SMS message conversation, the study staff member will direct the participant to call them to discuss it further over the phone.

4.3b Email: Participants will also be given the option to communicate (receive reminders, schedule, etc.) with study staff by email. If a patient chooses email as their preferred method of communication, study staff will explain the encrypted, Send Secure default feature of emails sent from within the Partners Healthcare network. Study staff will verify that no sensitive or patient health information will be disclosed in emails but ensure that the patient understands that by opting-out of the send secure feature, information will not be as secure. Upon explaining these ramifications, the patient has the option to provide their informed decision to opt-out of the send secure feature. In our sister protocol (DF/HCC #17-315), it was found experientially by study staff that participants much preferred the non-send secure emails, as the additional security is useful but difficult to operate.

4.4 Registration

Participants who provide informed consent will complete baseline study measures prior to registration. The research team will perform randomization procedures using computer generated randomization schema and assignments will be kept in concealed envelopes. We will complete the following registration procedures:

- Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore as required by DF/HCC SOP REGIST-101. When required by REGIST-101, registration must occur prior to the initiation of protocol-specific procedures or assessments.
- Registration requires a signed informed consent document and a completed eligibility checklist according to DF/HCC SOP REGIST-104.
- After randomization the research staff will inform the patients by phone, secure videoconferencing, or in-person of their study arm assignment.

If it is determined that a participant is ineligible or withdraws after signing consent and being enrolled on the study (i.e. unable to operate videoconferencing software, no longer interested in participating, etc.), their status on OnCore will be modified to "Off-Study" to reflect their status and a note will be added in the comments section. Additionally, study staff will add a Note to File as part of the regulatory documents of the study detailing any events of a lost participant.

5.0 STUDY DESIGN AND METHODS

5.1 Design / Study Type

This is a pilot RCT to examine the feasibility and acceptability of the 3RP-AYA among approximately 72 adolescent and young adult cancer survivors who are up to 5 years post-treatment. Participants who complete the baseline questionnaire and are randomized will be enrolled and counted toward the accrual goal of 72. As such, up to 72 participants may be enrolled in the study in order to allow approximately 60 patients to participate total in the intervention and waitlist arms (goal of 30 completer-participants per arm). Participants do not need to complete every study measure to be counted towards the 72-participant accrual goal (i.e., participants who only complete some measures/3RP-AYA sessions will still be counted towards the accrual goal); however, patients who do not complete <u>any</u> of the study measures or who do not participate in <u>any</u> intervention visits will not be counted towards this goal.

We plan to examine the proportion of patients who are eligible and the proportion who are found to be ineligible due to age, language, inability to use the videoconferencing software, oncologist refusal, and medically or psychiatrically unable to participate. Out of those who are eligible, we will examine the proportion of enrollments, refusals, lost-to-follow up, withdraws, and study completers. We will examine reasons for and rates of ineligibility and refusal, as these will inform the feasibility of the study and of delivering the program virtually. We will also examine the characteristics of non-completers and the circumstances of non-completion.

5.2 Selection of Instruments (refer to section 5.5 for schedule of measures):

5.2.1 Demographic Survey. We will gather important demographic information to characterize our sample, including participants' race, ethnicity, education, relationship status, health insurance, and annual household income (Appendix 8.17).

5.2.2 Primary Outcomes. 3RP-AYA Feasibility and Acceptability data will be collected electronically (via REDCap), on paper, or by phone:

> **<u>Feasibility</u>:** Feasibility metrics are modeled after resiliency studies led with survivors and other medical populations.[27,28] We will evaluate program feasibility by examining several process variables, including rates of study eligibility (percent of patients who are eligible), recruitment (number of eligible patients who express interest in our study), enrollment (percent of eligible pool who consents and enrolls), retention (percent of enrollees who complete the follow-up), and treatment adherence (number of days elicited relaxation response, number of participants who complete the follow-up surveys). We will also document reasons for ineligibility and refusal as well as sociodemographic characteristics, medical history, and cancer characteristics of refusers. Additionally, adherence to

recommended RR elicitation will be assessed via Weekly RR practice logs (Appendix 8.27). The Weekly RR practice logs are part of the standard 3RP program, and in order to reduce participant burden, only the questions about weekly RR elicitation, weekly appreciations, and stress, distress, and coping Likert scales are included, while the questions from the standard 3RP weekly practice logs about lifestyle behaviors (exercise and nutrition), social connectedness, and physical/emotional symptoms have been omitted.

Acceptability: Intervention acceptability will be assessed at the follow up data collection period with five questions on the 3RP-AYA acceptability questionnaire (Appendix 8.15) rated on a 4-point Likert scale (1=not at all to 4=very much). Items will prompt participants to rate the extent to which they found the program to be 1) enjoyable, 2) helpful, 3) applicable/relevant (i.e., is it appropriate and applicable), 4) convenient (i.e., in regards to delivery modality), and 5) likelihood of future use (e.g., "Will you continue to use RR strategies in the future?"). Treatment satisfaction will be assessed by items on the 3RP acceptability questionnaire which ask participants to rate their level of satisfaction with the following items using a 4-point Likert scale (1= not at all satisfied to 4 = very satisfied): 1) treatment structure, 2) treatment timing (i.e., early survivorship period) and 3) treatment content. We will also qualitatively explore overall satisfaction with three open-ended questions regarding treatment likes, dislikes and recommendations.

5.2.3. Exploratory Outcomes. We will collect hair samples for cortisol measurement by mail and psychosocial measures electronically or by mail to determine the preliminary efficacy of this program on stress reactivity and stress management.

5.2.3a Hair Cortisol Measurement: Participants will be asked to provide hair samples to measure potential changes in cortisol ("stress hormone"); this method has been used successfully in stress studies[29-31] and is currently being utilized in our sister 3RP protocols Dr. Perez is leading (Partners IRB Protocol #: 2016P001622; DF/HCC #17-063, PI: Perez). Hair grows roughly 1cm/month, thus ensuring sufficient growth for collection. The RA will mail or email detailed sampling instructions (Appendix 8.16) and stamped, addressed envelopes to facilitate returns. Participants will be instructed to provide one hair sample at baseline and one sample at the end of the intervention. Specifically, they will be instructed to cut a small sample of hair (approximately 150 strands, about the diameter of a pencil eraser) from the back of their head, as close to the scalp as possible. They will be asked to tie the strands near the scalp end, place the sample in aluminum foil, and mail to MGH. The hair sampling instructions also include 6 questions about hair care, exercise, and glucocorticoid use, as these can affect hair cortisol measurements. Hair samples will not be collected from participants who have taken glucocorticoid medications (e.g. prednisone) within the past 3 months, as these medications cause cortisol measurements to be inaccurate. However, hair that is chemically treated or dyed may still be used for hair cortisol analysis. We will track the reasons why any hair samples were not collected, as this informs the feasibility and acceptability of hair cortisol collection and analysis for this population. Rationale for hair cortisol versus salivary cortisol. Recent studies comparing salivary vs. hair cortisol have found that hair samples provide a more robust measure of chronic stress.[32] Specifically, hair cortisol provides a more complete snapshot of cortisol concentration levels across longer periods (e.g., over 3 months) whereas salivary cortisol captures the acute stress response.[29] As such, studies have been more likely to find changes in hair cortisol levels in response to stress management programs.[29] Further, hair sampling may be less burdensome, invasive, and easier to collect than saliva sampling, which requires subjects to provide several samples throughout the day. Saliva sampling is also subject to sampling errors due to incorrect timing, inefficient sampling, and inaccurate collection procedures.[29] We will collect feedback and perceptions of hair sampling measures at study completion. **Sample Processing:** Hair cortisol will be processed by Dr. Jerrold Meyer's laboratory at the University of Massachusetts, Amherst. Prior to shipping, samples will remain wrapped in aluminum foil, labeled with a study ID and stored at room temperature in a padded envelope.

5.2.3b Psychosocial Measures. We will gather relevant information related to current or past levels of distress from participants to examine the psychosocial impact of this program. Information that will be

collected from participants will include symptoms of stress, worrying, anxiety, and depression (Appendix 8.17). These measures take approximately 35 minutes to complete. Participants have the option to skip any questions they prefer not to answer.

- Patient-Reported Outcomes Measurement Information System (PROMIS) Measures: PROMIS is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. A variety of subscales will be used as exploratory outcomes including, PROMIS Anxiety PROMIS ED Anxiety – short form 4a, PROMIS ED depression – short form 4a, PROMIS ED anger – short form 5a, PROMIS fatigue short form 7b, PROMIS sleep disturbance short form 8a, PROMIS Social Isolation short form 4a

- Coping Self-efficacy Scale: The Coping Self-Efficacy Scale (CSES) is a 26-item measure of perceived self-efficacy for coping with challenges and threats.

- Interpersonal Reactivity Index: The Interpersonal Reactivity Index (Perspective-taking subscale) will be used to measure the level of dispositional empathy particopants have. The perspective-taking subscale consists of 7-items and measures the tendency of an individual to take on the perspective of another in daily life.
- Penn State Worry Questionnaire (PSW-Q): The Penn State Worry Questionnaire is a reliable self-report tool used to measure the trait of worry in individuals. The questionnaire consists of 16 items scored on a 5-point scale ranging from 1 (not at all typical of me) to 5 (very typical of me). This measure has been used to differentiate individuals who met varying criteria for general anxiety disorder, indicating the trait of worry is a related, yet independent, aspect of anxiety.[64, 65]
- Visual Analogue Scale 0-10: We are using 5 items rated on a visual analogue scale with response options ranging from 0=No [stress] to 10=Extreme [stress]. Items measure stress present over the past week, ability to cope with stress, fatigue, and level of distress. The Visual Analogue Scale is a standard measure used in the 3RP program.

5.2.3c. COVID-19 Measures. The COVID-19 supplementary questions are ten short questions that ask participants to reflect on their experience during the COVID-19 pandemic. This form will help us to interpret their responses to the battery of other psychosocial measures (listed in 5.2.3b) we are administering. This measure will be administered to participants in all upcoming surveys. To minimize burden, participants who have completed the study or any previous study surveys will not be asked to retroactively complete these measures.

5.2.3d Participant Locator Form The participant locator form (Appendix 8.28) is a single page form that participants will complete upon consenting for the study. This form asks a variety of questions about communication preferences for the duration of the study. Participants will be reminded that their communications preferences may change during the study, and they should let the study team know of any changes they decide.

5.2.4. **Qualitative Exit Interviews:** A randomly selected subset of study participants (N= approximately 30) will be invited to participate in one-on-one exit interviews after study completion (i.e., they have no more scheduled intervention sessions or follow up surveys) (Appendix 8.29). We are aiming to interview up to approximately 30 AYAs to ensure we capture a wide range of responses. Exit interviews may be completed over the phone or via Partners Telehealth videoconferencing, to explore additional barriers or facilitators to study participation, treatment adherence, program engagement, and study completion. Participants will be asked more detailed information about perceptions of the treatment and preferences for further adaptation after having participated in the program. A series of questions will be asked about using social media outreach for future research recruitment. We will also ask participants to report on how COVID-19 may have impacted their stress levels or ability to participate in the intervention. These interviews will be audiorecorded and

qualitatively analyzed for themes which will help to determine whether treatment modifications are needed in future work. It is estimated that the interviews will take approximately 45 minutes to complete. Participants will be informed that the qualitative exit interviews are an optional portion of the study. Participants who do complete a qualitative exit interview will receive $30.

To supplement these interviews, with up to 25 experts in the care and treatment of AYAs to inform the design of future psychosocial interventions. This will serve to inform the next iteration of this study. Given the low risk nature of these interviews (the overarching goal of informing future trials), we are requesting a waiver of documentation of consent. Instead, to minimize burden, experts will undergo a verbal consent process, as seen in Appendix 8.30. These individuals could include (but are not limited to) oncology clinicians, primary care providers, psychologists, nurses, social workers, and others who are integral to the treatment and post-treatment experience of AYAs. Experts will be invited to complete these optional interviews over the phone or via videoconferencing to help inform future research, but will not receive any compensation for their time. To offer maximum scheduling flexibility, both individual and group interviews will be conducted. Individual interviews will be approximately 30 minutes long and group interviews will be approximately 60 minutes long. These interviews will be audiorecorded and qualitatively analyzed for themes which will help to determine whether treatment modifications are needed in future work. A sample expert interview guide is provided in Appendix 8.30.

5.3 Randomization and Treatment Delivery.

Following completion of the baseline survey, participants will be randomized to the immediate start resiliency intervention group (IG) or waitlist control group (WG).Randomization will be conducted using a random plan generator. Groups will consist of up to approximately 8 participants. We will run approximately 6 or more separate intervention and waitlist control groups, for a total of 72 survivors. Dr. Perez, a psychology trainee in the BMED internship program, or a pre-doctoral medical student, all under the supervision of Dr. Perez as study staff, will lead the group sessions, some of which will be audio-recorded for fidelity. Medical students will not under any circumstances conduct consent in their role as study staff. Prior to running the groups, Dr. Perez will train study staff on the study protocol, and we will have weekly supervision meetings to provide feedback and ensure fidelity. To decrease participant burden and extend reach, both groups will be delivered via MGH Telehealth (as successfully done in our sister protocols: DF/HCC #17-063 & DF/HCC #17-315).

5.4 Description of the Interventions.

5.4.1 3RP-AYA treatment: Similar to our sister protocol (DF/HCC #17-063), and slightly adapted based on findings from our focus groups with AYAs (DF/HCC #17-315) The 3RP-AYA will be delivered in weekly sessions over the course of approximately 8 weeks, for a total of 8 sessions, which are approximately 90 minutes each. Modeled after the central tenets of the 3RP,[1] each session includes repetition of core components, which include: 1) 10-point analogue scales of stress, distress, and coping (resembles distress thermometer), 2) weekly goal check-ins, 3) RR-practice, and 4) mini relaxation practice. Participants will learn a new RR strategy at each session that will be based on identified mind-body interests, maximizing the likelihood of finding a technique that is helpful for them. Throughout treatment, participants will be encouraged to practice RR strategies at home for at least 10-20 minutes each day, and they will be asked to document the frequency and duration of practice in weekly practice logs (Appendix 8.27) to record RR adherence. Participants will receive the 3RP-AYA patient manual, which describes the content of the 3RP sessions, and RR-based guided meditation audio files to help them elicit the RR at home each day. The audio files that guide the subject through the procedures have been used in other clinical research studies and clinical practice. It introduces a relaxation sequence to help participants elicit the RR, including some of the key elements such as breath awareness, body scan and use of a focus word, while instructing the participant to

passively ignore intrusive thoughts. Additional treatment components based on the 3RP model (Figure 1) and identified qualitative interview themes (DF/HCC #17-315) include coping logs that provide examples drawn from common transitional challenges identified by survivors (e.g., starting/graduating college; getting follow-up scans), which will facilitate discussion and practice of restructuring and positive reframing techniques. Lastly, social and educational topics identified in our sister protocol (DF/HCC #17-315), such as how to tell friends about their cancer experience, having empathy for "small things" and relating to others post-cancer treatment, preparing for high school/college, and managing parents' anxieties, will be interwoven throughout the program and used to guide survivors in applying learned skills (e.g., identifying types of social support needed and developing strategies to facilitate social outreach and connection). We will also collect total number and timing of sessions per participant. The topics addressed in each of the eight 3RP sessions are described in Appendix 8.18. In order to remain transparent during the study and give back to those willing to participate, participants will be offered the chance to have a brief conversation with the study PI, Dr. Perez, at a future date by filling out a Results Reporting Form (Appendix 8.26). Participants will be given this form after they have completed the intervention and will be told of the results after preliminary study results are available.

5.4.2 Immediate start intervention group (IG). The immediate start group will receive the intervention immediately after completing the baseline assessment (T0), and they will complete a post-treatment questionnaire (T1) to examine pre-post treatment changes in exploratory measures. Completion of T2 measures will allow for us to examine potential maintenance of intervention benefits (by evaluating change in scores from T1 to T2) within the intervention group only.

5.4.3 Waitlist Control Group. The waitlist control design allows all participants who enroll in this study the opportunity to get the 3RP-AYA. Participants in the Waitlist Control Group will be enrolled and complete baseline at the same time as the 3RP Intervention Group, and they will will complete the baseline a second time after the immediate start group completes the 3RP-AYA to allow for pre-post treatment group comparisons (T0 vs T1). The waitlist control group will also complete an assessment after receiving the 3RP-AYA treatment to examine pre-post treatment changes in exploratory measures (T1-T2).

5.5 Data Collection and Storage.

Prior to study enrollment, study data will be collected via medical record review for Partners patients or through patient self-report, if no available EMR through the Partners Healthcare System, at screening to determine study eligibility. In addition, we will gather descriptive information about our sample via brief surveys and assess levels of the stress hormone cortisol via hair sample collection. Specifically, we will collect data on:

Data	At Screening	At Baseline	At 3RP	At Post-3RP	At 3-Month Follow-Up
Date of birth	x				
Gender	x				
Languages spoken	x				
Cancer diagnosis	x				
Date of diagnosis	x				
Treatment type(s)	x				
Date of treatment completion	x				

Data	At Screening	At Baseline	At 3RP	At Post-3RP	At 3-Month Follow-Up
Demographic factors		x			
Psychosocial measures:					
Visual Analog Scales		x		x	x
Intolerance of Uncertainty Scale		x		x	x
Measure of Current Status – Part A (MOCS-A)		x		x	x
Patient-Reported Outcomes Measurement Information System (PROMIS) Measures		x		x	x
Coping Self-efficacy Scale		x		x	x
Health Behavior Questions		x		x	x
Penn State Worry Questionnaire (PSW-Q)		x		x	x
Interpersonal Reactivity Index		x		x	x
Current Experiences Scale (CES)		x		x	x
Hair cortisol measurement		x		x	
3RP acceptability questionnaire				x (intervention arm only)	x (waitlist arm only)
Weekly RR practice logs (Appendix 8.27)			x		
COVID19 Supplementary Questions		x		x	x
Optional Exit Interview (Appendix 8.29)					x (after completion of all study measures)

To safeguard participant information and confidentiality, all data will be stored in locked cabinets at MGH and/or in password-protected computer files, accessible only to trained and IRB-approved study staff. Source documents completed by participants will be scanned and stored electronically as detailed in Section 4.2b of this protocol. Participants' data will be identified by an ID number only, and a link between names and ID numbers will be kept separately under lock and key or in a separate password protected document accessible only by study staff. Data identified by ID numbers (de-identified) may also be stored in REDCap, a secure, web-based application designed to support data capture for research studies. Audio-recordings of the exit interviews and expert interviews will be uploaded to our study access-restricted drive. In efforts to remain compliant with NIH guidelines for scientific record keeping, audio recordings will be retained for at least two years after the study has ended. After that point, the recordings will be deleted and only de-identified

transcripts will be stored on our secure study-access restricted drive to preserve patient anonymity. Audio files will be sent securely and transcribed by transcribeme.com. Transcripts of all interviews will be de-identified, and participants will be directed to avoid using personal identifiers (i.e., birthdays, home address, full names) during the course of the interview, thus maintaining patient anonymity and confidentiality during the interview.

5.51. Handling of Study Documents. Study source documents, including but not limited to signed informed consent forms, completed eligibility checklists, and participant questionnaires, will be scanned and stored digitally as certified copies on a secure drive only available for access to trained study staff working with the documents. The drive will be only accessible with proper invitation to the drive by the Principle Investigator through their Partners account, which will require personal username and password information to access. Trained study staff will follow specific standard operating procedures for handling source documents and certifying each copy appropriately. The procedures are as follows. After source documentation is filled out by the participant, study staff will collect the original source document. The study staff member scanning documents will be kept as consistent as possible throughout the duration of the study to ensure uniformity among source documentation handling. Location, time, and date of the scanning of the document will be recorded at the time of scanning. Study staff will fill out the Source Documentation Certified Copy Cover Sheet (Appendix 8.23) and include this as the first page of the electronic version of the source document. After the source document is scanned and the corresponding electronic document is confirmed to be legible, all facing the correct direction, and together as a single document, it will be collected and destroyed immediately. Study staff will destroy the original copy of the source document by following MGH procedures of destroying documents with Personal Health Information (PHI). Electronic versions of source documents will allow study staff to access these documents regardless of where the original copy is stored, which may be inconvenient, increase study staff burden, and study cost if storage of documents is far from the location where research activities will be conducted or required to be placed in long term storage. Electronic copies of these documents will eliminate the need for space concerns and cost of storage.

5.6 Description of Study Process

5.6.1 Instrument Administration: The Baseline (Timepoint 0), Post-3RP (Timeline 1), and 3-month Follow-up (Timeline 2) Questionnaires will be self-administered by participants either on paper or electronically via REDCap survey in accordance with patient preferences. Patients may also elect to complete the questionnaires at home and mail them back to the study staff in a stamped, pre-addressed envelope, or complete them with a member of study staff over the phone, via secure videoconferencing, or in clinic. Patients may be recruited for the study and enrolled when they become available for an upcoming intervention or WCG session in the future. As outlined in Section 4.4, participants will not be registered on the study until they complete the baseline questionnaire and are randomized. The Timepoint 1 (Post-3RP data collection for the intervention group and baseline data collection for the WCG) may be completed up to approximately 12 weeks (+/- 2 weeks) after Timepoint 0, and Timepoint 2 (Follow-up data collection for the intervention group and Post-3RP data collection for the WCG) may be completed approximately 24-weeks (+/- 2 weeks) after Timepoint 0.

5.6.2 Hair Cortisol: Similar to other studies which have utilized hair sample collection for cortisol measurement (Partners IRB Protocol#: 2016P001622; DF/HCC #17-063), participants will be asked to cut a small amount of hair (approximately 150 strands, which is about the diameter of a pencil eraser) as close to the scalp as possible (about 3 cm), and from the back of their head. They will be asked to band or tie the strands near the scalp end, place on the sample in aluminum foil, and return in an envelope to MGH. Participants will be sent detailed sampling instructions (Appendix 8.16) and stamped, addressed envelopes to facilitate mailing. Study staff will explain the purpose of hair collection to participants to facilitate transparency of the study and invite participants the opportunity to learn more about their stress levels. A member of study staff will review the sampling procedures in detail with participants either in-person at MGH or during the brief test call, according to patient preferences and availability. Participants will be asked to provide hair samples at Timepoints 0 and 1. Participants will also be provided with the Hair Cortisol Results

Form (Appendix 8.19), which will give participants the option to receive the results of their hair cortisol levels via a phone or secure videoconferencing conversation with the study PI, which will be scheduled after the completion of all study activities.

5.6.3 Intervention Administration: The 3RP-AYA will be administered virtually via Partners Telehealth videoconferencing software by the PI or by a member of the study team who has doctoral-level training in clinical psychology or medicine and is experienced in conducting the 3RP (e.g. clinical psychologists, fellows, post-docs). The 3RP-AYA consists of eight, 90-minute weekly RR-training group sessions conducted over the course of approximately 8 weeks, and there will be up to approximately 8 participants per group. The topics addressed in the eight 3RP-AYA sessions are listed in Appendix 8.18. As described in protocol section 4.2, in order to facilitate proficiency with the Telemedicine software, participants may test the software with a study staff member during a brief test call prior to the start of the intervention.

5.6.4 Special Concerns: Some participants may feel uncomfortable sending us a hair sample; participants will not be required to participate in the hair sample collection if they feel uncomfortable or are otherwise unable to provide a hair sample. Participants can still remain in the study if they do not wish to complete a hair cortisol sample. Additionally, some subjects may not wish to participate in the qualitative exit interview for the study; this component of the study will also be considered optional.

5.6.5 Compensation: Subjects will receive $10 in remuneration for completion of the baseline survey, and $20 in remuneration for completion of the post-3RP survey, and $25 for completion of the follow-up survey (up to $55 total). Participants will receive $15 and $20 in remuneration for completion of the baseline and follow-up hair sample(s), respectively (up to $35 total). Participants who complete the optional exit interview may receive $30. In total, participants may earn up to $120 throughout the duration of their entire participation. As required for compliance with Partners Healthcare remuneration policy, we will collect participants' contact information (see Remuneration Form in Appendix 8.20). If a participant is unable to provide a Social Security Number (SSN) or Individual Taxpayer Identification Number (ITIN) because of their citizenship status (e.g. non-US citizen), they will receive an eCheck or equivalent gift card payment for study participation, as per their preference. This gift card will be sent to them electronically or in the mail, as per the participant's preference. Gift card payment information will be documented to ensure that the participant has received the appropriate payment.

5.7 Adverse Reactions and Their Management

5.7.1 Reported Adverse or Unanticipated Events. We do not anticipate any adverse events as a result of study participation. The RA, in collaboration and discussion with the PI, will report to the Institutional Review Board (IRB) in a timely manner any discovery of an unanticipated or adverse event. An adverse event will be reportable to the IRB if it meets the following criteria: a) affects patient safety; b) affects patient risk-benefit assessment to participating in the study; and c) affects data integrity. Study staff will report adverse events to the IRB as soon as they are discovered and discussed with the PI or designee (within 24 hours). The PI will be responsible for cataloguing and tallying adverse events, and she will report these events to the DF/HCC IRB as well as review the report with the mentors of the proposed study. Study staff will also be required to undergo NIH training in the conduct of research with human subjects prior to engaging in any research activities.

5.7.2 Anticipated Reactions. We do not anticipate that participants will experience any serious adverse reactions. Some participants may experience feelings of distress, sadness or emotional/physical fatigue when discussing stress and/or cancer-related topics. The PI is a licensed clinical psychologist with advanced training in clinical interviewing and assessment. Participants will be instructed to skip or decline answering any survey that they find upsetting or uncomfortable.

While this study does not target participants with depression or anxiety, it is possible that some will experience these conditions and related symptoms. The study PI is a licensed psychologist, who will evaluate and meet with any patient experiencing distress related to study participation, to determine if the patient requires further intervention.

Although we will instruct participants to maintain the confidentiality of the group by not discussing anything that goes on in the group with others, we cannot guarantee that group members will not share the content of the group with others. Extra attention will be taken during the informed consent process to explain this risk to participants. In addition, participants will be advised to wear headphones and sit in a quiet place to protect their own, and other group members', privacy.

5.7.3 Reaction Management. If, during the course of the study, study participants become distressed, the PI will be available to discuss the patient's concerns. If any aspects of the study make the participant very upset, appropriate follow-up action will be taken by the PI who will assess for safety and make appropriate referrals for treatment (e.g., MGH oncology social services). Elyse R. Park, a clinical psychologist with extensive experience working with cancer patients, will consult with the study team on complicated situations involving psychological distress at team meetings or as needed.

6.0 STATISTICAL ANALYSIS

This study will assess the feasibility and acceptability of the 3RP-AYA among approximately 72 adolescent and young adult cancer survivors who are within 5 years post-treatment.

6.1 Primary and secondary endpoints.

The primary study endpoints are the feasibility and acceptability of the program for adolescent and young adult cancer survivors who are within 5 years post-treatment completion. These will be detailed further below in the data analysis section.

6.2 Sample Size and Power Calculations.

This phase of the study is designed as a pilot RCT and thus is exploratory. Though our analyses are not powered to detect an effect, the aim of this pilot is to adapt and test the feasibility and acceptability of a mind-body based stress management program. Our emphasis on establishing feasibility and acceptability is consistent with best practices in treatment development.[27,59] The sample size chosen provides sufficient power for the primary outcome and feasibility of the intervention based on enrollment and intervention session attendance ($\geq$6).) Our sample size of 72 allows us to account for study attrition (nonparticipation after signing study consent, as defined by not participating in any 3RP sessions), with the goal of having 60 active participants. We consider a 75% session completion rate (approximately 6 out of 8 sessions) as a threshold for establishing intervention feasibility. With a sample size of 60 3RP-AYA, we would have 90% power to demonstrate a mean participation rate 5.5% higher than the threshold with a one-sided significance level of 0.05, assuming the SD of participation rate is 10%. Therefore, we believe our sample size of 72 will be sufficient to answer our questions about feasibility and acceptability.

6.3 Stratification factors and intervention allocation plan for randomized studies. Participants will be randomized to the 3RP-AYA immediate start group (IG) or waitwait-list control group (WG) using a random plan generator. While we considered stratifying by gender, age and cancer type, we chose not to given our proposed sample size and the limited a priori evidence to suggest there would be differential effects on our proposed treatment outcomes.

6.5 Stratification factors and their impact on design. N/A

6.6 Early stopping rules, if appropriate. N/A

6.7 Definition of and allowance in design for unevaluable/ineligible participants. No unevaluable and/or ineligible participants will be included in this study.

6.8 Analysis Plan.

6.8.1 Aim a) To examine the feasibility and acceptability of a group-based, stress-management and resiliency intervention delivered via videoconferencing technology for adolescent and young adult cancer survivors who are within 5 years of having completed cancer treatment.

Descriptive statistics, including means, frequencies, and ranges will be used to describe the sample and to summarize feasibility, acceptability, and program satisfaction. Feasibility outcomes will be assessed by determining the proportion of individuals who were recruited, screened, and enrolled in the study. Response frequencies will summarize reasons for ineligibility and refusal. We will also determine the proportion of enrolled participants who complete the study. Participants who complete at least 75% of the treatment sessions (6 out of 8 sessions) will be identified as treatment completers. We will examine the proportion of individuals who attend each session and the percent that adhere to recommended RR practice (defined as RR elicitation at least 3 days/week). For acceptability, response frequencies will summarize quantitative feedback on the 3RP-AYA Acceptability Questionnaire (Appendix 8.15). Together with qualitative feedback from the Exit Interviews (Appendix 8.29) and Expert Interviews (Appendix 8.30), this information will be used to inform the feasibility and acceptability of the intervention.

6.8.2 Exploratory Aim b) We will examine the preliminary effects of the intervention on psychosocial measures of fatigue, mindfulness, depressed mood, anxiety, and stress.

Preliminary outcome data may be used to inform future assessment instruments and methods. We may also conduct exploratory hypothesis testing to examine preliminary changes in our proposed intervention targets (changes in psychosocial outcomes, including mindfulness, depressed mood, anxiety, stress). A priori statistical tests of intervention-related changes will be planned for a future efficacy trial of this intervention.

First, we will examine the frequency distributions of all variables. Potential variables of interest (e.g., gender, history of RR practice) will be included as covariates if they are significantly correlated with each outcome of interest at $p < .25$. We will compare the baseline characteristics of completers vs. study non-completers. The primary analysis will be a completer analysis limited to those with complete data, and we will conduct a sensitivity analysis using multiple imputation for missing data.

First, we will examine between group differences in change scores in our exploratory psychosocial outcomes from enrollment (T0) to T1 (post-treament for IG, 3-months post-enrollment/baseline #2 for WG). To further explore preliminary efficacy, we will evaluate within-group change from pre- to post-intervention (using T0 to T1 data for the IG and T1 to T2 data for the WG) for each condition separately, and then for both groups combined. Finally, within the IG only, we will explore potential maintenance of intervention benefits with a repeated measures ANOVA, including the 3 survey timepoints.

Exit interviews (Appendix 8.29) will be audio-recorded and transcribed; NVIVO software will be utilized in the thematic analysis, which will be led by members of the study staff under the mentorship of Dr. Perez. Coders will meet on a weekly basis to discuss the coding framework, categories, and coding plan. To ensure coding reliability, coding discrepancies will be resolved through discussion and comparison of raw data. Coding will continue until a high level of reliability (Kappa= >0.80) is established.

Expert interviews (Appendix 8.30) will be audio-recorded and transcribed; rapid coding will be utilized in the thematic analysis, which will be led by members of the study staff under the mentorship of Dr. Perez. Coders will meet on a weekly basis to discuss the coding framework, categories, and coding plan. To ensure coding reliability, coding discrepancies will be resolved through discussion and comparison of raw data. Coding will continue until consensus has been reached.

6.8.3 Exploratory Aim c) To explore the feasibility and acceptability of collecting hair samples to examine changes in stress reactivity.

Feasibility and acceptability: Feasibility metrics for the hair sampling include hair return rates. For measures of acceptability, response frequencies will summarize quantitative feedback from question 13 on the 3RP-AYA Acceptability Questionnaire (Appendix 8.15) about the acceptability of hair collection procedures. Together with qualitative feedback from the Exit Interviews (Appendix 8.29), this information will be used to inform the feasibility and acceptability of hair cortisol measurement.. Hair cortisol samples will be analyzed by Dr. Jerrold Meyer's laboratory at the University of Massachusetts, Amherst.

Preliminary effects: We will examine group differences in HCC at T1 using independent samples T-tests. Pearson correlation or Spearman's rank correlation will examine the association of HCC with each of our psychological outcomes, controlling for potential confounders.

6.9 Handing of missing data in the analysis.

This study is intended to test the feasibility and acceptability of the stress management program. We will explore differences between study completers and non-completers on patient demographic and other relevant variables to inform the next phase of this trial. We will assess whether the mechanism of missing data is missing at random. We will perform sensitivity analysis using: 1) a completer analysis limited to those who have complete data and 2) multiple imputations for missing data.[60] To address missing data at follow-up, participants who are no longer interested in participating in the 3RP-AYA sessions will still be given the option to complete follow-up assessments.

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