DF/HCC Social-Behavioral Research Protocol

Promoting Resiliency Among Lymphoma Survivors: The 3RP-Lymphoma

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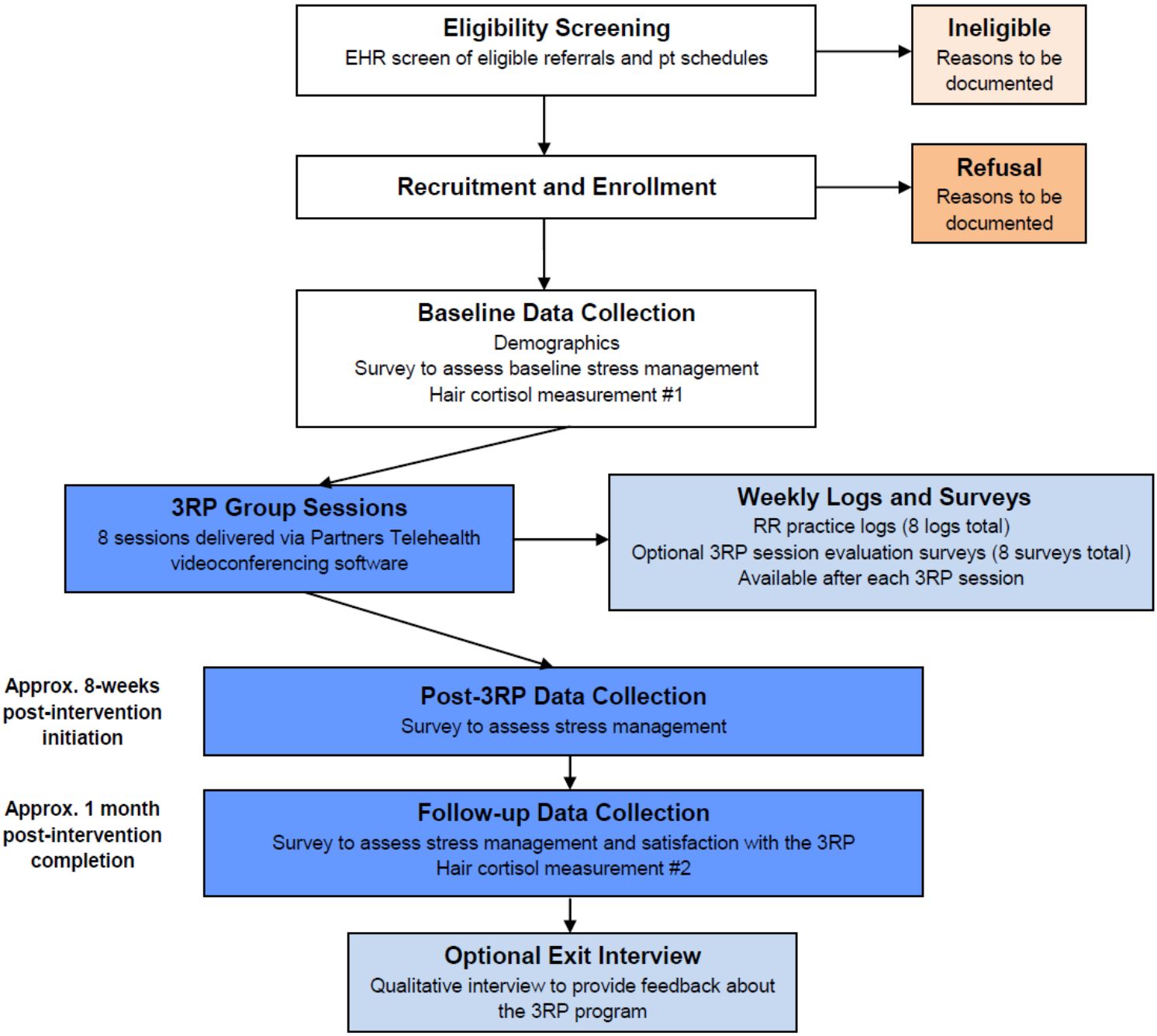
Section 1: Protocol Schema



Section 2: Body of protocol

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1.0 INTRODUCTION

1.1 Overview. Lymphoma survivors are a largely understudied and underserved group. Due to their cancer type and the invasive nature of their treatment, lymphoma survivors are at risk for chronic and persistent physical and psychosocial late effects of treatment. Stress associated with negative psychosocial experiences can contribute to long-term maladaptive health behaviors and lower quality of life. There are currently no targeted interventions that tackle the key transitional issues lymphoma survivors may grapple with following treatment completion. With funding support from an American Cancer Society (ACS) Institutional Research Grant (IRG), this study proposes to develop and pilot test a novel group program to reduce the deleterious effects of stress by promoting stress management and coping among lymphoma survivors. Using a 2-phase, mixed methods approach, we will modify an evidence-based multicomponent intervention, the Stress Management and Resiliency Training: Relaxation Response Resiliency Program (SMART 3RP),[1] to address the needs of lymphoma survivors who are within 2 years post-treatment completion.

This study protocol details study procedures for Phase 2 of this two-phase trial only. Phase 1 procedures are described in a separate protocol (DF/HCC 16-396). In Phase 1, we conducted up to 20 in-depth structured interviews with lymphoma survivors at the MGH Cancer Center who have completed treatment to explore: a) their preferences regarding program content, structure, delivery modality (Skype vs. phone), and intervention schedule (e.g., timing of the program, session length, number), and b) their preferences and needs for additional program content (e.g., treatment-related effects, coping with uncertainty, "reintegrating" into social networks). This phase included presenting the final program to two expert review panels, consisting of the MGH lymphoma clinicians and the MGH Cancer Outcomes Research Program (e.g., Drs. Jeffrey Peppercorn and Jennifer Temel) to further refine and optimize the intervention. Findings from Phase 1 guided the adaptation of the SMART 3RP program to be piloted among approximately 55 lymphoma survivors from the Massachusetts General Hospital (MGH) Cancer Center in Phase 2 of this trial, as described in this protocol. Phase 2 participants will be offered 8 weekly, virtually-delivered group 3RP sessions to test the feasibility, acceptability and preliminary effects of the adapted 3RP (via self-report surveys). We will also examine the feasibility, acceptability and preliminary effects of collecting and analyzing objective physiologic data (hair cortisol).

1.2 Background and Rationale. Lymphoma survivors are a largely understudied and underserved group. Although mortality rates continue to decline, lymphoma survivors are faced with a number of psychosocial and physical sequelae related to their cancer type and treatment that makes them susceptible to experiencing higher rates of distress compared to other survivor groups.[2] A prolonged recovery period marked by persistent physical and emotional symptoms, such as pain, fatigue, and fear of recurrence, has been evidenced to contribute to greater impairments in quality of life and survivorship experiences that uniquely differ from patients diagnosed with solid tumors.[2,3] In fact, rates of distress have been found to be as high as 31%, with chronic symptoms enduring for several years following treatment completion.[4,3] Despite their risks, few studies have explored the specific challenges that lymphoma survivors face in the post-treatment period; moreover, even fewer have explored the efficacy of targeted psychosocial treatments that may help reduce the distress that lymphoma survivors face during the transitional period from patient to survivor.[3,4] A recent qualitative study highlighted this service gap, describing survivors' concerns related to feeling disconnected from providers during the *reentry* period, feeling unprepared to cope with the unabating after effects that are unique to survivors of hematologic cancers, and lacking tailored resources and support to manage their distress.[4] This represents an important unaddressed factor contributing to cancer-related morbidity for an existing vulnerable population.

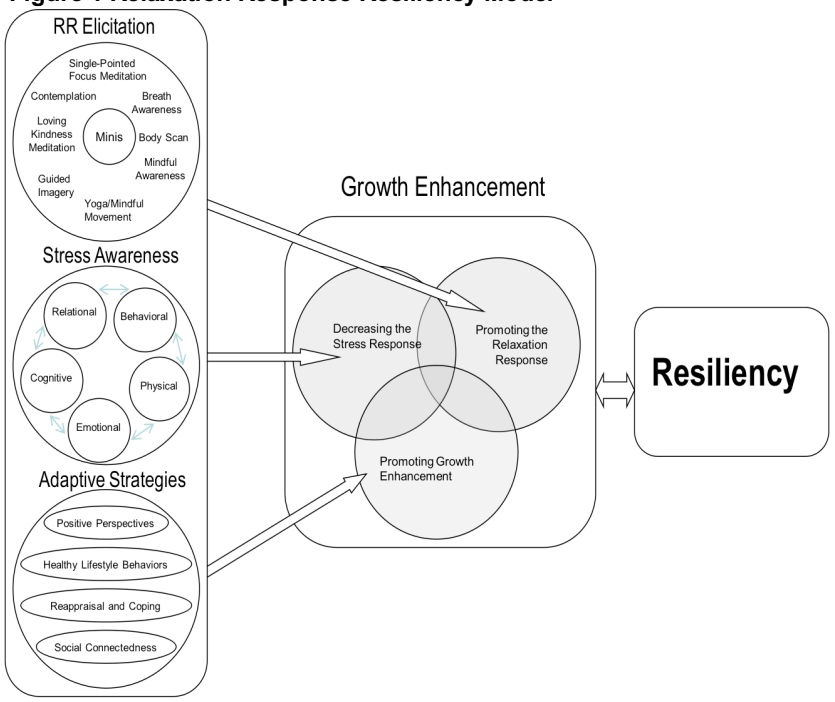
Stress can contribute to long-term maladaptive health behaviors and lower quality of life. Chronic stress leads to chronic activation of the HPA axis, which has been associated with decrements in immune functioning.[5,6] Indeed, stress has been consistently linked with increased risk for physical disease among the general population as well as, in many cases, poorer response to medical treatment among patients.[7,8] Stress has also

been linked to a variety of maladaptive health behaviors, including drinking, lack of physical activity, smoking, and substance use among survivors.[9,10] These findings are disconcerting, since engaging in risky behaviors can have harmful consequences for lymphoma survivors, placing this population at greater risk of cancer-related morbidity, impairment, and early mortality. Stress can also exacerbate many of the post-treatment symptoms lymphoma survivors experience, including pain, fatigue, and sleep difficulties.[11]

Mind-body programs centered on the relaxation response (RR) may be efficacious in mitigating the negative effects of stress. A converse to the stress response, the relaxation response is a physiological state characterized by decreased arousal of the sympathetic nervous system.[12] Randomized-controlled trials have found that elicitation of the RR may reduce adrenergic end-organ responsivity, suggesting that individuals eliciting the RR may be less responsive to stress.[13, 14] The Relaxation Response Resiliency Program (3RP[1]), a comprehensive, multimodal mind-body program developed by researchers at the Massachusetts General Hospital, is rooted in the elicitation of the relaxation response and was designed to promote adaptation to stress and enhance resiliency.[1]

Few studies have examined the utility of interventions, particularly mind-body resiliency programs, which focus on helping lymphoma survivors manage the psychosocial stressors associated with early survivorship. Existing interventions with survivor populations have successfully incorporated mind-body approaches, such as imagery, relaxation, and yoga, and have been illustrated to improve symptoms of distress,[15] fatigue,[16] and sleep disturbance; however, few have been carried out with lymphoma survivors.[2,17] Interventions targeting lymphoma patients have been primarily introduced during the time of cancer diagnosis and treatment.[3] Few, if any target the specific concerns that lymphoma patients may grapple with during the *re-entry* period.[3,4] Existing survivorship-based interventions have largely focused on breast cancer survivors, a population whose experience may not adequately generalize to patients treated for hematologic malignancies.[4] As such, this study proposes to pilot test a highly scalable virtual group program to mitigate the deleterious effects of stress by promoting stress management and coping among lymphoma survivors transitioning off treatment.

Figure 1 Relaxation Response Resiliency Model



Intervention Schematic: The 3RP (see Figure 1). Dr. Park (primary mentor) and colleagues at the Benson-Henry Institute for Mind Body Medicine (BHI) developed the *3RP[1] 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 3RP,[1] 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.

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,[18] insomnia,[19] infertility,[20] and other medical symptoms.[21] Recently, Drs. Park and Perez adapted the 3RP and conducted an NCI-funded pilot with 28 cancer interpreters.[22] 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).

Using information gained from qualitative interviews with lymphoma survivors conducted during Phase 1 of this trial (DF/HCC 16-396), we adapted the 3RP to target the needs of lymphoma survivors transitioning off treatment. In addition, Phase 1 interview participants endorsed hair cortisol as an acceptable method of cortisol sampling and expressed that they would be interested in providing hair samples to learn more about their change in stress levels. As such, we have included hair cortisol measurement as an optional portion of this Phase 2 study.

Significance and Innovation: The proposed program is unique in many ways**:** 1) It targets a group of survivors who are at high risk for negative psychosocial outcomes and for whom there is a paucity of targeted treatments; 2) It tests a unique, evidence-based treatment that is patient-centered in its development and delivery; 3) It offers a treatment modality (i.e., mind-body approach) that is widely accepted and used by survivors;[23,24] and 4) It offers a virtual delivery platform that may appeal to a population whose symptoms (e.g., chronic fatigue) may pose an obstacle to accessing support services.

2.0 OBJECTIVES

Primary aim:

a) We will conduct a single-arm feasibility trial to examine the feasibility and acceptability of delivering a group-based stress-management program delivered via videoconference technology for approximately 55 lymphoma survivors who are less than 2 years post-treatment. Specifically, we will assess whether a virtually-delivered, 8-week resiliency group intervention for survivors of lymphoma cancers is: **a1) Feasible** (assessed by evaluating recruitment and enrollment rates, adherence to session and relaxation response (RR) practice) and **a2) Well accepted** (defined by program satisfaction, ease and utility).

Secondary aims:

b) We will explore the feasibility and acceptability of collecting hair samples to examine intervention-related changes in cortisol, a stress biomarker.

c) We will examine the preliminary effects of the intervention on psychosocial measures of fatigue, mindfulness, depressed mood, anxiety, and stress. (exploratory)

3.0 RESEARCH SUBJECT SELECTION

Participants: Eligible subjects will include individuals who are 1) aged 18-64 2) within 2 years post-treatment completion for lymphoma 3) English speaking, and 4) able and willing to provide informed consent.

Subjects must also have received their cancer care or follow-up at the MGH Cancer Center. Patients will not be eligible if they are experiencing significant cognitive impairments, dementia, or are considered medically, psychiatrically, or otherwise unable to participate by their oncology provider or the principal investigator. Individuals who participated in qualitative interviews during Phase 1 of the study (DF/HCC 16-396) will not be eligible to participate in this phase of the research (Phase 2). Additionally, participants will be ineligible if they are unwilling or unable to participate in group 3RP sessions delivered online via Partners Health Care Telehealth Services videoconferencing software.

Rationale for eligibility criteria: Although we acknowledge the potential heterogeneity that may be present in defining this age range for this cohort, there is evidence that this group of survivors shares similar emotional and physical struggles that differ from the challenges faced by older survivors.[3] The topics addressed in the 3RP-Lymphoma program are tailored to the needs of survivors in the 18-64 age range, as participants in the qualitative interviews during Phase 1 (DF/HCC 16-396) were ages 18-64. The 2-year window for treatment completion is consistent with time frames used to define the "early survivorship" period.[25,26] Further, this period has been linked to higher rates of distress and greater transitional concerns.[2-4] Only patients with proficiency in English will be eligible to participate, as the existing 3RP program has not yet been translated into other languages. Though future work may examine the utility of this program among survivors who speak other primary languages, we have chosen to include patients who speak English due to the breadth and exploratory nature of this pilot. Phase 1 participants (DF/HCC 16-396) are ineligible for Phase 2, as the 3RP program was tailored based on the feedback they provided during the qualitative interviews. Therefore, the inclusion of Phase 1 participants would confound the generalizability of Phase 2 results. Also, given our intentions to deliver this intervention via videoconference technology (i.e., Partners Telehealth), patients who are unwilling or unable to participate in the 3RP sessions 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.

Inclusion Criteria	Exclusion Criteria
Ages 18-64	Unwilling or unable to participate in the study
Within 2 years post-treatment completion for lymphoma	Unable to speak or read English
Cancer treatment or follow-up for lymphoma at the MGH Cancer Center	Is medically, psychiatrically, or otherwise unable to participate (as determined by a physician or study PI)
	Unwilling or unable to participate in group 3RP sessions delivered via the Partners Telehealth videoconferencing software
	Participation in qualitative interview during Phase 1 (DF/HCC 16-396)

4.0 RESEARCH SUBJECT ENTRY

4.1 Recruitment

We will use a multi-modal approach to identify and recruit patients for this study. Participants may learn about the study through flyers (Appendix 8.10) placed throughout the cancer center or by provider referral (i.e., providers may reach out to study staff to refer patients who may be interested in participating); interested participants may choose to contact the study directly to inquire about participation. Additionally, study staff will review outpatient clinic schedules or patient lists to identify potentially eligible patients. Prior to contacting potential participants identified via screening, the patient's primary treating oncologist will be

contacted to inform them that we plan to approach the patient for study participation and to inquire about any concerns regarding study participation. If clinicians have specific concerns about the appropriateness of enrolling a particular patient, we will not contact that patient.

A member of the study staff will reach out to eligible patients utilizing our study script (Appendix 8.12) and any of three methods: by approaching patients at an upcoming clinic visit, by phone outreach, and/or by recruitment letter co-signed by a lymphoma clinic physician and the study PI (see Appendix 8.11). Information on potentially eligible and enrolled patients will be kept under lock and key or in password protected documents maintained on an access-restricted computer drive accessible only by study staff.

4.2 Enrollment

A member of the study staff will screen all interested participants by phone or at in-clinic approach to confirm study eligibility, explain the purpose of the study and study procedures as well as answer any questions; if they meet study criteria, they will complete the informed consent process. Patients who are within 2 years of completing treatment for lymphoma 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. Informed consent will be obtained by a bachelor's level trained Research Assistant (RA), the Principal Investigator, or a Co-Investigator, either in-person, or via mail correspondence, in accordance with patient preferences and availability, prior to completion of any study measures. Patients who would like more time to consider participation at in-clinic approach are able to take the forms home with them to review and mail back if interested. Patients who are recruited via opt out letter (Appendix 8.11) and phone outreach can also elect to conduct the entire enrollment process via mail correspondence; 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. Patients will be provided with study staff contact information if any questions or concerns regarding the research arise. The consent form will specify that this 3RP intervention is psycho-educational in nature and is not clinical care. In addition, special attention will be given to the implications of receiving an intervention online via Partners Health Care Telehealth Services. Subjects 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. Participants will also be advised to wear headphones and sit in a quiet place during the 3RP sessions to protect their own, and other group members', privacy. Participants will also be informed that they will complete a brief test call with a study staff member using the videoconferencing software in order to ensure proficiency with the software. Subjects who are found to be unable to use the videoconferencing software during the brief test call will be considered ineligible for the study.

4.3 Registration: 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.

5.0 STUDY DESIGN AND METHODS

5.1 Design / Study Type

This is a single-arm feasibility trial to examine the feasibility and acceptability of the 3RP among approximately 55 lymphoma survivors who are less than 2 years post-treatment. Participants who sign informed consent but who are found to be ineligible during the brief test call; those who do not complete any study

measures; and those who withdraw or are removed from the study prior to participating in any 3RP group sessions will not be counted towards the accrual goal of 55 participants. As such, up to 55 participants may be enrolled in the study in order to allow approximately 40 patients to participate in the 3RP. We will keep a detailed log of these instances, as this will inform the feasibility of the study. Participants do not need to complete every study measure to be counted towards the 55 accrual goal (participants who only complete some measures/3RP sessions will still be counted towards the accrual goal); however, patients who do not complete any of the study measures or who do not participate in any 3RP sessions will not be counted towards this goal.

All patients, regardless of whether they are counted towards the 55 accrual goal, will be included in the feasibility assessment. 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, 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 reasons for non-completion.

5.2 Selection of Instruments

Demographic factors: These include self-reported information about participants' race, ethnicity, education, religion, relationship status, children and caregiving responsibilities, employment status, health insurance, and annual household income. It is estimated that these questions (Appendix 8.1) will take approximately 1-3 minutes to complete.

PRIMARY OUTCOMES

3RP Feasibility and Acceptability data will be collected electronically (via REDCap), on paper, or by phone:

- **Feasibility:** 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 8.3). 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 one-month follow up data collection period with five questions on the 3RP acceptability questionnaire (Appendix 8.5) 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.

SECONDARY OUTCOMES

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 another 3RP study Dr. Perez is involved in (Partners IRB Protocol #: 2016P001622). Hair grows roughly 1cm/month, thus ensuring sufficient growth for collection. The RA will mail detailed sampling instructions (Appendix 8.8) and stamped, addressed envelopes to facilitate returns. Participants will be instructed to provide one hair sample at baseline and one sample at the one-month follow-up. 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 affects the feasibility and acceptability of hair cortisol analysis.

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 2 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. Hair cortisol collection was endorsed as an acceptable sampling method by participants interviewed during in Phase 1 of this study. **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.

Psychosocial Measures (EXPLORATORY OUTCOMES): The following self-report measures (Appendix 8.2) will be administered during baseline, post-3RP, and follow-up data collection periods. It is estimated that these measures will take approximately 30-35 minutes to complete.

- Distress Tolerance Scale (DTS): The DTS is a validated, 15-item measure of emotional distress tolerance. Items are rated on a 5-point Likert scale (5=Strongly disagree to 1=Strongly agree), with higher scores corresponding to greater levels of distress tolerance.[33]
- Measure of Current Status – Part A (MOCS-A): The MOCS-A is a 13-item self-report measure of perceived ability to cope with stress. Each item lists a technique for dealing with daily stressors, with responses ranging from 0 (I cannot do this at all) to 4 (I can do this extremely well). The MOCS-A has

been successfully used to document change in participants' ability to decrease the stress response, another element of the 3RP model.[34-36]

- Center for the Epidemiological Studies of Depression Short Form (CES-D-10): The CES-D-10 is a reliable, 10-item questionnaire that assesses depression symptoms during the past week. Response options range from 0 to 3 for each item (0 = Rarely or None of the Time, 1 = Some or Little of the Time, 2 = Moderately or Much of the time, 3 = Most or Almost All the Time). The CES-D-10 is commonly used in research, and it has been previously used to measure depression in cancer patient populations.[37,38]
- Cognitive and Affective Mindfulness Scale – Revised (CAMS-R): The CAMS-R is a 12-item self-report measure of daily mindfulness. It assesses the degree to which patients experience their thoughts and feelings. Statements are rated from 1=Rarely/Not at all to 4=Almost always. Scores range from 12-48; higher scores reflect higher levels of mindfulness. The CAMS-R has demonstrated reliability and validity, and it reflects the promoting growth enhancement component of the 3RP.[39]
- Assessment of Survivor Concerns Scale (ASC): The ASC is a validated self-administered questionnaire that measures fears about cancer recurrence and health in cancer survivors. Response options range from 1 to 4 for each item (1=Not at all, 2=A little bit, 3=Somewhat, 4=Very much). The ASC is brief, consisting of only 6 items, and has been used in previous studies with cancer populations. One item in the scale was adapted to: "I worry about my children's [or family members'] health" to capture participants' degree of health worry about other family members in addition to children.[40-42]
- Mishel Uncertainty in Illness Scale Community Sample (MUIS-C): We use a 5-item portion of the Mishel Uncertainty in Illness Scale intended for use among community-dwelling adults with chronic illness. The MUIS-C has been adapted from the MUIS-A, a validated, 33-item questionnaire developed to measure the role of uncertainty as a variable in influencing one's experiences as a patient during illness and treatment. Statements are rated from 1 ("Strongly Disagree") to 5 ("Strongly Agree"), on items such as "Because of the unpredictability of my illness, I cannot plan for the future."[43,44]
- Fatigue Symptom Inventory (FSI): The FSI is a 14-item self-report measure which assesses the severity, frequency, and daily pattern of fatigue as well as its perceived interference with quality of life. Severity is measured on an 11-point scale (0=not at all fatigued; 10=as fatigued as I could be). Frequency is measured as the number of days in the past week (0-7) that respondents felt fatigued and the extent of their fatigue on those days (0=none of the day; 10=the entire day). Perceived fatigue interference is rated in 7 different domains (e.g., ability to bathe and dress, normal work activity, ability to concentrate) on 11-point scales (0=no interference; 10=extreme interference). The FSI has been used extensively to assess fatigue in a number of clinical populations, including cancer patients.[45,46]
- Life Orientation Test – Revised (LOT-R): The LOT-R is a 10-item questionnaire that assesses the degree of generalized optimism vs. pessimism. It is frequently used in health-related settings, including in previous studies with cancer patients. Responses are rated from 0=strongly disagree to 4=strongly agree on items such as "In uncertain times, I usually expect the best."[47,48]
- Pittsburgh Sleep Quality Index (PSQI): The PSQI is a validated and reliable 4-item questionnaire that measures sleep quality and disturbance over the past month. Items ask about usual hours of sleep, bed time, wake time, and overall sleep quality.[49,50]
- Visual Analogue Scale 0-10: We are using 3 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, and level of distress. The Visual Analogue Scale is a standard measure used in the 3RP program.

- Generalized Anxiety Disorder 7-item scale (GAD-7): The GAD-7 is a validated brief measure for assessing Generalized Anxiety Disorder. Items are scored from 0 (not at all) to 3 (nearly every day), with total scores ranging from 0-21. It is frequently used in research and clinical practice, and it has previously been used to measure anxiety in cancer patient populations.[51-53]

- Intolerance of Uncertainty Scale – Short Form (IUS-12): We use the IUS-12, a validated 12-item short form of the 27-item Intolerance of Uncertainty Scale, which is the most frequently used measure of intolerance of uncertainty. The IUS-12 contains items such as "Uncertainty keeps me from living a full life" and "The smallest doubt can stop me from acting." Response options range from 1=Not at all characteristic of me to 5=Entirely characteristic of me.[54,55]

- General Self-Efficacy Scale (GSE): The GSE is a validated 10-item measure of perceived self-efficacy that aims to predict coping with daily hassles and adaptation after experiencing stressful life events. Responses are measured on a 4-point scale (1=Not at all true; 4=Exactly true) on items such as "I can remain calm when facing difficulties because I can rely on my coping abilities." Responses are summed, and final composite scores range from 10-40. The scale has previously been used to assess self-efficacy in cancer patient populations.[56-58]

3RP Session Evaluation Surveys: Session feedback (Appendix 8.4) will be collected electronically (via REDCap) following each 3RP session by asking patients to rate the extent to which they found the session content to be 1) enjoyable, 2) helpful, and 3) relevant, using Likert-type scale responses from 1=Not at all [enjoyable] to 4=Very [enjoyable]. Participants may also provide open-ended responses about the elements of each session which they liked and disliked, and they may also provide suggestions or recommendations for changes to the session. It is estimated that the surveys will take approximately 3-5 minutes to complete. Participants will be informed that these surveys are optional and that we will use the survey responses when making further modifications to the 3RP-Lymphoma program in the future.

Health Services Utilization Questionnaire: Health care utilization will be assessed with four self-report items (Appendix 8.6) at Baseline, Post-3RP, and 1-month follow-up. Questions will ask participants about the number of 1) calls and 2) unplanned visits made with the oncology care team, and 3) calls and 4) unplanned visits made with any other provider because of a cancer-related concern over the past month. In discussions with the MGH Lymphoma clinicians, health care utilization was identified as an important exploratory outcome measure for the intervention. It is estimated that these items will take approximately 1-3 minutes to complete.

Qualitative Exit Interviews: Before they exit the study, participants will be invited to participate in one-on-one exit interviews (Appendix 8.7), delivered over the phone, in-person at MGH, or via Partners Telehealth videoconferencing, to explore additional barriers or facilitators to study participation, treatment adherence, and study completion. They will be asked more detailed information about perceptions of the treatment and preferences for further adaptation after having participated in the program. We will also qualitatively explore survivors' preferences for other potential behavioral intervention modalities, such as the use of text-messaging, social media, and other web-based interventions. These interviews will be audiotaped and qualitatively analyzed for themes which will help determine whether treatment modifications are needed in future work. It is estimated that the interviews will take approximately 20 minutes to complete. Participants will be informed that the qualitative exit interviews are an optional portion of the study.

5.3 Description of the Intervention

In Phase 1 of this study (DF/HCC 16-396), qualitative interviews were conducted with up to 20 lymphoma survivors who were less than 2 years post-treatment completion to explore their needs for additional

program content (e.g., treatment-related effects, coping with uncertainty, "reintegrating" into social networks). Phase I participants reported loss of support after treatment completion, fear of cancer recurrence or a new type of cancer, and lack of opportunities to meet other survivors of a similar age as significant areas of concern. Participants endorsed that a group program with other survivors would be helpful, and they also believed that RR techniques could help them cope with uncertainty and loss of support after treatment completion, providing support that the 3RP would meet these survivors' unmet needs. Participants also expressed a desire to gain information about the ways in which stress, nutrition, sleep, and exercise affect the body, particularly in relation to cancer. As such, we have incorporated additional information on these topics specific to cancer survivors into the 3RP sessions manual. In addition, participants endorsed hair cortisol as an acceptable method of cortisol sampling and expressed that they would be interested in providing hair samples to learn more about their change in stress levels.

The 3RP will thus 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 8.3) to record RR adherence. Participants will receive the 3RP patient manual, which describes the content of the 3RP sessions, and RR-based guided meditation CDs or audio files to help them elicit the RR at home each day. The CDs 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 include coping logs that provide examples drawn from common transitional challenges identified by survivors in the Phase 1 interviews, which will facilitate discussion and practice of restructuring and positive reframing techniques. Lastly, social and educational topics identified in Phase 1 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 outreach and connection). At the end of each session, the interventionist will complete a process form indicating the length, location and content of the session. 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 8.9.

5.4 Data Collection and Storage.

Prior to study enrollment, study data will be collected via medical record review 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 1-Month Follow-Up
Date of birth	x				
Gender	x				
Languages spoken	x				
Cancer diagnosis	x				
Date of diagnosis	x				

Data	At Screening	At Baseline	At 3RP	At Post-3RP	At 1-Month Follow-Up
Treatment type(s)	x				
Date of treatment completion	x				
Demographic factors		x			
Psychosocial measures:					
Distress Tolerance Scale (DTS)		x		x	x
Measure of Current Status Part A (MOCS-A)		x		x	x
Center for the Epidemiological Studies of Depression Short Form (CES-D-10)		x		x	x
Cognitive and Affective Mindfulness Scale – Revised (CAMS-R)		x		x	x
Assessment of Survivor Concerns Scale (ASC)		x		x	x
Mishel Uncertainty in Illness Scale Community Sample (MUIS-C)		x		x	x
Fatigue Symptom Inventory (FSI)		x		x	x
Life Orientation Test – Revised (LOT-R)		x		x	x
Pittsburgh Sleep Quality Index (PSQI)		x		x	x
Visual Analogue Scale 0-10		x		x	x
Generalized Anxiety Disorder 7-item scale (GAD-7)		x		x	x
Intolerance of Uncertainty Scale – Short Form (IUS-12)		x		x	x
General Self-Efficacy Scale (GSE)		x		x	x
Hair cortisol measurement		x			x
Health services utilization questionnaire		x		x	x
3RP acceptability questionnaire					x
3RP session evaluation surveys			x		
Weekly RR practice logs			x		

To safeguard participant information and confidentiality, all data will be stored in locked cabinets at MGH as well as in password-protected computer files, accessible only to trained and IRB-approved study staff. 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. Transcripts of all exit 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. Audio-

records of these interviews will be uploaded to our study access-restricted drive. Interviews will either transcribed by research study staff or be sent securely and transcribed by transcribeme.com.

5.5 Description of Study Process

5.5.1 Instrument Administration

The Baseline, Post-3RP, and Follow-up 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, or complete them with a member of study staff over the phone or in clinic. Participants may complete the Baseline questionnaire approximately 1-3 weeks prior to the first 3RP session. Participants who have not completed the baseline questionnaire at 1 week prior to the first 3RP session will be instructed by study staff to complete it as soon as possible. The Post-3RP questionnaire may be completed up to approximately 2 weeks after the final 3RP session, and the Follow-up questionnaire may be completed approximately 4-6 weeks after the final 3RP session.

After each weekly 3RP session, a 3RP session evaluation survey will be sent electronically via REDCap to each participant's preferred email address. Participants may choose whether to complete the survey to provide feedback on the 3RP session. In addition, as part of the standard 3RP program, participants will be asked to complete weekly RR practice logs (Appendix 8.3) to record their RR elicitation throughout the week. These will be completed online via REDCap survey or on paper.

Hair Cortisol: Similar to other studies which have utilized hair sample collection for cortisol measurement (Partners IRB Protocol#: 2016P001622), 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 8.8) and stamped, addressed envelopes to facilitate mailing. 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 baseline and one-month follow-up (1-3 weeks prior to the first 3RP session and 4-6 weeks after the final 3RP session, respectively). Participants will also be provided with the Hair Cortisol Results Form (Appendix 8.14), which will give participants the option to receive the results of their hair cortisol levels via a phone conversation with the study PI, which will be scheduled after the completion of the 1 month follow-up.

Qualitative exit interview: After completion of the one month follow-up survey, a member of the study staff will contact participants to see if they would like to complete a qualitative exit interview to provide feedback on the 3RP program and study procedures. Interviews may be conducted via phone, Partners Telehealth videoconferencing software, or in-person at MGH, according to patient preferences and availability. A member of the study team trained in qualitative interviewing will facilitate the interviews in-person, via telephone or Skype using a semi-structured interview guide with open-ended questions and response probes (see Appendix 8.7), and they will last approximately 20 minutes. All interviews will be audio-recorded; study staff will ask for permission to turn on the audio-recorder prior to beginning each interview.

5.5.2 Intervention Administration

The 3RP 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 and is experienced in conducting the 3RP (e.g. clinical psychologists, fellows, post-docs). The 3RP consists of eight, 1.5 hour weekly RR-training group sessions conducted over the course of approximately 8 weeks, and there will be approximately 6 patients per group. The topics addressed in the eight 3RP sessions are listed in Appendix 8.9. Prior to the first 3RP session, participants may have the option to complete a brief, approximately 10-minute

initial visit with a 3RP provider over the phone, via Partners Telehealth videoconferencing software, or in-person at MGH, in accordance with patient and provider availability. The purpose of the initial session is to identify participants' goals for the program. Additionally, as described in protocol section 4.2, in order to facilitate proficiency with the Telemedicine software, participants will test the software with a study staff member during a brief test call prior to the start of the intervention.

5.5.3 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 weekly 3RP Session Evaluation Surveys or a qualitative exit interview for the study; these components of the study will be considered optional.

5.5.4 Compensation.

Subjects will receive $10 in remuneration for completion of the baseline survey, and $15 in remuneration for completion of the post-3RP and follow-up surveys (up to $45 total). Participants will receive $15 in remuneration for completion of the baseline and follow-up hair sample(s) (up to $30 total). As required for compliance with Partners Healthcare remuneration policy, we will collect participants' contact information (see Remuneration Form in Appendix 8.13).

5.6 Adverse Reactions and Their Management

5.6.1 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.

5.6.2 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 or interview questions that they find upsetting or uncomfortable. We also aim to reduce participant burden by allowing for the option to complete interviews via the phone or Partner's Telehealth videoconferencing software.

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.

As described in section 4.2 of the protocol, 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.

5.6.3 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 among approximately 55 lymphoma survivors who are less than 2 years post-treatment using descriptive analyses.

6.1 Primary and secondary endpoints.

The primary study endpoints are the feasibility and acceptability of the program for lymphoma survivors who are within 2 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 an open pilot 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] We consider a 75% session completion rate as a threshold for establishing intervention feasibility. With a sample size of 30 for the 3RP-Lymphoma, 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 55 will be sufficient to answer our questions about feasibility and acceptability.

6.3 Stratification factors and intervention allocation plan for randomized studies. N/A

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.

Aim a) To examine the feasibility and acceptability of a group-based, stress-management and resiliency intervention delivered via videoconferencing technology for lymphoma survivors who are within 2 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 as well as the percent who adhered to recommended relaxation practice (defined as RR

elicitation at least 3 days/week, as measured by the RR practice logs (Appendix 8.3). For acceptability, response frequencies will summarize quantitative feedback on the 3RP Acceptability Questionnaire (Appendix 8.5).

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

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 Acceptability Questionnaire (Appendix 8.5) about the acceptability of hair collection procedures. Together with qualitative feedback from the Exit Interviews (Appendix 8.7), 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. Pearson correlation or Spearman's rank correlation will be used to examine the association of hair cortisol with each of our exploratory psychosocial outcomes.

Exploratory Aim c) 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 fatigue, mindfulness, depressed mood, anxiety, stress). A priori statistical tests of intervention-related changes will be planned for a future efficacy trial of this intervention. We will compare baseline demographic and clinical characteristics between completers and non-completers using chi square tests and t-tests. Paired samples T-tests will be used to examine pre and post-intervention differences (T2 vs T1) at $p<.05$ for each of our exploratory outcomes (e.g. CAMS-R). We will also assess the sustained effects of treatment with a repeated measures ANOVA analysis, including the 3 survey time points. This analysis will allow us to assess if there is a trend towards maintenance of treatment effects but is not powered to detect significant differences.

Exit interviews (Appendix 8.7) will be audio-recorded and transcribed; NVIVO software will be utilized in the thematic analysis, which will be led by Dr. Perez and the study RA under the mentorship of Dr. Park, who directs the Qualitative Research Core at MGH. Dr. Perez and the study RA 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.

6.9 Handing of missing data in the analysis.

This phase of the 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 sessions will still be given the option to complete follow-up assessments.

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