PROTOCOL TITLE:

Building Resiliency Among Caregivers of Curvivors and Metavivors: A Pilot Randomized Trial

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1.0 Objectives

This is a randomized controlled trial assessing an evidence-based mind-body group resiliency treatment, the Stress Management and Resiliency Training-Relaxation Response Program (SMART-3RP) to intervene on 58 caregivers and cancer survivor dyads with the following aims:

Aim 1. To determine the feasibility and acceptability of the SMART-3RP for cancer caregivers and survivors. Feasibility will be assessed by the percent of survivor/ caregivers who are eligible and enroll, complete the follow-up survey, and intervention session attendance. Acceptability will be assessed by intervention satisfaction (e.g., structure, delivery and content) reported via the follow-up survey and exit interview. *Hypothesis 1a*: We hypothesize: > 45% enrollment of eligible participants, >70% completion of 3-month follow-up survey, and >70% complete 6/9 intervention sessions (intake + 8 sessions). *Hypothesis 2a:* We hypothesize >75% satisfaction (4/5) with the study intervention. **Aim 1b. We will also examine the feasibility** and acceptability of collecting hair samples to examine intervention-related changes in cortisol, a stress biomarker.

Aim 2. To determine the preliminary efficacy of the SMART-3RP for improving resiliency in caregivers and survivors. *Hypothesis:* Caregivers and survivors randomized to SMART-3RP will demonstrate greater improvements in resiliency compared to those randomized to enhanced usual care (online support groups). Secondary outcomes include (a) caregiver and survivor stress management and growth enhancement processes and (b) biobehavioral assessment of chronic stress (hair cortisol).

Aim 3: To explore effects of SMART-3RP on caregivers' and survivors' health care utilization (e.g., hospitalizations, ED visits, surveillance, preventive services, and mental healthcare services).

2.0 Background

2.1 Overview

Caregivers of cancer survivors experience chronic, ongoing stress which affects their emotional and physical health. Caregivers of cancer survivors experience chronic ongoing stress that spans the survivorship continuum. When unmanaged, this chronic stress leads to substantial emotional distress as caregivers help patients navigate the physical and psychological toll of the patient's illness.[1] Caregivers for cancer survivors report unaddressed needs (e.g., psychosocial, medical, financial),[2] in particular multiple unmet psychological needs (e.g., anxiety, distress)[3, 4] extending years following a patient's diagnosis.[5] Furthermore, caregivers of cancer survivors report low levels of resilience, which contribute to difficulties managing stress; this leads to high caregiver burden and low quality of life.[6] These chronic caregiving roles may lead to worsening physical health,[7, 8] placing them at risk for morbidity.[9] While the majority of caregivers of cancer survivors report a willingness to accept psychological support, treatments to address the

needs of this population are lacking.[3] *We propose a novel, virtual group intervention to intervene upon caregiver resiliency and emotional distress.*

A growing number of cancer "curvivors" and "metavivors" has resulted in a growing population of caregivers who face ongoing stressors- irrespective of cancer diagnosis. With advances in early detection and cancer treatments, there is a growing population of cancer survivors who have completed curative therapy (i.e., curvivors). Similarly, targeted therapies and immunotherapy have revolutionized cancer care leading to a growing population of cancer survivors who live for many years with metastatic disease (i.e., metavivors). While metavivors is a term initially coined in describing survivors living with metastatic breast cancer, the advances in oncological therapies have created a rapidly growing population of metavivors across cancer diagnoses. Caregivers of curvivors and metavivors face similar ongoing challenges, such as fear of cancer recurrence/ progression, addressing treatment toxicities and late effects, emotional and financial distress.[10, 11] The immense unmet needs of caregivers of curvivors and metavivors have been described across the continuum of survivorship, irrespective of cancer type. *We propose fill the critical need to support these caregivers.*

Caregivers' and survivors' stress regulation and distress are often related. There is increasing recognition regarding the importance of reciprocal dynamics between patient and caregiver distress, underscoring the importance of addressing needs among caregivers and patients to improve health outcomes.[12] Patient distress is associated with poor caregiver health and vice versa.[13, 14] Similarly, stress regulation among cancer survivors and their caregivers is interdependent,[15] and benefit finding (i.e., deriving a positive growth from cancer) experiences are also interdependent.[16] It is critical to attend, simultaneously, to the needs of caregivers and cancer survivors. *We propose to intervene simultaneously, yet separately, on caregivers and survivors.*

Chronic stress may affect caregivers' health through physiological mechanisms. Chronic stress can lead to the metabolic wear and tear described as allostatic load.[17] Chronic stress is associated with increased adrenergic activation and an increase in cortisol levels over time, which may be reduced through skills that elicit the Relaxation Response (RR) state. RR is a physiological state of decreased arousal of the sympathetic nervous system.[18-20] RR strategies are aimed at reducing muscle tension, breathing rate, heart rate, and blood pressure. Eliciting RR lessens the adverse physiological effects of stress.[19-21] Cortisol assessments provide a biobehavioral measure of chronic stress. *We will examine the biobehavioral effects of an RR-based intervention.*

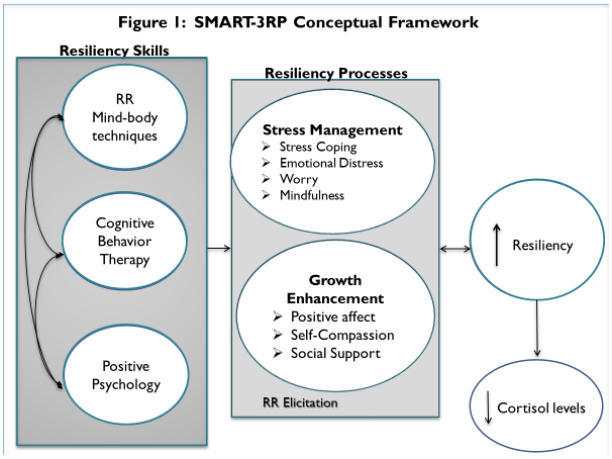
Emotional distress may affect caregivers' health due to deleterious healthcare utilization. Caregivers often have the responsibility of overseeing survivors' follow-up care and appropriate use of health care services, such as cancer screening, preventive services[22] and surveillance for late effects. Unmanaged emotional distress could result in underutilization of appropriate healthcare services or overutilization of ED or urgent care visits and hospitalizations. Caregivers are at risk for underutilizing appropriate healthcare

services,[23] including mental healthcare.[24] *We will assess the impact of our intervention on healthcare utilization.*

Resiliency skills leveraging growth enhancement can ameliorate the deleterious health effects of chronic stress. Resilience is often characterized as a *response to adversity*; specifically, it refers to a set of protective factors and resources within an individual and their environment that facilitate one's ability to "bounce back."[25-33] Resilience is demonstrated when one is able to maintain adaptive functioning when faced with ongoing chronic stress,[30, 34-37] as experienced by caregivers of curvivors and metavivors. Post-traumatic growth (i.e., positive changes that occur after a trauma) can occur among caregivers.[38-41] *Growth enhancement skills (i.e., skills focused on post-traumatic growth, a positive change that occurs after a trauma) can increase resiliency and ameliorate the deleterious health effects of chronic stress.*

Interventions are needed that simultaneously address the needs of caregivers and cancer survivors. Caregiver intervention studies have primarily focused on the impact of caregiving during active treatment or at the end of life in patients with advanced illness.[42-50] Few have addressed the chronic, unrelenting demands facing caregivers of cancer curvivors and metavivors during the survivorship phase of illness. Interventions conducted to support cancer survivors and caregivers have cognitive-behavioral therapy (CBT) skills [51] have yielded small effect sizes. Pilot studies explored the effects of mindfulness and positive psychology approaches for caregivers;[48, 52-54] but differ from the proposed study in terms of the targeted population, delivery time, delivery modality, and outcomes. *Resiliency interventions are critically needed that are delivered virtually, incorporate mind-body, CBT and positive psychology skills, and simultaneously address the needs of caregivers of curvivors and metavivors.*

Resiliency intervention conceptual framework. Our team has developed a resiliency intervention, the Stress Management and Resiliency Training: Relaxation Response Resiliency Program (SMART-3RP)[55] which has shown promising efficacy for improving resilience and reducing stress among individuals with a myriad of physical and psychological symptoms.[56] This framework (Figure 1) is informed by the diathesis-stress model,[57] which posits that resilience is the outcome of an individual's experiences and environment, in combination with one's coping ability. The SMART-3RP emphasizes the elicitation of the Relaxation Response (RR) as an internal physiological state that facilitates the effective use of coping skills to combat the deleterious effects of chronic stress. (1) Mind-body techniques promote elicitation of the RR through mind-body practices, such as meditation,



mindfulness, guided imagery, and contemplation. (2) CBT skills teach individuals to reappraise their thoughts, beliefs, and expectations about stressors to promote adaptive coping and to better manage stressors. This work is guided by Lazarus and Folkman's transactional model of stress and coping,[58] which suggests that the experience of stress depends on the interplay between the situation and a person's appraisal of it. (3) Positive psychology strategies focus on increasing positive affect, self-compassion, and connectedness to oneself and to others. This component is guided by a positive psychology[59] lens and post-traumatic growth perspective that stressful events can lead to greater personal growth.[60, 61] The resiliency processes that result are achieving RR state, stress management, and growth enhancement, which collectively build resiliency.

3.0 Inclusion and Exclusion Criteria

3.1. Screening Procedures

The study team will utilize an EHR-based screening algorithm to identify potentially eligible survivors, which we have utilized in MGH-based clinical and research programs. A dashboard of potentially eligible survivors will be generated from the EHR program. The research assistant (RA) will then review the survivors' EHR to ensure they meet the study eligibility criteria.

3.2. Eligibility Criteria.

Patient Eligibility Criteria
Patient Inclusion Criteria

1. English speaking adult patients with cancer (18 years or older)
2. Treated at MGH, who are either within approximately:
    - 3 months to 5 years after completing potentially curative therapy for cancer diagnosis including surgery, radiation, and/or chemotherapy or other novel therapies (e.g., immunotherapy, biological therapy). Patients can be on long-term maintenance hormonal or biological therapy at the time of enrollment.
    - 3 months after diagnosis of metastatic disease with an expected prognosis of >1 year as confirmed by the treating oncology clinician
3. Able to identify a caregiver (i.e., spouse/partner or patient-identified family member or friend) who is willing to participate in the study

Patient Exclusion Criteria:

1. Prognosis less than one year as determined by the treating oncology clinician
2. Active psychiatric or cognitive comorbidity that prohibits the capacity to provide informed consent as determined by the treating oncology clinician
3. Patients without a caregiver who is willing to participate
4. Patients enrolled in another supportive care trial

Caregiver Eligibility Criteria
Caregiver Inclusion Criteria:

1. English speaking adult caregiver (age 18 years or older)
2. Identified by the patient as the spouse/partner or family member/friend[62]

3.3. Special populations

We will not enroll the following special populations: adults unable to consent, individuals who are not yet adults, pregnant women, and prisoners.

4.0 Study-Wide Number of Subjects

This study will enroll 58 patient-caregiver dyads (n=116 total) from the MGH Cancer Center.

5.0 Study-Wide Recruitment Methods

Participants will be recruited through an EHR-based screening tool that uses a tailored algorithm to identify cancer survivors who have completed cancer treatment and metavivors who are on active therapy. The EHR-based algorithm has been previously used at MGH for clinical and research programs. The RA will review survivors identified through the EHR-based algorithm to ensure they meet study eligibility criteria. Additionally, participants will be recruited from referring oncology clinicians, local support groups, survivorship events, flyers posted in MGH Cancer Center clinics, and social media using IRB-approved flyers. Study staff will also submit a recruitment advertisement to the MGB Rally Recruitment Portal. Through this portal, interested and potentially eligible patients will be able to send their contact information to the study staff.

Once a potentially eligible patient-caregiver dyad is identified, the RA will then communicate with the oncology clinician (i.e., attending physician, or the advance practice provider) via email, through the electronic health record, or verbally to notify them that the patient is eligible for the study and inquire about any concerns regarding their participation. For metavivors, the RA will also ask the oncology clinician to confirm their eligibility for study participation using the surprise question "*Would you be surprised if this patient died within 12 months*" (Y/N)[63] and confirm an expected prognosis >12 months as well as confirm cognitive and psychiatric fitness to participate.

If the oncology clinicians have objections to their patients' or caregivers' participation in the study, we will document the reason and not approach those individuals. If the oncology clinicians have no objections, the RA will approach the potentially eligible patient-caregiver dyad and inform them that their oncology clinician have agreed for them to be contacted for the study and review the details the nature of all study procedures. The RA will also ask to send the patient a recruitment letter via Patient Gateway or email that provides an overview of the study and a link to an outreach informational video. The RA can approach the patient-caregiver dyad in-person during their oncology visit or over the telephone/video or mail and obtain verbal consent. Reasons for refusal and ineligibility will be documented. Eligible and interested survivors will be asked to identify a caregiver. If

eligible, the RA will review the study procedures with potential dyads and obtain verbal consent from each person.

We are requesting a Waiver of Written Documentation of Consent
This Waiver is being requested to assist with patient and caregiver recruitment. Our study meets the waiver requirements given our study is considered minimal risk and all study procedures could be conveyed orally. This waiver will reduce the risk to patients and caregivers who may not be coming regularly to the cancer center for their care and is necessary for our research procedures to continue.

We are requesting a HIPAA Waiver of Authorization to Review Preparatory to Research from the IRB. We are requesting this Waiver to identify potential patient participants from a minimal chart review. In accordance with the DF/HCC policy, this Waiver: (1) is being sought solely to review Protected Health Information as necessary to prepare a research protocol, (2) will not include removing Protected Health Information from the Covered Entity by the researcher, and (3) is necessary for the research purposes.

The RA will then administer the baseline questionnaire (detailed on section 9.1) in-person, online via REDCap, text, or by phone. If a patient-caregiver dyad signs the consent form but does not complete the baseline questionnaire within approximately 40 business days, they will neither be registered on the study nor count towards the accrual numbers. Participants who withdraw from the study or die during the study period will not be replaced and they will count towards the accrual numbers.

We will register eligible participants in the Clinical Trials Management System (CTMS) Oncore as required by DF/HCC SOP REGIST-101. Registration must occur prior to the initiation of protocol-specific procedures or assessments. For registration of patients, study staff will complete the DF/HCC protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. Study staff will confirm that the participant meets all inclusion criteria as described in this protocol and the criteria on the eligibility checklist.

Participants will be randomized to the SMART-3RP intervention or enhanced usual care using a computer-generated 1:1 randomization schema, stratified by survivor status (curvivor/metavivor). Patients who have completed the baseline survey will be assigned to treatment arm according to the randomization schema list.

6.0 Multi-Site Research

Not applicable since this is a single center study.

7.0 Study Timelines

Patient-caregiver dyads will remain on the study for approximately 6 months. Participants will be consented prior to randomization. Enrollment of all study subjects will occur over

approximately 12-15 months. It will take approximately two years to complete the primary analyses.

8.0 Study Endpoints

8.1. Primary study endpoint.

- To examine the feasibility of SMART-3RP for cancer caregivers and survivors (feasibility a priori defined in section 11.1)
- To examine the acceptability of SMART-3RP for cancer caregivers and survivors

8.2. Secondary endpoints.

- To determine the preliminary efficacy of SMART-3RP to improve resilience in cancer caregivers and survivors
- To determine the preliminary efficacy of SMART-3RP on improving stress management in cancer caregivers and survivors
- To determine the preliminary efficacy of SMART-3RP in promoting growth enhancement
- To determine the preliminary efficacy of SMART-3RP in reducing chronic stress (hair cortisol)

8.3. Exploratory endpoints.

- To compare hospitalizations between survivors receiving SMART-3RP versus enhanced usual care
- To compare urgent care and emergency department (ED) visits between survivors receiving SMART-3RP versus enhanced usual care
- To compare primary care visits between survivors receiving SMART-3RP versus enhanced usual care
- To explore use of mental health services (e.g., social work, psychiatry, psychology, and other mental health professionals, and support groups, occurring within and outside of MGH) and psychiatric medication between survivors receiving SMART-3RP versus enhanced usual care
- To compare hospitalizations between caregivers receiving SMART-3RP versus enhanced usual care
- To compare urgent care and ED visits between caregivers receiving SMART-3RP versus enhanced usual care
- To compare primary care visits between caregivers receiving SMART-3RP versus enhanced usual care
- To explore use of mental health services (social work, psychiatry, psychology, and other mental health professionals, and support groups, occurring within and outside of MGH), psychiatric medication between caregivers receiving SMART-3RP versus enhanced usual care

9.0 Procedures Involved

9.1. Study Design

This is a single site pilot randomized clinical trial of SMART-3RP versus enhanced usual care to simultaneously intervene with 58 caregiver and cancer survivor dyads (n=116) (Figure 1). Survivors and caregivers will be randomized together, stratified by survivor status (curvivor/metavivor), using a random plan generator with 1:1 randomization.

9.2. Study Intervention and Comparator

This pilot randomized controlled trial assesses the feasibility, acceptability, and efficacy of SMART-3RP for improving resiliency among caregivers and cancer survivors compared to enhanced usual care.

Intervention. The SMART-3RP has been created at the 8th grade reading level. [64] The intervention components include: 1. Eliciting the relaxation response (RR) involves sustained mental focus with an attitude of open receptive awareness. 2. CBT to improve stress management involves increasing awareness and identification of the components of one's stress response (negative thoughts, emotions, physical reactions, behaviors, and relational) and learning skills at each session to alter these components (e.g., cognitive restructuring). 3. Positive psychology strategies to achieve growth enhancement focus on utilizing techniques and skills to promote positive growth. Skills focus on increasing social support, positive affect, and compassion. Study interventionists trained in the SMART-3RP (e.g., participated in the Benson-Henry Institute for Mind Body Medicine SMART-3RP training program https://bensonhenryinstitute.org/training-apply-for-certification/ and/or co-facilitated a clinical SMART-3RP group within the MGH Cancer Center) will deliver the SMART-3RP via virtual HIPAA-compliant videoconferencing technology, Zoom, that is accessible via smartphone, laptop, tablet, desktop. The intervention consists of a group intake session and eight 1.5 hour sessions. The sessions will be conducted separately, with survivors and caregivers (n= approximately 8 per group). A recording link with the session's RR-elicitation method will be sent via REDCap after each session. The session content is detailed on Table 2. Participants may be sent reminders (e.g., emails and/or text messages, phone calls) to remind of them of the group time prior to each session. The RA may assist participants with teleconferencing software set up and may complete test calls to ensure proficiency with the software prior to the group initiation. The RA will be available to assist with any questions. Participants will also be sent a link via REDCap for an option to document their practice of skills provided in the intervention.

Table 2. Resiliency Program Content

Intake Session *Introducing Resiliency and the Relaxation Response*	• Resiliency and the Relaxation Response • Core components of the program • Setting SMART and resiliency goals • Monitoring Stress and Coping
Session 1 *Stress Management and Resiliency Training*	• Stress & Relaxation Response and Allostatic Load • Energy Battery: stress and resiliency inducing factors • Appreciation

	• RR-elicitation method: single pointed focus mediation and breath awareness
Session 2 *The Relaxation Response*	• Stress Warning Signs • Recuperative Sleep • Mini RR • RR-elicitation method: body scan or autogenic training
Session 3 *Stress Awareness and Buffering*	• Identifying emotions and positive physical sensations • Social Support • RR-elicitation method: Mindful Awareness
Session 4 *Mending the Mind and Body*	• Thoughtful Distortions • Negative Automatic Thoughts • RR-elicitation method: chair yoga
Session 5 *Creating an Adaptive Perspective*	• Creating adaptive perspectives • Problem-Solving vs Acceptance • Healthy Eating • RR-elicitation method: insight imagery
Session 6 *Promoting Positivity*	• Strategies for enhancing positivity • Relaxation Signals • Promoting physical activity • RR-elicitation method: lovingkindness meditation
Session 7 *Healing States of Mind*	• Empathy and self-compassion • Creativity • RR-elicitation method: compassion meditation
Session 8 *Humor & Staying Resilient*	• Staying Resilient • Humor • RR-elicitation method: idealized self

Enhanced Usual Care. Survivors and caregivers randomized to enhanced usual care will be referred to an online support group at cancare.org. The MGH Cancer Center resource center refers patients to these groups. These groups are held separately for cancer survivors and caregivers. Participants use a password-protected message board format to participate in groups that are facilitated by oncology social workers who provide support for loneliness and emotional distress; teach coping, enhancing feelings of hope and empowerment, and promote use of social support. Participants´ attendance data will be provided by Cancare.org. Patient data will be transferred using a HIPAA-compliant Dropbox account for secure file transfer.

9.3. Fidelity of Study Design, Methods, and Intervention

We will monitor treatment fidelity following recommendations of the Treatment Fidelity Workgroup of the NIH Behavior Change Consortium.[65] An evidence-based intervention manual will be used. Systematic screening and enrollment strategies will minimize participation bias. Participation rates will be tracked and characteristics between participants and non-participants examined. To ensure that the delivery of SMART-3RP is consistent, all intervention sessions will be audio-recorded. The study interventionists will complete post-session REDCap surveys indicating attendance and session topics

covered. Drs. Park and Perez will oversee all intervention delivery and treatment fidelity aspects of the project, as well as the exit interview qualitative data collection and analyses to ensure intervention fidelity.

9.4. Study Measures

Participants Self-Report Measures. Caregivers and survivors will complete self-report measures at baseline, 3 and 6 months after enrollment (Table 3). Participant-reported measures are selected based on our prior studies and the theoretical framework of our SMART-3RP, documenting resiliency, coping, and psychological distress. Participants will receive a $20 gift card for each survey completed.

Patient and Caregiver Measures

Baseline only:

- Demographics and Health Measures: age, sex, gender identity, ethnicity, race, marital status, language, religiosity, education, employment status and health insurance coverage. For caregivers only: caregiver type and whether or not living with patient).
- Self-Administered Comorbidities Questionnaire (SACQ-16): 14-item assessment of common medical problems and severity (survivors only)
- PROMIS Cognitive Function (PROMIS-CF): 8-item scale assessing cognitive functioning (survivors only)

Baseline and 3-month follow-up:

- The Current Experiences Scale (CES):[67] 23-item measure of resilience
- Measure of Current Status (MOCS-A):[68] 13-item scale examining coping skills
- Distress Scale: 3 0-10 analog scale items examining distress, stress, and coping ability
- Generalized Anxiety Disorder Scale (GAD-2):[69] 2-iem scale examining symptoms of anxiety
- Patient Health Questionnaire (PHQ-2):[69] 2-item scale examining symptoms of depression
- Penn State Worry Questionnaire (PSWQ-3):[70] 3-item subscale of the tendency towards worry
- Cognitive and Affective Mindfulness Scale-Revised (CAMS-R-12):[71] 12-item scale of mindfulness
- Self-Compassion Scale-Short Form (SCS-SF-12):[72] 12-item short form scale for self-compassion

- Patient Reported Outcome Measure Information System for Social Support (PROMIS-Social Support-8):[73] 8-item subscale to examine emotional and informational support
- Positive and Negative Affect Schedule (PANAS-A-10):[74] 10-item scale assessment of positive affect
- World Health Organization Wellbeing Index (WHO-5):[84] 5-item scale examining current mental-wellbeing
- Measure of Relationship Quality: 5-item scale examining perceived quality of caregiving relationship
- Measure of Communication: 7-item scale examining perceived quality of communication in caregiving relationship (survivors only)
- Cancer Screening Questions: 6-item scale for females and 4-item scale for males examining cancer screening history
- Likert scale: 3 or 5-response scale to examine intervention satisfaction, needs met, program quality structure (delivery methodology, length and number of sessions), and helpfulness (intervention group only)
- Group Cohesiveness Scale (GCS-7):[75] 7-item scale examining level of perceived connectedness (intervention group only)
- Participants self-reported use of health care: see Section 9.5. for more detail

Table 3. Survivor and Caregiver Outcomes

Outcome	Name of outcome	Measure	Survivor/Caregiver	Timepoints
Primary	Feasibility	Percentage of enrollment, follow-up survey completion, and intervention session attendance	Both	Baseline, 3 months, 6 months
Primary	Acceptability	Likert scale items of satisfaction, needs met, program quality, structure and helpfulness GCS Participant-reported RR practice	Both	3 months
Secondary	Resilience	CES	Both	Baseline, 3 months
Secondary	Stress management: coping	MOCS-A	Both	Baseline, 3 months
Secondary	Stress management:	Distress Scale cortisol levels from hair samples	Both	Baseline, 3 months

[84]

	distress, stress and coping ability			
Secondary	Stress management: emotional distress	GAD-2, PHQ-2	Both	Baseline, 3 months
Secondary	Stress management: worry/stress cognitions	PSWQ-3	Both	Baseline, 3 months
Secondary	Stress management: mindfulness	CAMS-R-12	Both	Baseline, 3 months
Secondary	Growth enhancement: self-compassion	SCS-SF-12	Both	Baseline, 3 months
Secondary	Growth enhancement: social support	PROMIS-Social Support-8	Both	Baseline, 3 months
Secondary	Growth enhancement: positive affect	PANAS-A-10	Both	Baseline, 3 months
Exploratory	Growth enhancement: well-being	WHO-5	Both	Baseline, 3 months
Exploratory	Growth enhancement: relationship quality	Measure of Relationship Quality	Both	Baseline, 3 months
Exploratory	Growth enhancement: communication quality	Measure of Communication	Survivors	Baseline, 3 months
Exploratory	Healthcare utilization: participant-reported	Cancer Screening Questions	Both	Baseline, 6 months
Exploratory	Healthcare utilization: EHR data extraction (survivors only)	Overutilization: number of hospitalizations, number of ED visits Underutilization: adherence to NCCN cancer restaging recommendations (e.g., surveillance scans), age-appropriate cancer screening, primary care visits, vaccines, and mental health services (e.g., outpatient psychological or psychiatric visits)	Survivors	6 months
Exploratory	Healthcare utilization: participant-reported (survivors and caregivers)	Overutilization: number of hospitalizations, number of urgent care and ED visits Underutilization: age-appropriate cancer screening, primary care	Both	6 months

		visits, vaccines, and mental health services and psychiatric medications		
Covariates	Medical problems/severity	SACQ-16	Survivors	Baseline
Covariates	Cognitive functioning	PROMIS-CF	Survivors	Baseline

Hair cortisol sampling. At enrollment and 6-month follow-up, participants will be asked to provide a hair sample. Hair cortisol collection at the 6-month follow-up will reflect cortisol concentration in the 3-month period following the end of the intervention. Participants will not be required to provide a sample; participants with insufficient hair length will be excluded from sample collection. Participants who are taking hormonal or steroidal medications will also be excluded from sample collection. Cortisol assessments provide a biobehavioral measure of stress level. Hair cortisol provides a more robust assessment of cortisol concentration levels across longer periods[68, 77] and may be less burdensome and easier to collect than saliva sampling.[78] Participants will receive a $25 gift card for each hair cortisol sample collected. A hair cortisol collection instruction sheet will be mailed/emailed to participants.

9.5. Data collection

We will develop data collection tools, dictionaries, collection instructions and the REDCap database to ensure that we collect data systematically from all study participants. We will ask participants to provide their email address to allow us to send study assessments via REDCap and will inquire their preferences for encrypted or unencrypted delivery. Preference for unencrypted delivery will be documented prior to email delivery. Participants can also choose to complete the questionnaire verbally over the telephone. The participant-reported assessments take approximately 10-15 minutes to complete and qualitative interviews approximately 30 minutes to complete. We will also track the method of assessment completion.

Data obtained from Electronic Health Records (EHR). In addition to collecting data on healthcare utilization from the EHR, the study staff will also extract clinical and treatment data at 6 months including survivor status (curvivor vs. metavivor), ECOG performance status, cancer type, cancer diagnosis date, treatment(s) completion, treatments received, cancer stage, time since diagnosis, second primary tumors/recurrence and death, and clinical comorbidities

Data reported by participants. Participants will complete <u>self-reported measures</u> at baseline, 3 and 6 months (Table 3) in-person, online via REDCap, or by phone or mail. <u>Exit interviews:</u> Following completion of their 3-month follow-up measures, approximately 10 intervention curvivor-caregivers and 10 metavivor-caregivers will be randomly selected to participate in in-depth interviews. We estimate the 10 are needed for each strata (survivor status/caregiver status) to reach thematic saturation (no new data are

obtained).[77] Using a semi-structured interview guide, study staff will conduct virtual interviews. Participants will be asked open-ended questions about a) study outreach (video, modality), b) intervention content (topics most and least helpful), c) group format, d) virtual delivery (simultaneous intervention, group), and e) participation barriers/challenges. Participants will receive a $25 gift card for completion of the exit interview.

Data on feasibility, acceptability and preliminary efficacy. Feasibility (Aim 1) will be assessed by 1) the percent of eligible participants (survivors, caregivers) approached that enroll, 2) the percent of participants who complete the follow-up survey, and 3) the number of sessions attended (interventionists after session surveys and cancare.org). Additionally, we will analyze the exit interviews to assess the study outreach strategies, intervention content (topics most and least helpful), c) group format, d) virtual delivery (simultaneous intervention, group), and e) participation barriers/challenges. Acceptability (Aim 1) will be examined on overall intervention satisfaction, program quality, structure, needs met and helpfulness as well as level of perceived connectedness and between session RR practice. We will also examine the results of the survey and exit interviews to assess the intervention content, group and format delivery. Efficacy (Aim 2, Table 3) will be evaluated based on the comparative effectiveness of SMART-3RP and enhanced usual care on patient-reported measures documenting resiliency, coping, and psychological distress (see Figure 1). All participant-reported measures have strong psychometric properties with high internal and external validity and responsiveness to change, are well validated and commonly used in this population in our trials as well as in other studies.[55, 79-82]

Data on healthcare utilization (Aim 3, Table 3). At around 6 months, data on health care utilization will be collected from the EHR (survivors) and the self-report forms (survivors and caregivers) that have been previously used in prior studies.[83] Survivor´s data collected from EHR will include number of primary care visits, ED visits, and hospitalizations, as well as the use of mental health services including outpatients psychological or psychiatric visits. Survivors and caregivers will self-report healthcare utilization in measures previously used[83] that capture number of urgent visits, visits to the ED, use and frequency of mental health services (including social work, psychiatry, psychology, and other mental health professionals, and support groups) over the past months at and outside of MGH. We will also ask psychiatric medications used (e.g., anxiolytics, antidepressants, sedatives, and stimulants).

Hair cortisol collection. Participants will be asked to provide hair samples at enrollment and 6-month follow-up to measure potential changes in cortisol ("stress hormone") except those on hormonal or steroidal medications. This method has been used successfully in stress studies and is currently being utilized in other 3RP studies led by study co-investigator, Dr. Perez (DF/HCC #17-063 and DF/HCC #18-248 PI: Perez). Hair grows roughly 1cm/month, thus ensuring sufficient growth for collection. The RA will mail/email detailed sampling instructions (See instructions sheet) and stamped, addressed envelopes to facilitate returns. Participants will be instructed to provide one hair sample at baseline and one sample at the 6-month follow-up. Hair cortisol collection

at 6-month follow-up will reflect cortisol concentration in the 3-month period following the end of the intervention. Participants will be instructed to cut a small sample of hair (approximately 150 strands, about the diameter of a small paperclip) 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. See section 10.0 for storage of hair samples collected.

10.0 Data and Specimen Banking

Hair samples will be collected, labeled with study ID, stored at room temperature, and sent to Dr. Kestutis Bendinska´s laboratory at State University of New York at Oswego. Prior to shipping, samples will remain wrapped in aluminum foil, labeled with a study ID, and stored at room temperature in a padded envelope.

11.0 Data Management and Confidentiality

11.1. Sample Size and Power

Sample size was based on the primary feasibility aim. Efficacy analyses will have 80% power at a significance level of 0.05 to detect an effect size of 0.57 for the mean difference at 3-months based on a mixed models test for slope difference in a three-level hierarchical design with 2 measurements per subject, 2 subjects per dyad (1 survivor, 1 caregiver), and 24 dyads per intervention group and assuming the correlation between baseline and 3-month values is 0.5. We have decided on a larger sample size than 24 dyads per intervention group to ensure adequate number of participants in the last SMART-3RP groups. We chose the sample size and decision rules so that the probability of declaring feasibility would be approximately 5% under unacceptable rates and at least 80% under anticipated rates—see table below. If true enrollment, retention, completion, and acceptability rates were ≤39%, ≤60%, ≤58%, and ≤62%, respectively, which we would consider too low to continue with an efficacy trial, then the probability of declaring feasibility would be ≤5%. If the true rates align with our anticipated rates, the probability of declaring feasibility would be ≥80%.

Feasibility Measure	Anticipated Rate	Acceptable Rate	Unacceptable Rate	Decision Rule for Feasibility	Prob. of Declaring Feasibility Under Anticipated Rate	Prob. of Declaring Feasibility Under Unacceptable Rate
Enrollment of eligibles	50%	45%	39%	≥96 enrolled of 213 eligible	93%	4%

Retention	75%	70%	60%	≥67 of 96 enrolled complete 3-month follow-up survey	90%	3%
Intervention attendance	75%	70%	58%	≥34 of 48 intervention participants attend ≥6 of 9 sessions	80%	5%
Intervention acceptability	80%	75%	62%	≥36 of 48 intervention participants report overall intervention satisfaction (4/5 on Likert scales)	85%	4%

11.2. Data Analysis

Aim 1: We will evaluate feasibility using rates of eligibles enrolled, retention, and intervention session attendance.[55, 80-82] Descriptive analyses (frequencies, means/medians, confidence intervals) will be used to evaluate hypotheses regarding enrollment (≥45% of eligible), retention (≥70% follow-up survey completion) and intervention attendance (≥70% attending at least 6 of 9 sessions). Acceptability of the intervention will be examined by patient-reported overall intervention satisfaction (≥75%) and group cohesiveness ratings. Fisher's exact and Wilcoxon rank sum tests will be used to explore whether feasibility and acceptability outcomes are affected by sociodemographic (e.g. age, sex), clinical (e.g. metavivor vs curvivor), medical, and baseline efficacy outcome characteristics. We will collect similar metrics for hair cortisol collection. In particular, 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. Exit Interview Data analysis. The exit interview data will be transcribed and analyzed using NVivo qualitative software. Content analysis will be conducted by the study members who will iteratively create themes, categories, and codes. Coding matrices will be used to compare caregivers of curvivors and metavivors. To ensure coding reliability, coding discrepancies will be resolved through discussion and comparison of raw data. 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. To ensure validity, Dr. Haman (consultant) will provide the expert review of the final analyses.

Aim 2: Linear regression models will be used to evaluate the preliminary efficacy on change in resiliency and other secondary outcomes (stress management and growth

enhancement processes; biobehavioral assessment of chronic stress). We will first assess for intra-cluster correlation in our groups and if the intra-cluster correlation is very small (< 0.1), we will employ linear regression models, adjusting for baseline criterion score, to examine the preliminary effects of the intervention on study outcomes at 3 months. Analyses will be conducted across all study participants, as well as by caregiver and survivor cohorts, separately. If intra-cluster correlation is >0.1, , sensitivity analyses will be conducted using mixed linear models to account for the intraclass correlation within intervention group cohorts and caregiver-survivor dyads. Cohen's d effect size will be calculated by dividing the group differences in outcomes at 3 months by the pooled standard deviation. These models will include random effects to account for the correlation between measurements from the same individual and the same survivor-caregiver dyad. The interaction between timepoint and intervention will be used to evaluate whether the change in outcome differs between the two groups. We will assess our assumption that the intervention effect is similar for caregivers and survivors using models with a three-way interaction (time by intervention by participant type) and conduct subgroup analyses within caregivers and survivors if there is evidence of a differential effect. Moderation of the intervention effects will be examined using linear regression models within caregiver/survivor subgroups. Interaction terms (time by intervention by potential moderator) will be assessed to determine whether intervention efficacy is associated with sociodemographic (e.g. age, sex), clinical (e.g. metavivor vs curvivor), medical characteristics, and baseline efficacy outcome.

Aim 3: Health care utilization analyses: We will explore the effect of the intervention on participants' (survivors and caregivers) utilization of healthcare, with outcomes including hospitalizations, ED visits, urgent care visits, primary care visits, mental health visits, and use of psychiatric medications. These exploratory analyses will be carried out separately for caregivers and survivors due to fundamental differences in the healthcare needs of caregivers and survivors. Intervention effects on dichotomous healthcare utilization outcomes will be explored using Fisher's exact test

Covariate and Moderator variables will include sociodemographic, clinical and medical characteristics described on Section 9.5. (data reported by participants and data obtained from the EHR). Additionally, survivors´ reported physical symptoms will be extracted from the PROMIS-CF and survivor reported comorbidities will be captured on the Self-Administered Comorbidities Questionnaire.[76]

Missing Data Analyses will be based on the intention-to-treat principle with participants analyzed according to their randomly assigned group regardless of how many intervention sessions they attend. Efficacy analyses will initially focus on study completers to estimate the effect of SMART-3RP on study participants who completed the protocol assessments. We will also conduct sensitivity analyses to explore how various assumptions about missing data and differences between completer and non-completers affect the estimated outcomes. If data appear to be missing at random, we will employ multiple imputation methods, maximum likelihood estimate approach with EM algorithm, and mixed effect modeling that can adequately account for data missing at random. However, if we find that

participants do not complete the study because of disease worsening suggesting that data are not missing at random, we will employ joint modeling approaches to handle incomplete data and perform sensitivity analyses to assess the impact of missing data.

Randomization. Survivor-caregivers will be randomized together, stratified by survivor status (curvivor/metavivor), using a random plan generator with 1:1 randomization.

11.3. Data Storage

All participant information and study source documents will remain confidential and be scanned and stored on secure institutional computers and in REDCap. The REDCap survey is a tool for building and managing online surveys. Our research team has extensive experience using REDCap and will create and design the surveys in a web browser, with institutional information technology support. Data abstracted from the EHR (see Section 9.5) will be maintained in REDCap. The REDCap Survey system offers secure, HIPAA compliant, web-based applications that provide an intuitive interface for participants to enter data, with real-time validation rules at the time of entry. Exit interviews will be recorded. All digital recordings will be immediately uploaded to a MGB secure study folder, which is password protected and only accessible to study staff. The files will be immediately deleted from the audio recorder. Audio recordings will be destroyed after we complete all transcriptions. Only the Principal Investigators and the RA will have access to identifiable patient information, which will be stored only in a password protected file on the secure MGH network.

Hair cortisol will be collected and stored as outlined in sections 9.5 and 10. In brief, samples will remain wrapped in aluminum foil, labeled with a study ID and stored at room temperature in a padded envelope within a locked, filing cabinet in our team lab.

Drs. Park and El-Jawahri will oversee all aspects of data collection and will develop study specific data management protocol and standard operating procedures for the creation and testing of all study forms, data collection, quality control, and data extraction. They will provide ongoing oversight of data management throughout the study and will be responsible for generating reports and datasets for quality control and data analysis.

We will comply with all requirements for data safety and monitored specified by the IRB and NIH. As per Public Law 110-85, this is an applicable trial and will be registered and results reported with ClinicalTrials.gov. Ms. Horick will be responsible for handling ClinicalTrials.gov requirements for this project under Drs. Park and El-Jawahri oversight. She will work closely with the Partners Human Research Affairs QI Program to register the trial prior to enrolling the first subject. Once a record is established, she will confirm accuracy of record content, resolve problems, and maintain records including content update and modification.

11.4. Data Quality

Drs. Park and El-Jawahri will train the study RA in administration and data management of participant self-report questionnaires. Data extraction from participants' EHR will be supervised by Dr. El-Jawahri who is a board-certified oncologist possessing the necessary expertise to oversee collection of patient clinical characteristics and oncology treatment information. For hair cortisol, samples will be dissolved in phosphate-buffered saline, randomly distributed on different plates to avoid a batch effect and analyzed in quadruplicate using Saltimetrics cortisol ELISA. If readings for a sample differ by more than 10%, of the measurements will be repeated; also, 5% of samples will be randomly reanalyzed to ensure reproducibility. Study fidelity will be ensured as described on Section 9.3. Fidelity of Study Design, Methods, and Intervention.

11.5. Data Security

Participant data will be collected using REDCap and exit interviews saved on MGB secure study folder. Data collected from participants will be kept confidential and accessible only to trained study staff. Participants will be assigned a study identification number and all collected data will be stored securely with this identification number in files which do not include patient names or any other identifiable information. A link between names and identification numbers will be stored separately in a password protected file. All electronic data will be stored in password protected computer files. Any data files exported from the database will be de-identified, with only a case number identifying each participant, and no other identifying information.

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

This research involves no more than minimal risk to subjects.

13.0 Withdrawal of Subjects

We do not anticipate that any research participants will be withdrawn from the study without their consent. If a participant requests withdrawal from the study, we will ask them if they are comfortable sharing the reason for withdrawal to ensure that there are no adverse events to report to the IRB. We will ask the study participant if they are still willing to permit the study team to continue to monitor their health record, but withdraw from all other study procedures.

14.0 Risks to Subjects

The risks involved in the study are minimal and will be clearly delineated on the consent form. It is unlikely that participants will be at any risk for physical harm as a result of study participation. We experienced no adverse events in our prior clinical work and studies with survivors. Confidentiality will be detailed on the consent form and discussed in detail so that participants are fully informed of their right to request information and to withdraw from the study at any time without impacting their care. We will also discuss the importance of maintaining confidentiality at the beginning of each intervention group so as to keep information shared confined to the group. Participants will also be made aware of the limits of confidentiality, including that confidentiality would be broken if participants reported thoughts of harming themselves or others, in order to obtain

appropriate care for the participant. Participants may choose not to participate in the study or any of the study procedures without penalty. Those who do agree to participate may withdraw their participation at any time without penalty.

Potential risks to participants are minimal across various study procedures. Questionnaire batteries. Participants may experience some discomfort answering questions on surveys; however, they may choose not to answer questions that are distressing. Group videoconferencing. Participants may have concerns about the security of videoconferencing and will be informed that the system is HIPPA compliant and sanctioned by MassGeneral Brigham HealthCare to protect privacy. SMART-3RP and support groups. Participants might find some of the exercises (e.g., meditation training in the SMART-3RP, discussing concerns with fellow group participants) to be difficult or uncomfortable at first. These difficulties are typically minimal and temporary and are often a natural and valuable part of the treatment process. Hair samples. Participants might find it distressing to cut their hair for the hair sample, though this procedure has been tested in prior protocols and has been typically well-tolerated. Provision of a hair sample is not a requirement for study participation.

15.0 Potential Benefits to Subjects

It is possible that some patients and caregivers may benefit from the intervention or enhanced usual care. Some may value the possibility that their contribution to the study may benefit other cancer survivors and their caregivers. It is also possible that some may not derive these benefits. However, the risk from participation in the study is small (and will be minimized by the procedures outlined above), and the overall risk to benefit ratio is favorable.

16.0 Vulnerable Populations

Not applicable

17.0 Community-Based Participatory Research: Not applicable

18.0 Sharing of Results with Subjects

Given the nature of the population included in the study, it is not appropriate to proactively contact participants at the conclusion of this study. We anticipate that a proportion of our participants will die during or within months of completing the study. We do not wish to cause unnecessary distress to participants' family members by attempting to contact participants who have died. Therefore, we provide the research team contact information to each participant and encourage them to contact us if they would like to receive updates and information on the research findings.

19.0 Setting

The study will include participants with cancer treated at the Massachusetts General Hospital. Participants will be approached for participation in-person, phone or email, or via

patient gateway. The intervention will be delivered via a virtual-HIPPA-compliant videoconferencing technology, Zoom, that is accessible via smartphone, laptop, tablet, or desktop. Randomly selected participants will take part on an exit interview that will be conducted virtually or in person. Hair cortisol collection will be sent to Dr. Kestutis Bendinska´s laboratory.

20.0 Resources Available

20.1. Team Qualifications and Oversight

The overall MPI of the project (Drs. Park and El-Jawahri) are responsible for full oversight of the project at MGH. They will meet with the CRC on weekly basis (and more often as urgent issues arise) to ensure the study process is being followed accurately and to address potential challenges or issues that occur. The MGH research team will also review the CONSORT diagram, recruitment and enrollment procedures, and any potential problems or issues related to the study operations on weekly basis. Drs. Park and El-Jawahri have extensive experience conducting supportive care intervention clinical trials.

20.2. Other Resources

Drs. Park and El-Jawahri are members of the MGH Cancer Outcomes Research and Education Program (CORE). CORE has extensive experience conducting randomized clinical trials of supportive care interventions in oncology and has the necessary expertise to ensure the success of the proposed project. Drs. Park and El-Jawahri are also members of the MGH Health Promotion and Resiliency Intervention Research Program, which houses expertise and research staff focused on mind-body interventions.

21.0 Prior Approvals

The DF/HCC will serve as the IRB of record for this trial.

22.0 Recruitment Methods

Please see section 5.0 for recruitment methods.

23.0 Local Number of Subjects

We will include 58 caregiver and cancer survivor dyads (n=116) that will be randomized 1:1 to SMART-3RP and enhanced usual care.

24.0 Provisions to Protect the Privacy Interests of Subjects

The main risk to participants in this study is loss of privacy or confidentiality. Data collected from participants will be kept confidential and accessible only to trained study staff. To protect against this risk, the participants will be assigned a study identification number and all collected data will be stored securely with this identification number in files which do not include patient names or any other identifiable information. A link between names and identification numbers will be stored separately in a password protected file. All electronic data will be stored in password protected computer files. Any data files

exported from the database will be de-identified, with only a case number identifying each participant, and no other identifying information.

25.0 Compensation for Research-Related Injury

We do not anticipate any research-related injury due to involvement in this supportive care trial.

26.0 Economic Burden to Subjects

We do not anticipate any financial burden on study participants. Participants will not be financially responsible for the intervention.

27.0 Consent Process

The RA will review the study procedures, required data collection, and consent process with the participants either in-person during their oncology follow-up or over the telephone or video. The verbal consent form will include all of the study procedures, information about potential risks and benefits of participation, and information regarding who participants can contact for further questions (PIs and study staff). It also will state that participation is voluntary, that participants can refuse to answer any question, that they can withdraw from the study at any time, and that study participation is in no way related to their medical care. The verbal consent form will identify alternatives to participation. Willing participants will be asked to provide verbal consent and to complete the baseline questionnaires. Participants will also be provided a copy of the verbal consent document in-person, electronically, or by mail. As stated previously, we are requesting a Waiver of Written Documentation of Consent given that this is a minimal risk study and that all of the study procedures could be easily conveyed orally. This waiver will reduce the risk to patients and caregivers who may not be coming regularly to the cancer center for their care and is necessary for our research procedures to continue.

28.0 Process to Document Consent in Writing

As stated previously, the RA will conduct informed consent procedures with potential participants and obtain verbal consent. We will follow all the requirements of SOP: Informed Consent Process (CON-100) in obtaining informed consent for study participants and participants will be consented via verbal consent.

29.0 Drugs or Devices

Not applicable

30.0 References

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