Protocol #: 20-2458
Project Title: eCare: Developing a virtual stress management intervention for spousal/partnered employed caregivers of solid tumor cancer patients.

Principal Investigator: Cathy Bradley, PhD
Version Date: 7 JUL 2023

I. Specific Aims and Hypotheses

Please note that the following aims and hypotheses differ slightly from the approved NIH R01 application that was included with this application because some accommodations were required to execute this project under the restrictions of social distancing necessitated by the COVID-19 pandemic. All changes have been tracked and COMIRB approved.

Aim 1: Evaluate the impact of PsychoEducation Paced Respiration and Relaxation (PEPRR) delivered remotely as Virtual-PEPRR or online as Pep-Pal on CGs employed at the time of their patient's cancer diagnosis and preselected based on high self-reported distress.

- H1a: As *the primary trial outcome*, CGs randomized to **Virtual-PEPRR or Pep-Pal versus treatment as usual (TAU)** will have reduced depressive symptoms at 3 mo. (efficacy) as well as 6, 9 and 12 mo. follow up (sustainability).
- H1b: As secondary psychological and medical outcomes, CGs randomized to **Virtual-PEPRR or Pep-Pal versus TAU** will have lower anxiety and perceived stress as well as fewer CG outpatient visits and fewer CG medications prescribed based on their EMR at 3 mo. (efficacy) and at 6, 9 and 12 mo. follow up (sustainability).
- H1c: As secondary biomarker outcomes, CGs randomized to **Virtual-PEPRR or Pep-Pal versus TAU** will have stabilized or reduced biomarkers of allostatic load (including hair cortisol and telomere length, at 3 mo. (efficacy) and at 6, 9 and 12 mo. follow up (sustainability).

Aim 2. Evaluate patient psychological status (including distress associated with COVID-19) and healthcare utilization in patients whose CGs received Virtual-PEPRR or Pep-Pal versus TAU:

- H2a: As secondary psychological outcomes, patients whose CGs received **Virtual-PEPRR or Pep-Pal versus TAU** will have reduced anxiety and depression, on self-report at 3 mo. (efficacy) and at 6, 9 and 12 mo. follow up (sustainability).

- H2b: As a secondary outcome based on patient EMR, healthcare utilization will be lower in those patients whose CGs participated in **Virtual-PEPRR or Pep-Pal versus TAU** at 3 mo. (efficacy) and at 6, 9 and 12 mo. follow up (sustainability).
- H2c: As a secondary outcome, patients whose CGs received **Virtual-PEPRR or Pep-Pal versus TAU** will have improved symptom management as measured by the MD Anderson Symptom Inventory at 3 mo. (efficacy) and at 6, 9 and 12 mo. follow up (sustainability).

Aim 3: Evaluate whether CG employment outcomes are associated with patient symptom management as an exploratory question.

- H3a: **For currently employed caregivers,** hours worked, and job satisfaction will be positively associated with improved patient symptom management and improved patient psychological outcomes.
- **H3b: For caregivers currently looking for work, improvement in patient symptom management and patient psychological outcomes will be positively associated with job applications submitted and interviews given and negatively associated with days to finding a new job.**

II. Background and Significance:

Spousal and partnered caregivers (CG) serve an important role in ensuring the health of our nation but they are at risk for increased morbidity and mortality in association with this challenge. Few family CGs receive support for themselves during this experience particularly when the CG is employed. The present protocol represents a submission for an NCI funded grant that was reviewed, approved, and funded (8/2019) immediately prior to the COIVD-19 pandemic[1]. Consequently, the aims were modified slightly from the original application to include COVID-19's impact on changes in employment characteristics of this population of caregivers, as well as incorporating entirely remote (telehealth) implementation of all aspects of this study[2]. These changes have been made with the knowledge of our NCI program officer. This randomized control trial will investigate the impact of a stress management intervention called Psycho-Education and Paced Respiration and Relaxation (PEPRR) or a mobilized version called Pep-Pal on CGs that are employed at the time of their patient's diagnosis with a solid tumor cancer) at any stage treated at the University of Colorado Cancer Center (UCCC). Inclusion criteria have been adjusted to account for the high rates of unemployment since the onset of the COVID-19 pandemic. To emphasize, all contact with the participants (caregivers and their cancer patient) will be accomplished using approaches such as Zoom or telephone. Biomarkers will also be collected remotely by the caregivers themselves and returned via mail using established protocols developed in this laboratory or that of our collaborators. Minor additions or modifications to the approved grant have been tracked in the previous Aims and Hypotheses.

Sixty-six million Americans cared for a disabled or ill person in 2015, reflecting a 49% increase over the number of caregivers (CGs) since 2008 [3,4]. Of these caregivers, 3.9 million cared for a cancer patient. The need for cancer CGs will continue to rise with increased survivorship associated with new treatments and targeted therapies [5-7] . These unpaid care

services were valued at over $450 billion/year in 2010 [4] and are often performed by individuals who must also continue to work for pay. Only 1 in 4 CGs receive supportive care themselves [8]. CGs have become a priority of the NCI [9]. Working age CGs face the additional challenge of meeting work demands while pursing professional goals and caring for their loved one. **To our knowledge few studies have addressed the unique needs of employed CGs.** Among cancer caregivers, 25-29% made employment adjustments in the face of a cancer caregiving challenge [10]. Given that employment is essential for family income and/or employment-based health insurance coverage as noted for patient groups under age 65 [11], it is no surprise that caregiving also interferes with work performance, stress, and health for the CG [12]. These factors likely affect the patient's health and wellbeing as well.

The workplace provides both financial security and needed insurance at a highly critical juncture for both the patient and the CG. Health shocks (e.g., significant change in health) [13] affect decisions to retire or remain employed by a patient and may be just as likely to influence a CG's decision to remain in the work force to guarantee both income and health insurance [11].

A recent survey by the American Cancer Society found that the COVID-19 pandemic has had a substantial financial impact affecting ability to pay for care which is added to the recent unemployment rate of 13.3% in May 2020. Patients and their families are concerned that they cannot pay for the medical care they need to address their cancer. Overall COVID-19 must be factored into our project both as a financial impact, and also in how the intervention will be delivered, biomarkers will be collected, participants will be recruited and consented, and questionnaires completed. All changes made at the onset of this RCT will remain in place for the duration of the trial.

III. Preliminary Studies/Progress Report:

We noted that at the onset of caregiving, HSCT caregivers who change employment status are significantly more anxious and depressed[14]. This suggested a clear need to more fully understand the impact of employment on caregiving distress and additionally COVID-19's impact on family finances. As far as influencing caregiver distress, we have shown that our stress management intervention, **P**sycho**E**ducation, **P**aced **R**espiration, and **R**elaxation (**PEPRR**, pronounced "pepper") reduced distress among CGs of adult Allo-HSCT patients in a randomized control trial (RCT) [15,16]. **PEPRR** was adapted for Allo-HSCT CGs based on a cognitive behavioral stress management program designed for cancer patients [17]. CGs of Allo-HSCT patients are unique because they must be available 24/7 for the first 100 days post-transplant to provide complex supportive care for their patient. This experience is quite distressing [18]. We have also shown that CGs of cancer patients participating in Phase 1 trials are similarly distressed[5]. **PEPRR** reflects an important intervention for mitigating distress in HSCT CGs but it has not been corroborated for solid tumor cancer patient caregivers. **Pep-Pal** is a mobilized version of **PEPRR** that has been shown to be acceptable and useful as well for cancer caregivers[19,20]. However, **PEPRR** was established using face-to-face interactions between the CG and the interventionist. The advent of COVID-19 has made this approach more difficult due to social distancing[21]. Fortuitously prior to the onset of COVID-19, we were testing **Pep-Pal**[20]. Choice between **Pep-Pal** or face-to-face **PEPRR** meetings by the caregiver was incorporated into the original grant application as a means of reducing CG burden while testing the intervention in solid tumor patients. We have previously reported that a telehealth approach to **PEPRR** using smartphone technology occasionally (e.g. during times of inclement

weather or to protect a caregiver from exposure to an ill interventionist) was acceptable to the CGs[22]. Thus, in the present study we have made the decision to go exclusively to telehealth for the administration of **PEPRR**, which will be called **Virtual-PEPRR** for the purposes of this protocol.

Thus, our prior work allows us to address the new challenges presented by COVID-19 by providing a remote intervention and data collection while addressing the impact of the changing economy on caregiver distress during this unique RCT.

IV. Research Methods

1. Outcome Measure(s):

Caregiver (CG)

A. CG Background and Demographics

B. CG Self report outcomes

- **a. CG Depressive Symptoms (Primary Outcome).**
- **b. CG Anxiety**
- **c. CG Stress**
- **d. CG Employment status/hours worked**
- **e. CG Work setting**
- **f. CG Job Tasks**
- **g. CG Job accommodations**
- **h. CG Job satisfaction**
- **i. CG Insurance**
- **j. CG Burden**
- **k. CG Healthcare Utilization**
- **l. CG COVID-19 Distress**
- **m. CG Monthly PROMIS Assessments**
- **n. CG Measure of Current Status- Part A**
- **o. Number of times EMwave2 used in past weeks**

C. CG Biomarker Outcomes

- **a. CG Telomere Length (TL)**
- **b. CG Hair cortisol**

Patient

A. Patient Background and Demographics

B. Patient Self-Report Outcomes

a. **Patient Distress**
b. **Patient Satisfaction with CG Support**
c. **Patient Healthcare Utilization**
d. **Patient Symptom Management**
e. **Patient Insurance**

2. Description of Population to be Enrolled:

Inclusion/exclusion: Both patient and CG must consent and participate.

Caregiver inclusion criteria: 1) A primary caregiver for a patient with a diagnosis of solid tumor cancer at any stage who are within 12 weeks of initiating treatment, (12 weeks or less since treatment started).Treatment may include chemotherapy, immunotherapy, oral targeted agents, and/or radiation. 2) Spouse or partner of the patient for at least a year and must live with patient. 3) Caregiver must score 1 or greater on the PHQ-2 (depression) and/or GAD-2 (anxiety) during pre-screening. 4) Caregiver must be employed **at the time** of the patient's diagnosis for a minimum of 20 hours/week with **plans** to remain employed and working during their patient's treatment. Caregivers that were furloughed or laid off due to Covid-19 who are actively looking for work will be included. 5) Participants must read and speak the English language. 6) Participants must be able to use a smartphone. 7) Age 25 (inclusive) 65 (non-inclusive).
We expect that COVID-19's impact on employment and the national economy will likely result in higher rates of unemployment.

Exclusion criteria: 1) Having a serious medical condition likely to influence neuroendocrine parameters, 2) chronic use of steroid medications, 3) if female, pregnant or planning to become pregnant in the next year, 4) history of a psychiatric illness unrelated to their experience as a caregiver within the past 18 months.

Patient inclusion criteria 1) Patients who have a primary diagnosis of solid tumor cancer at any stage that are within 12 weeks of initiating treatment, (12 weeks or less since treatment started). Treatment may include chemotherapy, immunotherapy, oral targeted and/or radiation. 2) Patient must be spouse or partner of the caregiver for at least a year and must live with caregiver 3) Must be able to read/speak English. 4) 18 years of age or older.

The study will follow CONSORT guidelines for conduct of a randomized control trial[23,24] and be registered at ClinicalTrials.gov prior to beginning recruitment.

3. Study Design and Research Methods

Recruitment: We will recruit 300 pairs (CG and patient) from the University of Colorado Cancer Center (UCCC) or a total of 600 participants. In 2018, UCCC encountered 4370 patients who had breast, lung cancer, or colorectal cancer and were on therapy. Breast, lung, and colorectal cancer are the most common types of solid tumor cancer. While we will accept all types of solid tumor cancer into the study, we will prioritize these three groups and then

recruit other solid tumor cancer patients and their caregivers as needed. We conservatively estimate that less than half of this group will be beginning treatment protocol in a calendar year or about 2100. Of these, we estimate that 50% or more (1050) will have a spousal or partnered caregiver of whom only 50% will have an ***employed*** caregiver (including those furloughed or laid off due to COVID and actively looking for work), bringing the available CG and patient pairs to approximately 525 in a single year. We further estimate 75% (390) will prescreen ≥1 using the sum of the GAD-2 and PHQ-2 scores based on our prior studies[5,18] and the increased distress created by COVID-19. If we conservatively recruit at a minimum 20-25%, 7-8 patient and CG pairs/month from the available population meeting eligibility criteria is reasonable (2/week). We hope to meet our goal of 300 pairs in <40 mo.

Since we are recruiting from a busy employed caregiver population that is notoriously stressed and in which engagement is generally low, we will be using a multifaceted recruitment approach. Potentially eligible patient/caregiver dyads will be identified through electronic medical records to identify patients who are newly diagnosed, within 12 weeks of initiating treatment, and married/partnered. As a first contact, an electronic letter will be sent to patients introducing the study (enclosed) via the secure patient portal, My Health Connection or via US Postal Service if patients do not have My Health Connection. The study letter will have the delegated Site-PI's name and Dr. Cathy Bradley's (PI) names listed. Patients will be informed that a member of the study team will contact them unless they opt out of the study within 3-5 business of receiving the electronic study letter or 10 days of sending the letter through the US postal service. Follow up attempts may be done by phone or email. In addition, a study team member will approach the patient, and when available, their caregiver, in the clinic setting to assess interest and eligibility in the study. Upcoming patient appointments will be identified using electronic appointment scheduling through EPIC. The study team member will contact the oncology care team or clinic staff prior to the appointment to communicate their purpose in speaking with the identified patient or caregiver. The study team member may show the patient the recruitment video or ask an oncology team member to show the patient the video in the clinic. This in person communication will count as an attempt in place of a phone call or email with the total number of contacts not to exceed five attempts.

We also plan to place COMIRB approved fliers and/or brochures across the Anschutz Medical Campus as well as in the UCH Outpatient Cancer Pavilion, and across all UCCC locations. We will also share posts on the UCCC, the Department of Psychiatry and on personal social media pages with our contact information so potential participants can contact the study team. We will utilize the free CU research studies website.

All eligible patients will have the following data removed from EPIC and kept in our secure database, REDCap, for tracking and reporting purposes. MRN, number of weeks since starting treatment, first cancer diagnosis date, first beacon report date, department name, type of cancer, surgery, type of treatment, type of cancer treatment, treating provider, patient marital status, patient age, vital status, race, ethnicity, gender, and preferred language. For ineligible patients we will only keep their MRNs for tacking while recruiting. Any reporting done with ineligible participants will only show the overall number of ineligible participants that we screened.

Recruitment Facilitation, Adherence, and Retention: Combining our prior trials (n=303 dyads) of HSCT CGs, attrition at six months was approximately 39%; of those, 25% were due

to patient death which we expect to be lower in this study. Supplemental follow-up calls improve overall retention[25,26]. Follow-up calls to all randomized groups will serve as reminders of upcoming study activity. We will send birthday cards from the team to CGs and patients (birthdays will occur during the yearlong study) thanking them for continued involvement in the study. Participants will receive thank you notes for their efforts at conclusion of the study. Finally, we will share study results in a user-friendly format after the trial is completed. All have been shown to improve recruitment and retention in a variety of studies[26-33]. At consent, we will inquire of all participants what they prefer for scheduling reminders (text, email, or phone). Use of text messages improves patient adherence[34]. We will emphasize support by UCCC for this study, focus on each person's self-worth and contribution to the science of the study to evoke altruistic feelings, emphasize support of participants by the research and medical staff, and describe how their participation will ultimately serve themselves as well as all patients and CGs. These factors improve willingness to participate[26].

Participant Reimbursement

Participants (CGs and patients) will be reimbursed at 3, 6, 9, and 12 months in proportion to completed study tasks according to Table 1. To encourage improved completion, we will also provide a completion bonus at month 12 to those participants who complete 85% of biomarker collections (CGs only) as well as 85% of questionnaires (caregiver and patient).

Table 1. Caregiver Compensation

	Study Month														
	Base	1	2	3	4	5	6	7	8	9	10	11	12	Reimburse	Total
Hair collect	X			X			X			X			X	5 X $5	$25
Saliva collect	X			X			X			X			X	5 X $5	$25
PROMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	13 X $2	$26
RedCap Survey	X			X			X			X			X	5 X $10	$50
							Completion Bonus								$50
							Maximum Possible								**$176.00**

Patient Compensation

	Study Month							Reimburse	Total
RedCap Survey	X		X		X		X	5 X $10	$50
				Completion Bonus					$25
				Maximum Possible					**$75**

All consented and prescreened participants will complete self-report questionnaires using an electronic data capture approach, REDCap™[105] before randomization by **permuted block design** with stratification for patient condition of palliative versus non-palliative (i.e. curative) to a mode of **PEPRR** (**Virtual-PEPRR** or **Pep-Pal)** or **TAU** (allocation ratio 1:1:1). After

completing and returning baseline questionnaires, treatment assignment will be revealed to the participant. Study flow is indicated in Figure 1.

Remote CG Biomarker collection will be performed *without a need for face-to-face contact* between study staff and consented participants as follows for the two biological matrices.

Hair is collected remotely from the posterior vertex (by the participant) as previously described (10, 13) and assayed using methodology refined for smaller amounts of hair (14). This region is more resistant to hair loss for example in male pattern baldness (e.g., one of the last areas to be lost). Cosmetically one cannot tell the hair was removed. In brief, the hair is parted, and the sample is collected along a horizontal part in the target area using carefully developed instructions for remote collection (see Attachment 1). Approximately 50 strands along the 2-3 cm part line will be cut as close to the scalp as possible with scissors, carefully aligned along the scalp end. The strands are taped to foil with the scalp end marked for long term storage at room temperature (as shown in Figure 2). The samples are labeled only with bar codes for de-identification. Subsequent samples will be collected from the same general area in an identical manner.

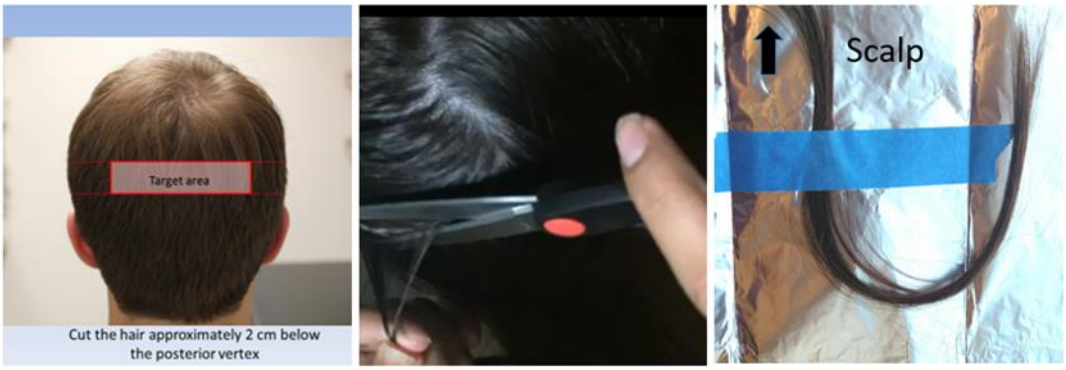
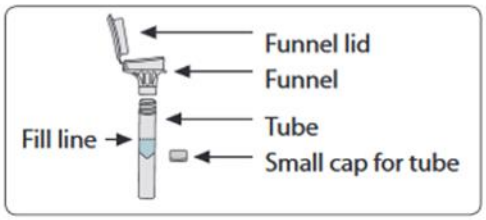
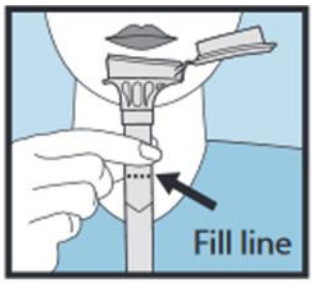


Figure 2. Hair collection

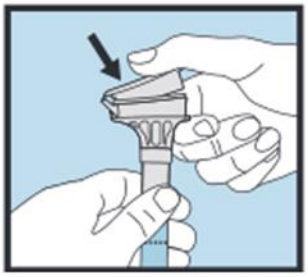
Saliva DNA will be collected by the participant using Oragene 500 saliva collection kits (DNAgenotech #ORG500) as indicated in Figure 3. In brief, the participant is instructed to briefly rub under their chin, hold their tongue toward the roof of their mouth, and suck their cheeks inward to stimulate saliva flow, and spit into the funnel until 2 ml of saliva is collected. This can be accomplished by repeatedly following this procedure until the fill line is met. The funnel cap is snap closed to release the stabilizing agent, the funnel is removed, and the small cap is securely closed, the tube is inverted several times, and stored at room temperature until returned to the lab. Samples are stable for more than a year stored in this manner. Detailed participant instructions for collection are included as Attachment 2. In addition to provision of paper instructions (Attachment 2), participants will access an online instructional video https://youtu.be/jwXKwPuLx9Q.

Figure 3. Oragene Saliva Collection System

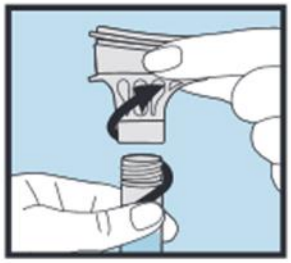




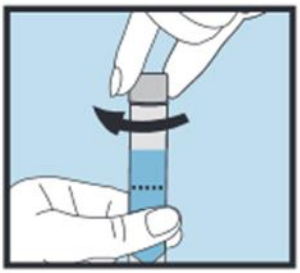
Collect saliva



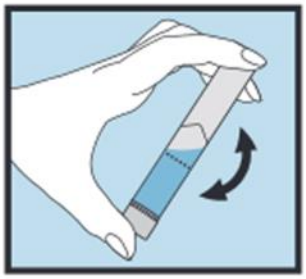
Funnel lid closed to add stabilizer



Twist off funnel lid



Twist on small cap



Carefully invert closed tube several times

Randomization to groups

Three hundred total dyads (patient and CG) will be randomized by permuted block design stratified by patient condition of palliative versus non-palliative (i.e. curative) by the study statistician to either **TAU, Virtual-PEPRR**, or **PepPal** (allocation ratio 1:1:1), 100 dyads/group. Treatment assignment will be revealed to the participant after baseline questionnaires are completed and returned.

Treatment as Usual (TAU)

The TAU condition for this study takes into account published recommendations for an adequate representation of **TAU**[35]. All participants regardless of randomization will be encouraged to use available psychological resources. Participants in **Virtual PEPRR**, **PepPal,** and TAU will receive a staff call informing them what group they have been assigned to after randomization. We will ask what method they prefer to receive reminder "check-ins" (email, call, or text). "Check-in" times will follow the biomarker and redcap questionnaires table: 3m, 6m, 9m, 12m. There will be a standard email to all participants as "check-in" and a reminder that the biomarker collection period is coming up. We will specify in email to *please reply.* People that stated a preference for call or text will also receive a call or text in addition to the email. These calls will help maintain participant engagement in completing questionnaires as well as returning biomarkers they have collected.

Study Month

	Base	1	2	3	4	5	6	7	8	9	10	11	12
Hair collect	X			X			X			X			X
Saliva collect	X			X			X			X			X
PROMIS	X	X	X	X	X	X	X	X	X	X	X	X	X
RedCap Survey	X			X			X			X			X
Staff Check-in	After randomization			X			X			X			X

Information collected during each staff call			
	Virtual PEPRR	**PepPal**	**TAU**
Was contact made?	**X**	**X**	**X**
Any study problems?	**X**	**X**	**X**
What?	**X**	**X**	**X**
Your biomarker collection period is approaching (months 3, 6, 9, and 12)	**X**	**X**	**X**

Virtual-PEPRR

Virtual-PEPRR evolved in response to social distancing due the COVID-19 pandemic from a face-to-face CG intervention targeting CGs of stem cell transplant patients. That work began almost a decade ago when we began testing efficacy of **PEPRR-1.0** in these CGs**.** We found that **PEPRR-1.0** effectively lowered depression, anxiety, and stress [15]. **PEPRR-1.0** was developed from a stress management program for *patient* populations[36-38], which we manualized for CGs[15,16]. We observed that flexibility was core to retention and success[16]. In a second RCT**, PEPRR-2.0** included video chat sessions via smartphone to substitute for 1-on-1 sessions at times when it was more convenient for the CG[39] than coming to the clinic for the intervention. We have completed a series of focus groups to gather more information on the needs of employed caregivers for the current RCT.

Based on previous CG exit interviews, **Virtual-PEPRR** content has incorporated important aspects of **PEPRR 1.0** and **2.0,** as well as recent focus group input related to how employment factors impact caregiving. In the present study, all CGs assigned to **Virtual-PEPRR** will participate solely using either virtual (Zoom) or telephone chat modalities without in-person meetings. Selection between Zoom or telephone allows somewhat greater flexibility for preferences of the participants. Preferences and potential relationships to outcomes for a modality (video versus audio) will be evaluated in exploratory analyses.

Each CG, randomized to **Virtual-PEPPR,** will schedule 8 sessions within a 12-week period at the time of their convenience, preferably to be completed within 8 weeks. Modality (video versus audio) will be selected at the CG's discretion. In the face of any scheduling difficulties, the CG is in control. Regardless of specific modality selection, all will be treated as **Virtual-PEPRR**. Unpacking which modality (video or audio) is preferred will be only exploratory since we are seeking provision of a maximally flexible intervention.

The initial session provides an overview and introduction to stress management, the biofeedback device (emWave2 described below), as well as order of presentation. CGs

assigned to **Virtual-PEPRR** will also be provided with a workbook including session materials and homework assignments as used previously[15,40]. This session must be held using Zoom to establish a more personal link with the interventionist; audio alone (e.g., telephone) is not allowed for the first session. This provides a visual connection for training in the use of the biofeedback device. Remaining sessions can be either video or telephone mode.

All CGs randomized to **Virtual-PEPRR** will receive in their package a user-friendly biofeedback device, *emWave2* (Heartmath, Inc), that will serve as a tool to improve relaxation. It will be introduced and demonstrated in the first session. In brief, it is a small device (8X4X1 cm) on which the user places their index finger or clips a sensor to their ear. Pulse during contact assesses heart rate variability[41,42] with a visual output representing level of vagal tone (a sign of relaxation)[43-46]. Using this device, the participant learns to pace their respiration while relaxing to a synchronous display, which increases vagal activity and reduces blood pressure[47-50] and contributes to relaxation. The emWave2 will serve as an additional tool for coping when distressed. It also stores device usage. CGs will be requested to use the device for 5-10 minutes 4-5 times each week or any time they feel distressed. At the beginning of sessions, the interventionist will ask the participants the number of times they have used the emWave in the previous week. The participants will return the device by mail at the three-month assessment and the interventionist will download usage data. We will then return the device to the Caregiver. We will additionally ask the caregiver to report the number of days (or times) they used the emWave2 in the preceding week during each weekly call during the first two months of the study. At study exit, we will ask that it be returned with the last 12-month sample collection.

Each 60 min, **Virtual-PEPRR** session (provided by a trained social worker) will be devoted to a specific topic with the goal of assisting CGs in developing and applying stress-management skills both in caregiving as well as in their work setting. Sessions include problem-solving, identifying cognitive distortions, application of relaxation techniques such as the emWave2, acquiring new coping skills, utilizing social support, and establishing appropriate goals. It will include addressing needs specifically identified by employed CGs[51] such as working from home, disruption of their work day by medical appointments, "I am replaceable in my job," or guilt associated with neglecting job responsibilities. Briefly presented in the following order, sessions will include: 2) Stress and the mind-body connection, 3) How our thoughts can lead to stress, 4) Coping with stress, 5) Strategies for maintaining energy and stamina at home and the work setting, 6) Coping with uncertainty and fear of unknown with their patient as well as in the work setting, 7) Managing changing relationships within the family and work environment, and 8) Getting the support they need including work accommodations and/or legal protections (e.g., Family Medical Leave Act, Americans with Disabilities Act). Intervention fidelity for sessions will be determined from recordings made during sessions. The Interventionist will record the sessions via Zoom if the participant is in agreement. The recordings are explained in the consent form (under optional procedures) and the participants can agree or disagree to having their sessions recorded. If they disagree, they are still included in the study. The interventionist will confirm agreement again with the subject before recording the sessions. Recordings will be stored on the secure Department of Psychiatry server in a team folder that is password protected. Twenty percent of these recordings will be randomly reviewed monthly for adherence to an 8-11 item check list for each session. In our first trial, overall fidelity was 96% across all sessions [15] for these items. In a trial recently concluded,

fidelity was 100% across 3 interventionists and 2 sites for more than 100 random sessions. Detailed descriptions of session content have been published[40].

The interventionist is a licensed social worker. She was trained by the previous PEPRR social worker and by viewing the previously recorded intervention sessions from the prior PEPRR study. She was also involved in developing and editing the caregiver manual that is given to the Virtual-PEPRR groups. She will be receiving further ongoing training from one of the primary authors of the manual, Teri Simoneau, who will be responsible for monitoring ongoing fidelity.

Content will be identical for video or audio-based chat. Most CGs own a suitable phone (93%) based on our studies to date. CGs who do not have a Smartphone will be provided a smartphone with service contracts at no charge.

Participants assigned to **virtual-PEPRR** will receive a **PEPRR** based workbook (Attachment 3). This workbook contains exercises covered in the session as homework assignments. During the weekly phone call, we will verify if have they used it. We will not engage in specific discussion about the workbook contents.

Pep-Pal.

Despite a movement toward application of mobile applications for psychological interventions[52], testing remains inadequate[53]. **Pep-Pal** is a mobilized version of **PEPRR** developed by Dr. Amoyal-Pensak, a member of our team[19,20]. She mobilized content of **PEPRR** into **Pep-Pal** to create web-based modules matching each **PEPRR** session to augment accessibility for CGs. **Pep-Pal** sessions will replicate essential components of each session of **Virtual-PEPRR,** but in shorter format while providing relaxation exercises (**mini-Peps**). CGs randomized to **Pep-Pal** will receive a unique ID/password allowing us to track participant use of **Pep-Pal**.

Pep-Pal is web-accessible by smartphone, tablet, laptop, or desktop computer and covers material presented in **Virtual-PEPRR** sessions but <20 min. duration. **Pep-Pal** was determined to be usable and acceptable by transplant CGs[54,55]. **Pep-Pal** includes "**Mini-Peps**" which are video guided, 3 min. stress reduction exercises that the CGs can access any time. Our recent pilot study found that **Pep-Pal** was associated with reduced perceived stress and improved ability to learn coping strategies. Screen shots of **Pep-Pal** are shown below in Figure 5 as well as **Mini-Peps** in Figure 6.

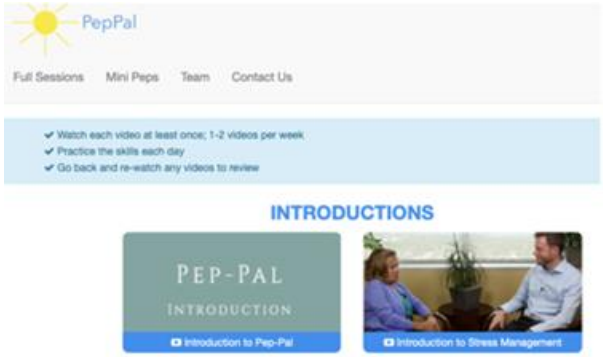
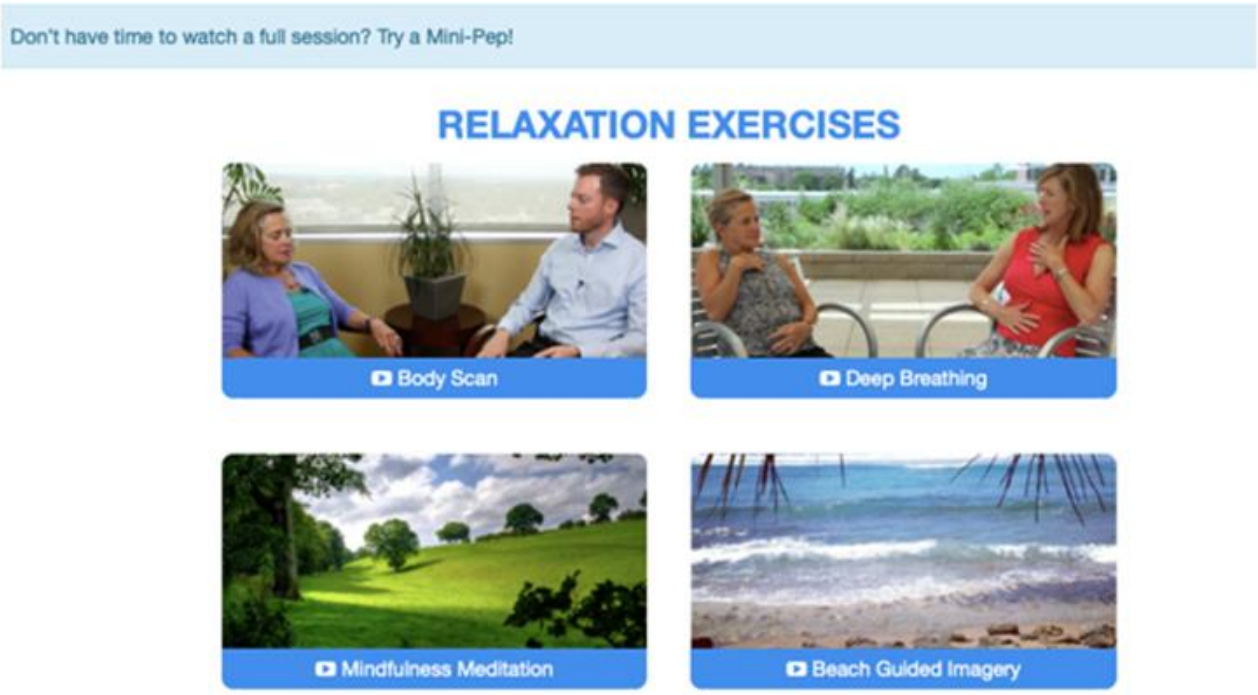


Figure 5. PepPal Screen shots



Figure 6. Screen shots of Mini-Peps



Each CG, randomized to **Pep-Pal,** will complete *modules at times that are convenient*. Each participant will be advised to watch all sessions at least once. Session content will follow the order recommended. In the face of scheduling difficulties, the CG is in control of when they log in to the online site 24/7. If desired, they can complete more than one module a week, repeat any session, and access the Mini-Peps as frequently as desired. This information is

recorded for later analysis through back-end data monitoring. To encourage adherence, participants will receive a call if they have not logged in for the initial 2 weeks. We will also send automatic weekly email reminders to use Pep-Pal.CGs randomized to Pep-Pal who do not have a Smartphone will be provided one with service contracts at no charge as needed.

4. **Description, Risks and Justification of Procedures and Data Collection Tools:**

Due to social distancing restrictions, we have converted this study to rely entirely on self-collected biomarkers which will be returned to the laboratory via USPS or FedEx. This is a low risk study. All questionnaires will be completed using HIPAA compliant, secure REDCap questionnaires[56] via the CG's or patient's mobile device or personal computer. CGs report this as less burdensome. Reminders to complete questionnaires will be sent via preferred modality (e.g., email, text messaging, phone messages). Additionally, paper instruments will be available via the USPS if requested. Paper instruments returned via USPS will be entered in REDCap via double entry for verification. Detailed descriptions of outcomes for CGs and patients are described as follows:

Caregiver Outcomes All caregivers will complete questionnaires remotely using RedCap. If requested, they can complete paper versions instead. These will be sent via USPS with return envelopes if requested. During consent the caregivers will also provide permission to access their EMR as defined below. If they do not have a UCHealth Patient ID number, one will be assigned. Caregiver Questionnaire pack is included as Attachment 3.

.

CG Background and Demographics. CGs will complete the demographic questionnaire. It includes questions regarding CG age, sex, education, total household income, estimated hours/day caregiving, sources of social or psychological support, alcohol and drug history, and a brief CG medical history. For subsequent assessments, changes in use of medication or individual psychosocial/medical services will be obtained from electronic medical records (EMR).

CG Self-report outcomes will include instruments measuring depressive, anxious and stressed phenotypes for which we have previously determined effect sizes (ES) for **PEPRR** (ES=.39-.66). We will select CGs scoring ≥1 based on the PHQ2 (depression) and/or GAD2 (anxiety)[57]. These are frequently used for preselecting on distress in clinical settings[58].

1) CG Depressive Symptoms. Knowing that the present CGs have prescreened high on depression and/or anxiety, both of which are common[5,18], we readjusted our primary outcome to focus on depressive symptoms which are also associated with telomere length[59]. As the **primary CG outcome**, depressive symptoms will be assessed with the **Center for Epidemiological Studies Depression Scale (CESD)** [60] based on the past 2 weeks; a 20-item scale with good validity [60-63]. Cronbach's alpha for our recent trial ranged .64-.83 across subscales and full-scale outcomes for caregivers and patients. Scores over 16 (range 0-60) are viewed as suggesting potential clinical problems[64]. CESD-based participant alerts to clinical staff at the cancer center are based on scores ≥ 16. *The ES of **PEPRR** on the CESD at 3 mo. post-transplant for HSCT CGs was 0.46* [15].

2) CG Anxiety. Anxiety, as a secondary outcome, will be assessed using the **Spielberger State Anxiety Inventory (SSAI)** [65]**.** Anxiety is elevated in CGs [5,18,66-70] and is

mitigated by **PEPRR** [15]. The SSAI is a 40-item scale on which participants indicate how they feel "right now" (state) on a 4-point Likert scale. Internal consistency is .89 to .91. In our recent trial, Cronbach's alpha was .95 and .94 for caregivers and patients, respectively. *The effect size (ES) of **PEPRR-1.0** on SSAI at 3 mo. post-transplant was 0.66* [15].

3) CG Stress. The **Perceived Stress Scale (PSS)** [71,72] will be a secondary outcome of stress. It is a well validated measure[71,72], i.e., how much participants feel their life is unpredictable, uncontrollable, and overwhelming over the past month. Based on our studies, Cronbach's alpha is .89 and .86 for CGs and patients, respectively. *The ES for **PEPRR-1.0** on PSS 3 mo. post-transplant was 0.39* [15].

4) CG Employment status/hours worked. Employment status and weekly hours worked (including absenteeism or hours missed) will be assessed using questions drawn from the Current Population Survey (CPS). The Bureau of Labor Statistics administers the CPS nationwide. It is the leading source of employment information in the US. Dr. Bradley has used these questions successfully in over 2000 cancer patients[11,13,73]. This will be asked in reference to the time of patient diagnosis or if unemployed, prior to furlough or layoff due to COVID-19, and currently.

5) **Health insurance**. Health insurance source (employer-based, public, other, uninsured) and family members covered will be asked to determine whether the caregiver and patient (and other dependents) are reliant to employment for the health insurance. In addition, caregivers will be asked if their employer offers health insurance and whether they declined it.

6) CG work setting. Based on prior studies, key characteristics are important: number of employees (determines whether policies such as Americans with Disabilities Act and Family Medical Leave Act apply and is a good predictor of other benefits), sector (private for-profit, private non-profit, government), and type of firm (manufacturing, professional, etc.). This will be asked in reference to time of patient diagnosis or if unemployed, prior to furlough or layoff due to COVID-19, and currently. These items are for descriptive information and exploratory analysis.

7) CG Job Tasks. Job task questions come from the Health and Retirement Study (HRS)[74,75]. These questions assess the extent to which the respondent performs tasks requiring physical effort, keeping the pace set by others, memory, concentration, and analytical skills. This will be asked in reference to the time of patient diagnosis or if unemployed, prior to furlough or layoff due to COVID-19, and currently.

8) CG Job accommodations. Job accommodations questions will come from HRS and query whether employers provide: flexible work schedules, more rest breaks, someone to help with task, special equipment, arrange transportation, and connect to services outside the workplace[76]. This will be asked in reference to the time of patient diagnosis or if unemployed, prior to furlough or layoff due to COVID-19, and currently.

9) CG Job satisfaction. We will use a single question to assess job satisfaction[77]. This will be asked in reference to the time of patient diagnosis or if unemployed, prior to furlough or layoff due to COVID-19, and currently.

10) CG Burden. To evaluate CG burden as a covariate we will use the Caregiver Reaction Assessment (CRA)[78], a highly recommended measure[79] developed by one of our consultants (Given). The CRA uses a 5-point Likert scale for 24 items with good reliability[79]. As recommended by Dr. Given, we will target Schedule and Health subscales, with Cronbach's alpha for subscales of .76 and .68, respectively.

11) CG Healthcare Utilization (EMR). As an important feature of this study, secondary healthcare utilization outcomes will come from two sources: CG self-report and the UCCC's electronic system, EPIC, to measure outpatient visits and medication usage which are the two utilization measures most likely affected by **PEPRR-3.0**. Medical records will be accessed through Health Data COMPASS, which brings together the hospital's EPIC database with the cancer registry, pharmacy data, and laboratory clinical testing. It has detailed information on outpatient visits including laboratory test results for all activities within the CU system. In addition, COMPASS merges its patient-level data with Colorado's All Payer Claims Database (APCD). The APCD includes claims data from commercial health plans, Medicare, and Medicaid. The APCD is the most comprehensive source of health claims data from public and private payers in Colorado. These data allow us to estimate care received outside of the system. The APCD are key to ensuring the completeness of utilization data for patients and caregivers who may receive care outside of the UCHealth. For our prior study, 85% of CGs of University of Colorado Health (UCH) patients were seen within the UCH system. CG self-reported outpatient visits and medications are needed to capture real-time utilization and to corroborate data in COMPASS. There will be a delay of several months from a visit outside of the UCHealth system to when COMPASS updates through the APCD. Although we will collect other units of utilization (e.g., hospitalizations, emergency department use), these may be rare within study period.

12) CG CCOVID-19 Distress The COVID-19 pandemic has altered all aspects of medical care, including cancer care[80]. CGs are concerned for their safety as well as that of their loved one. COVID-19 has also impacted the international economy with US employment rates at 13.3% at the end of May 2020 (US Bureau of Labor Statistics). Since employed CGs were a focus of our initial application, we must consider the impact of COVID-19 more generally. To this end, we will include a Coronavirus Impact Scale. It is a 12-item Likert scale questionnaire recently assembled by Stoddard and Kaufman (Personal communication). This is an exploratory measure and may be included as a covariate in secondary analyses.

13) CG Monthly PROMIS Assessments. Because biomarker outcomes described in the following section cover a longer time frame than the time anchors (one month or less) for the psychological questionnaires above, we will include monthly assessments using the NIH PROMIS system questionnaires for depression and anxiety which have high reliability and convergent validity[81,82]. These are exploratory outcomes to be used in conjunction with the biomarker outcomes. PROMIS measures for depression and anxiety will be averaged over the previous three-month interval, which coincides more precisely with the time frame of hair cortisol encompassing the past three months of hair growth. Questionnaires will be sent securely via RedCap to the participant's smartphone for completion.

14) CG MOCS- Measure of Current Status- Part A measures current self-perceived ability to utilize stress management skills that are targeted by the interventions: the ability to relax at will, recognize stress-inducing situations, restructure maladaptive thoughts, be assertive about needs, and choose appropriate coping responses as needed. We are adding these to further evaluate if there are any changes in caregivers' ability to learn and use stress management strategies as a result of participating in the interventions. Furthermore, this scale could allow us to further investigate the different affects each intervention (PEPRR or Pep-Pal) may have on the participants.

14) CG EMWave2 usage (Virtual PEPRR only) Caregivers randomized to Virtual PEPRR will report the number of times they use the EM Wave2 for the past week to the interventionist at each session.

15) CG Exit questionnaire. At the end of the study each participant will complete an exit questionnaire that asks a number of questions regarding their perspective on the intervention (usefulness, difficulty, burden, new technique they may have developed, areas in which it helped, areas in which it was lacking), participating in the study itself,

CG Biomarker Outcomes These outcomes include systems that influence telomere stability[83,84] pointing to an easily obtained set of CG biomarkers that may be influenced by our intervention[85,86]. Biomarkers are secondary outcomes. All biomarkers will be collected by the participants themselves as described earlier. This will allow for social distancing throughout the course of this trial.

1) CG Telomere Length (TL). Samples will be collected by the participant using Oragene saliva collection kits. Of importance, the stabilizing agents in this kit inactivates COVID-19 virus (https://www.dnagenotek.com/US/pdf/MK-01430.pdf) which might be present in samples. TL represents a secondary CG outcome. TL assays will be performed on de-identified samples in the laboratory of Dr. Elizabeth Blackburn under the direction of Dr. Jue Lin (University of California San Francisco) using well established protocols [87]. Longitudinal samples from a participant will be assayed in the same batch to minimize differences due to assay variance.

3) Hair cortisol. A possible influence on inflammation is the activity of the hypothalamic pituitary adrenal axis (HPA)[88] as measured indirectly by hair cortisol[89]. Hair grows about 1 cm/mo. with the proximal 3 cm representing the most recent 3 mo. HPA activity[89]. The relation of hair cortisol to HPA activity is analogous to hemoglobin A1c as an indicator of the last three months of glycemic control[90]. We require 1/10 of the original amount of hair used for cortisol assay[91], which significantly improves participants consenting to hair collection. Hair cortisol (hCORT) is a novel approach to assessing chronic HPA activity [92] in distressed CGs[93], in job-stress[94], or in job-stress related depression[95]. hCORT is also modified by behavioral interventions[96]. The proximal 3 cm (3 mo.) from the scalp will be assayed at each collection. Participants refusing hair samples (or lacking sufficient hair) will simply be treated as missing in the analysis for this variable. Hair is ground, extracted, and processed by immunoassay (Salimetrics, LLC, State College, PA) according to our published methods with intra and inter-assay CVs < 5 and 10%, respectively [97-99]. Our procedure is highly reliable with other laboratories [100]. All longitudinal samples from a participant will be assayed in the same batch to minimize differences due to assay batch.

Patient Self-Report Outcomes

Patients will complete a limited number of questionnaires remotely using RedCap. They have an option of paper instruments if requested. These will be sent via USPS with return envelops as requested. During consent the patients will also provide permission to access their EMR. Patient questionnaire packet included as Attachment 5.

1) Patient background and demographics. Patients will complete demographic questionnaires. They include questions regarding age, sex, education, total household income (cross validates with CG), employment status, insurance source, sources of social or psychological support, alcohol and drug history, a brief medical history, and diagnosis. EMR also serves to fill in missing information.

2) Patient Distress. As *secondary outcomes*, patient distress will be based on self-reported depression (CESD), anxiety (STAI), and perceived stress (PSS) as described for the CG.

3) **Health insurance**. Health insurance source (employer-based, public, other, uninsured) and family members covered will be asked to determine whether the patient (and other dependents) is reliant to employment for the health insurance. In addition, patients will be asked if their employer offers health insurance and whether they declined it.

4) Patient Healthcare Utilization. We will use the COMPASS system as the EMR source of information on patient treatment like the CG. Outcomes include all healthcare utilization data associated with adverse events and/or poor symptom management. Exploratory outcomes include care associated with treatment-induced toxicities (e.g., emergency department visits, hospitalizations, and outpatient visits) and dose delays or stoppages. These will be available at each assessment interval, i.e., baseline and 3, 6, 9, and 12 mo. post treatment and will reflect the past 3 mo.

5) Patient Symptom Management. We will use the MD Anderson Symptom Inventory (MDASI) core scale[101,102], which assesses 13 symptoms (pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, memory problems, lack of appetite, drowsiness, dry mouth, numbness, sadness, and vomiting) on a 0-10 scale. Mean item scores (+ SD) track symptoms from beginning treatment (1.55 + 1.47) to conclusion (3.34 + 1.87)[103] and serves as an accepted marker for symptom severity longitudinally[104] with excellent reliability[104,105].

6) Patient Exit questionnaire. At the end of the study each participant will complete an exit questionnaire that asks questions regarding their perspective on specific changes they have noted in their caregiver during the course of the study.

E. Potential Scientific Problems:

An unexpected and primary limitation to this study includes the unknown and continuing impacts of COVID-19 on the execution of all studies remotely. COVID-19 is a significant psychological stressor which we are attempting to assess. COVID-19 may slow participant accrual due to our inability to speak face-to-face with caregivers. However, we have learned that patients are supportive of telehealth visits with their oncologists and hope this new technology will spill over in a significant manner to the present study. Remote collection of biomarkers is new to our group as far as hair cortisol. We have processed samples for hair cortisol collected remotely by a collaborator and were quite excited with the quality of samples participants collected themselves. We do not see saliva collection for Telomere length assessment as posing a problem.

Although the risks are considered minimal for this randomized control study, we will create a data safety and monitoring board (DSMB) to monitor the progress of the protocol, the safety

of the research subjects, and data. The DSMB will consist of one physician, a psychologist, and biostatistician familiar with cancer patients and their families. None of these individuals will have any direct involvement in the proposed project. The DSMB will meet once a year to evaluate progress to date, the status of all subjects unless an adverse event occurs at which time an emergency meeting of the DSMB will be called. [Drs. Bradley, Mikulich] will hold monthly study review meetings with the study staff involved in the study. During these meetings, subject recruitment, subject drop-out, and any difficulties encountered in collecting and processing the data or providing the treatment interventions will be discussed. Minutes from these meetings will be kept on file for future reference as needed. Members of the team will monitor the data for consistency of collection. Although this is a treatment study, we do not anticipate any severe adverse events to occur associated with the intervention. In the unlikely event that a subject might suffer an adverse event this will be reported to both the DSMB and the Colorado Multi-Institutional Review Board (COMIRB) which oversees the project. Data will be stored in a database located on a secure password-protected, HIPAA compliant university server.

F. Data Analysis Plan:

Data Aggregation, Distributional Assumptions, Missing Data/Attrition. Prior to analyses, data will be screened for errors and outliers. When necessary, appropriate transformations will be made for non-normal outcomes. The pattern of participant dropout across participant characteristics and for all variables specified in the hypotheses will be examined to ensure a reasonably equal distribution of participants lost to follow-up between groups. The analytic approach proposed uses maximum likelihood techniques that can include participants with incomplete data without need for imputation. These techniques are robust under certain conditions such that group comparisons will not be biased if missing data is ignorable. If this is not enough to minimize influences of observations, a sensitivity analysis will be conducted to help determine effects of missing data. Separate analyses of participants who complete the study will be conducted.

Verification of Randomization and Inclusion of Covariates. Preliminary analyses will validate that there are no baseline differences between intervention groups. We expect potential differences between groups in either demographics or baseline outcome measures to be accounted for by the permuted block randomization with stratification for patients palliative condition (yes, no) as they have in previous trials[6]. Should differences remain, we will co-vary variables that are both correlated with the outcome and differ by group. All CG models for each aim include CG age to control for its noted associations with the primary and other psychological outcomes based on our previous work, [6,12] as well as cancer type and the stratification within randomization for patient's palliative condition (yes, no). Additionally, we will evaluate appropriateness of controlling for CG sex, patient age, illness duration, assay control parameters, and COVID-19 measures in exploratory models. An alpha level of 0.05 will be used to evaluate significance of *a priori* planned comparisons and all tests will be two-tailed, non-directional.

Analytic Strategy

SAS statistical software will be used including the following procedures: PROC MIXED, PROC NLMIXED, and PROC GENMOD. Aims and hypotheses are briefly stated, followed by analytic plans.

Aim 1: Impact of Virtual-PEPRR or Pep-Pal compared to TAU on employed CGs with high distress

- H1a: As the primary trial outcome, CGs randomized to either **PEPRR-Virtual or Pep-Pal versus TAU** will have reduced depressive symptoms at 3 months (efficacy), as well as 6, 9, and 12 mo. follow up (sustainability).
- H1b: As secondary psychological and medical outcomes, CGs randomized to either **PEPRR-Virtual or Pep-Pal** versus **TAU** will have lower anxiety and perceived stress, as well as fewer outpatient visits and fewer medications prescribed based on their EMR at 3 mo. (efficacy) and at 6, 9, and 12 mo. follow up (sustainability).
- H1c: As secondary biomarker outcomes, CGs randomized to either **PEPRR-Virtual or Pep-Pal** versus **TAU** will have reduced or stabilized biomarkers of allostatic load (including hair cortisol and telomere length at 3 months (efficacy) and at 6, 9, and 12 mo. follow up (sustainability).

Graphs of outcomes over time for individuals and for each group will be visually compared. For hypotheses addressing group differences for CGs, primary and secondary outcomes will be evaluated similarly: 3 groups (**Virtual-PEPRR, Pep-Pal**, **TAU**) over times (baseline, i.e. prior to treatment, 3 mo., 6 mo., 9 mo., and 12 mo.). Linear mixed models, i.e. mixed model analyses of covariance (ANCOVA) will minimally specify group, time, cancer type, patient palliative condition (yes, no) and the group by time interaction as fixed effects; potential interactions with type will be evaluated and remain in the model when significant. Subject (CG) will be specified as a random effect, assumed independently normally distributed with mean 0 and variance independent of the random errors. All models for CG outcomes will include CG age as a covariate because it has related to CG distress and other CG outcomes in our prior studies[6,12]. We will evaluate stage of cancer as an exploratory covariate.

Within models for outcomes that have significant group by time interactions, efficacy will be evaluated through 3 months as the difference between **Virtual-PEPRR** and **TAU** groups in the change from baseline to 3 months in depressive symptoms (primary outcome) and other indicators of distress (secondary outcomes). Similarly, efficacy will be evaluated as the difference between **Pep-Pal** and **TAU** groups in the change from baseline to 3 months in depressive symptoms (primary outcome) and other indicators of distress (secondary outcomes). If there is no difference in separate comparisons of the intervention groups with **TAU**, those participants the **Virtual-PEPPR** and **Pep-Pal** groups will be combined and compared with **TAU** on change in primary and secondary outcomes as secondary analyses. All results will be discussed.

To assess sustainability of intervention effects, the intent-to-treat sample for these analyses will include those participants that complete the 3 month assessment. Sustainability will be evaluated as the difference between **Virtual-PEPRR** and **TAU** groups in the change from 3 months (end of treatment) to subsequent time points (6, 9, and 12 months) in depressive symptoms (primary outcome) and other indicators of distress (secondary outcomes). Similarly, sustainability will be evaluated as the difference between **Pep-Pal** and **TAU** groups in the change from 3 months (end of treatment) to subsequent time points (6, 9, and 12 months) in depressive symptoms (primary outcome) and other indicators of distress (secondary outcomes). If there is no difference in separate comparisons of the intervention groups with **TAU**, those participants the **Virtual-PEPPR** and **Pep-Pal** groups will be combined and compared with **TAU** on change in primary and secondary outcomes as secondary analyses. All results will be discussed.

Aim 2: Impact of CGs receiving Virtual-PEPRR or Pep-Pal compared to TAU on patient outcomes.

- H2a: As secondary psychological outcomes, patients whose CGs received either **Virtual-PEPRR or Pep-Pal** versus **TAU** will have reduced anxiety, depression, and stress at 3 mo. (efficacy) and at 6, 9 and 12 mo. (sustainability).
- H2b: As a secondary outcome based on patient EMR, healthcare utilization will be lower in patients whose CGs received either **Virtual-PEPRR or Pep-Pal** versus **TAU** at 3 mo. (efficacy) and at 6, 9 and 12 mo. (sustainability).
- H2c: As a secondary outcome, patients whose CGs received either **Virtual-PEPRR or Pep-Pal** versus **TAU** will have improved symptom management as measured by the MD Anderson Symptom Inventory at 3 months (efficacy) and at 6, 9 and 12 mo. follow up (sustainability).

Graphs of outcomes over time for individuals and for each group will be visually compared. The same analysis plan as in **Aim 1** will be used to evaluate hypotheses addressing group differences for patients: 3 groups (**Virtual-PEPRR, Pep-Pal** ,**TAU**) over times (baseline, i.e. prior to treatment, 3 mo., 6 mo., 9 mo., and 12 mo.). Mixed model ANCOVAs will minimally specify group, time, cancer type, patient palliative condition (yes, no) and the group by time interaction as fixed effects; potential interactions with type will be evaluated and remain in the model when significant. Subject (patient) will be specified as a random effect, assumed independently normally distributed with mean 0 and variance independent of the random errors.

Within models for outcomes that have significant group by time interactions, efficacy will be evaluated through 3 months as the difference between **Virtual-PEPRR** and **TAU** groups in the change from baseline to 3 months in depressive symptoms (primary outcome) and other indicators of distress (secondary outcomes). Similarly, efficacy will be evaluated as the difference between **Pep-Pal** and **TAU** groups in the change from baseline to 3 months in depressive symptoms (primary outcome) and other indicators of distress (secondary outcomes). If there is no difference in separate comparisons of the intervention groups with **TAU**, those participants the **Virtual-PEPPR** and **Pep-Pal** groups will be combined and compared with **TAU** on change in primary and secondary outcomes as secondary analyses. All results will be discussed.

To assess sustainability of intervention effects, the intent-to-treat sample for these analyses will include those participants that complete the 3 month assessment. Sustainability will be evaluated as the difference between **Virtual-PEPRR** and **TAU** groups in the change from 3 months (end of treatment) to subsequent time points (6, 9, and 12 months) in depressive symptoms (primary outcome) and other indicators of distress (secondary outcomes). Similarly, sustainability will be evaluated as the difference between **Pep-Pal** and **TAU** groups in the change from 3 months (end of treatment) to subsequent time points (6, 9, and 12 months) in depressive symptoms (primary outcome) and other indicators of distress (secondary outcomes). If there is no difference in separate comparisons of the intervention groups with **TAU**, those participants the **Virtual-PEPPR** and **Pep-Pal** groups will be combined and compared with **TAU** on change in primary and secondary outcomes as secondary analyses. All results will be discussed.

Patient psychological outcomes (H2a) and symptom management (H2c) will be analyzed with linear mixed models as described above if they are normally distributed as expected; alternatively generalized linear mixed models will be utilized. Patient self-reported outpatient visits and medication usage (i.e. patient utilization, H2b) will be obtained from COMPASS records as monthly and one year counts following enrollment and will be modeled with a similar design using generalized linear mixed models assuming a gamma or negative binomial distribution for counts as appropriate. We will adjust for differences in survival among patients. The estimation of utilization is completely observable if the death times are observed by follow-up or if the CG/patient completes the study. We use a modification of the regression model to account for incomplete observation of utilization of those who drop out of the study based on the inverse-probability-weighted method. All patient models will secondarily explore inclusion of CG depression as a covariate. CG self-reported outpatient visits and medication usage (i.e. H1b) will be obtained from COMPASS records as monthly and one-year counts following enrollment and will be modeled with a similar design using generalized linear mixed models assuming a gamma or negative binomial distribution

for counts as appropriate.

Aim 3: Evaluate whether CG employment outcomes are associated with improved patient symptom management.

- H3a: **For currently employed caregivers,** hours worked, and job satisfaction will be positively associated with improved patient symptom management and improved patient psychological outcomes.
- **H3b: For caregivers currently looking for work, patient symptom management will be positively associated with job applications submitted and interviews given and negatively associated with days to finding a new job. .**

Graphs of outcomes over time for individuals and for each group will be visually compared. As described under Aims 1 and 2, patient symptom management and psychological outcomes will be analyzed over time (baseline, 3 month, 6 month, 9 month, 12 month) with mixed model ANCOVAs if they are normally distributed as expected with models evaluating hours caregiver worked in the week prior to assessment (specifying 0's for non-employed caregivers) and job satisfaction scores in the subset of currently employed caregivers and adjusting for stratification on patient palliative condition. In the subset of caregivers who are looking for work at baseline, patient symptom management and patient psychological outcomes at 3 months will each be described by linear regressions evaluating potential caregiver predictor variables such as number of days to finding a new job, job applications submitted, and number of interviews given while adjusting for stratification on patient palliative condition (yes, no).

The likelihood of remaining employed at each time point beginning with 3 months will be estimated using logistic models (yes/no). Weekly hours worked will be estimated using ordinary least squares regression. In addition to measuring raw hours, we estimate change and percent change in hours worked from baseline. Primary models will include covariates for patient healthcare utilization (e.g., emergency department visits, outpatient visits, dose delays, etc.) and patient responses to the MDASI and patient palliative condition (yes, no). These models can be expanded to accommodate covariates for baseline worksite and job characteristics as well as baseline accommodations and job satisfaction. The impact of COVID-19 (job loss, layoff, insurance status change, seeking new employment) will be evaluated in these models as appropriate.

Potential group differences in CG employment outcomes will be evaluated using generalized linear mixed models specifying distributions appropriate to the employment outcome (e.g. logit distribution for employed yes, no; negative binomial for counts of days worked past week) to implement the same design described for the prior two aims

(specifying group, time, group by time as fixed effects with random subject effects) and including CG age, cancer stage and patient palliative condition (yes, no) as covariates.

Exploratory Analyses.

For outcomes where visual assessment warrants it, we will compare Virtual-PEPPR and Pep-Pal interventions over time for differences in efficacy and sustainability as described previously. Although this study is not powered to address the equivalence of these two interventions visual comparability and any detectable differences between them will be reported and discussed.

In a novel application, we will use multivariate generalized linear mixed models in an approach recently published by our biostatistician, Mikulich [208], to simultaneously model trajectories of outcomes in CGs and their patients (e.g. CG depression with Patient depression) as a dyadic analysis. Each set of analyses will result in: (1) estimates of overall associations between trajectories (e.g. correlations among the slopes of patient and CG depression from baseline through 12 month time points), (2) estimates of associations between two variables at the same and different time points, as well as (3) estimates of the times at which those associations are maximum. These multivariate generalized linear mixed model techniques are highly flexible in allowing outcomes with different conditional distributions to be simultaneously modeled by assuming conditional independence given random subject effects. In general, we hypothesize there will be positive relationships between trajectories of CG and patient outcomes.

Power.

Using SAS Proc Power software, we have specified a significance level of alpha= 0.05, two-tailed, and allowed for increased variability as well as conservative estimates of attrition (20-30%) to determine the minimum detectable difference between groups at any time point that we will have at least 85% power to detect. For the primary caregiver outcome (CG depressive symptoms), this corresponds to a standardized effect size. With 100 caregivers per group adjusted for increased variability due to attrition and different cancer types, this study provides 80%-85% power to detect as significant a minimum difference between **Virtual-PEPPR or Pep-Pal** and **TAU** of 0.45-0.52 (medium effect size comparable to that detected in our prior two trials of **PEPRR**[6,14]) as significant at a specific time point (e.g. 3 months). Realistic between-group differences can be detected in secondary physiological CG outcomes as well. For TL (mean=1.0; standard deviation (SD)=0.20), the proposed study provides 80%-85% power to detect as significant a minimum difference between groups of 0.089 to 0.102 (i.e. approximately 8.9% to 10.2%) at a specific time point (e.g. 3 months). For the primary patient outcome of MD Anderson Symptom Inventory scale score, we used estimates from a sample of n=134 patients at the time of treatment

completion (Mean=3.34, SD=1.87, [184,185]) to estimate that this study provides 80%-85% power to detect as significant a minimum difference between groups in score of 0.83 to 0.95 at a specific time point (e.g. 3 months).

G. Summarize Knowledge to be Gained:

Spousal and partnered CGs serve an important role in ensuring the health of our nation but they are at risk for increased morbidity and mortality in association with this challenge. Few family caregivers receive any support for themselves during this experience particularly when the caregiver is employed. The present study investigates the ability of an effective stress management program to be tailored for employed caregivers to mitigate psychological distress and pathophysiology in spousal or partnered caregivers of patients treated for cancer. Furthermore, this will test the efficacy of this approach delivered remotely which is an important goal in the time of the COVID-19 pandemic.

H. References:

Literature Cited

1. Rafiq D, Batool A, Bazaz MA. Three months of COVID-19: A systematic review and meta-analysis. *Rev Med Virol.* 2020:e2113.
2. Koonin LM. Novel coronavirus disease (COVID-19) outbreak: Now is the time to refresh pandemic plans. *J Bus Contin Emer Plan.* 2020;13(4):1-15.
3. Family-Caregiver-Alliance T. Selected caregiver statistics. https://www.caregiver.org/selected-caregiver-statistics. Published 2015. Updated 2015. Accessed.
4. Feinberg L, Reinhard SC, Houser A, Choula R. Valuing the Invaluable: 2011 Update The Growing Contributions and Costs of Family Caregiving. . In: Institute APP, ed. *Insight on the Issues.* Washington DC: AARP Public Policy Institute; 2011:28.
5. Kessler ER, Moss A, Eckhardt SG, et al. Distress among caregivers of phase I trial participants: a cross-sectional study. *Support Care Cancer.* 2014;22(12):3331-3340.
6. Kaplan JB, Guitart J, Giles FJ. Targeted therapies for cutaneous T-cell lymphomas. *Expert Rev Hematol.* 2014;7(4):481-493.
7. Khan K, Cunningham D, Chau I. Targeting Angiogenic Pathways in Colorectal Cancer: Complexities, Challenges and Future Directions. *Curr Drug Targets.* 2017;18(1):56-71.
8. Wolff JL, Spillman BC, Freedman VA, Kasper JD. A national profile of family and unpaid caregivers who assist older adults with health care activities. *JAMA Internal Medicine.* 2016.
9. Kent EE, Rowland JH, Northouse L, et al. Caring for caregivers and patients: Research and clinical priorities for informal cancer caregiving. *Cancer.* 2016:n/a-n/a.
10. de Moor JS, Dowling EC, Ekwueme DU, et al. Employment implications of informal cancer caregiving. *Journal of Cancer Survivorship.* 2017;11(1):48-57.
11. Bradley CJ, Neumark D, Barkowski S. Does employer-provided health insurance constrain labor supply adjustments to health shocks? New evidence on women diagnosed with breast cancer. *J Health Econ.* 2013;32(5):833-849.
12. Kenny P, King MT, Hall J. The physical functioning and mental health of informal carers: evidence of care-giving impacts from an Australian population-based cohort. *Health Soc Care Community.* 2014;22(6):646-659.
13. Bradley CJ, Neumark D, Motika M. The effects of health shocks on employment and health insurance: the role of employer-provided health insurance. *Int J Health Care Finance Econ.* 2012;12(4):253-267.
14. Natvig C, Mikulich Gilbertson S, Bradley CJ, Laudenslager ML. Relationship of depressive and anxious symptoms to employment status in allogeneic stem cell transplant caregivers. Under review.
15. Laudenslager ML, Simoneau TL, Kilbourn K, et al. A randomized control trial of a psychosocial intervention for caregivers of allogeneic hematopoietic stem cell transplant patients: effects on distress. *Bone Marrow Transplant.* 2015;50(8):1110-1118.
16. Simoneau T, Kilbourn K, Spradley J, Laudenslager ML. An Evidence-based Stress Management Intervention for Allogeneic Hematopoietic

Stem Cell Transplant Caregivers: Development, Feasibility and Acceptability. *Support Care Cancer.* in press.

17. Antoni MH, Lehman JM, Kilbourn KM, et al. Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among

women under treatment for early-stage breast cancer.[see comment]. *Health Psychol.* 2001;20(1):20-32.
18. Simoneau TL, Mikulich-Gilbertson SK, Natvig C, et al. Elevated peri-transplant distress in caregivers of allogeneic blood or marrow transplant patients. *Psychooncology.* 2013;22(9):2064-2070.
19. Carr AL, Jones J, Mikulich Gilbertson S, et al. Impact of a Mobilized Stress Management Program (Pep-Pal) for Caregivers of Oncology Patients: Mixed-Methods Study. *JMIR Cancer.* 2019;5(1):e11406.
20. Pensak NA, Joshi T, Simoneau T, et al. Development of a Web-Based Intervention for Addressing Distress in Caregivers of Patients Receiving Stem Cell Transplants: Formative Evaluation With Qualitative Interviews and Focus Groups. *JMIR Res Protoc.* 2017;6(6):e120.
21. Stein R. COVID-19 and Rationally Layered Social Distancing. *Int J Clin Pract.* 2020:e13501.
22. Laudenslager ML, Simoneau TL, Mikulich-Gilbertson SK, et al. A randomized control trial of stress management for caregivers of stem cell transplant patients: Effect on patient quality of life and caregiver distress. *Psychooncology.* 2019;28(8):1614-1623.
23. Boutron I, Moher D, Altman D, G., Schultz K, F., Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: Explanation and evaluation. *Ann Intern Med.* 2008;148:295-309.
24. Hopewell S, Clarke M, Moher D, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet.* 2008;371(9609):281-283.
25. Deans K. Fostering genuine stateholder engagement. Paper Presentation presented at The 2015 PCORI Annual Meeting; October 8, 2015, 2015; Washington, DC.
26. Murphy MR, Escamilla MI, Blackwell PH, et al. Assessment of caregivers' willingness to participate in an intervention research study. *Res Nurs Health.* 2007;30(3):347-355.
27. Steinhauser KE, Clipp EC, Hays JC, et al. Identifying, recruiting, and retaining seriously-ill patients and their caregivers in longitudinal research. *Palliat Med.* 2006;20(8):745-754.
28. Fredman SJ, Baucom DH, Gremore TM, et al. Quantifying the recruitment challenges with couple-based interventions for cancer: applications to early-stage breast cancer. *Psychooncology.* 2009;18(6):667-673.
29. Caldwell PH, Hamilton S, Tan A, Craig JC. Strategies for increasing recruitment to randomised controlled trials: systematic review. *PLoS Med.* 2010;7(11):e1000368.
30. Foster CE, Brennan G, Matthews A, McAdam C, Fitzsimons C, Mutrie N. Recruiting participants to walking intervention studies: a systematic review. *International Journal of Behavioral Nutrition and Physical Activity.* 2011;8(1):137.
31. Hopkinson JB, Brown JC, Okamoto I, Addington-Hall JM. The effectiveness of patient-family carer (couple) intervention for the management of symptoms and other health-related problems in people affected by cancer: a systematic literature search and narrative review. *J Pain Symptom Manage.* 2012;43(1):111-142.
32. Trivedi RB, Szarka JG, Beaver K, et al. Recruitment and retention rates in behavioral trials involving patients and a support person: a systematic review. *Contemp Clin Trials.* 2013;36(1):307-318.
33. Martin MA, Press VG, Erwin K, et al. Engaging end-users in intervention research study design. *J Asthma.* 2018;55(5):483-491.

34. DeKoekkoek T, Given B, Given CW, Ridenour K, Schueller M, Spoelstra SL. mHealth SMS text messaging interventions and to promote medication adherence: an integrative review. *J Clin Nurs.* 2015;24(19-20):2722-2735.
35. Lindquist R, Wyman JF, Talley KM, Findorff MJ, Gross CR. Design of control-group conditions in clinical trials of behavioral interventions. *J Nurs Scholarsh.* 2007;39(3):214-221.
36. Antoni MH, Lechner S, Diaz A, et al. Cognitive behavioral stress management effects on psychosocial and physiological adaptation in women undergoing treatment for breast cancer. *Brain Behav Immun.* 2009;23(5):580-591.
37. Antoni MH, Lutgendorf SK, Blomberg B, et al. Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. *Biol Psychiatry.* 2012;71(4):366-372.
38. Antoni MH. Psychosocial intervention effects on adaptation, disease course and biobehavioral processes in cancer. *Brain Behav Immun.* 2013;30 Suppl:S88-98.
39. Laudenslager ML, Simoneau TL, Mikulich-Gilbertson S, et al. A randomized control trial of stress mangement for caregivers of stem cell transplant patients: Effect on caregiver distress and patient quality of life. . In review.
40. Simoneau TL, Kilbourn K, Spradley J, Laudenslager ML. An evidence-based stress management intervention for allogeneic hematopoietic stem cell transplant caregivers: development, feasibility and acceptability. *Support Care Cancer.* 2017;10:10.
41. McCraty R, Zayas MA. Cardiac coherence, self-regulation, autonomic stability, and psychosocial well-being. *Front Psychol.* 2014;5:1090.
42. McCraty R, Shaffer F. Heart Rate Variability: New Perspectives on Physiological Mechanisms, Assessment of Self-regulatory Capacity, and Health risk. *Glob.* 2015;4(1):46-61.
43. Grossman P, Kollai M. Respiratory Sinus Arrhythmia, Cardiac Vagal Tone, and Respiration - Within-Individual and Between-Individual Relations. *Psychophysiology.* 1993;30:486-495.
44. Berntson GG, Cacioppo JT, Quigley KS, Fabro VT. Autonomic Space and Psychophysiological Response. *Psychophysiology.* 1994;31:44-61.
45. Jennings JR, McKnight JD. Inferring vagal tone from heart rate variability. *Psychosom Med.* 1994;56:194-196.
46. Porges SW. Cardiac vagal tone: A physiological index of stress. *Neurosci Biobehav Rev.* 1995;19(2):225-233.
47. Rosenthal T, Alter A, Peleg E, Gavish B. Device-guided breathing exercises reduce blood pressure: ambulatory and home measurements. *American Journal of Hypertension.* 2001;14(1):74-76.
48. Viskoper R, Shapira I, Priluck R, et al. Nonpharmacologic treatment of resistant hypertensives by Device-Guided slow breathing exercises. *American Journal of Hypertension.* 2003;16(6):484-487.
49. Elliot WJ, Izzo JL, Jr., White WB, et al. Graded blood pressure reduction in hypertensive outpatients associated with use of a device to assist with slow breathing. *Journal of Clinical Hypertension.* 2004;6(10):553-559; quiz 560-551.
50. Gavish B. Device-guided breathing in the home setting: technology, performance and clinical outcomes. *Biol Psychol.* 2010;84(1):150-156.
51. Simoneau T, Kilbourn K, Mikulich SK, et al. Feasibility, Acceptability and Challenges to Conducting a Randomized Behavioral Intervention for Allogeneic Stem Cell Transplant Caregivers. In Review.

52. Miller G. The smartphone psychology manifesto. *Perspectives on Psychological Science.* 2012;7(3):221-237.
53. Andersson G. Internet-Delivered Psychological Treatments. *Annu.* 2016;12:157-179.
54. Amoyal Pensak N, Joshi T, Simoneau T, et al. Development of a web-based intervention for addressing distress in caregivers of patients receiving strem cell transplants: Formative Evaluation with qualative interviews and focus groups. . *J Med Internet Res.*6(6).
55. Carr AL, Jones J, Mikulich-Gilbertson SM, et al. Improvements on a Mobilized Stress Management Program (Pep-Pal) for Caregivers of Oncology Patients In review.
56. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, COnde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.
57. Machin A, Hider S, Dale N, Chew-Graham C. Improving recognition of anxiety and depression in rheumatoid arthritis: a qualitative study in a community clinic. *Br J Gen Pract.* 2017;67(661):e531-e537.
58. Gilbody S, Richards D, Brealey S, Hewitt C. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. *J Gen Intern Med.* 2007;22(11):1596-1602.
59. Phillips AC, Robertson T, Carroll D, et al. Do symptoms of depression predict telomere length? Evidence from the west of Scotland twenty-07 study. *Psychosom Med.* 2013;75(3):288-296.
60. Radloff LS. The CESD Scale: A self report depression scale for research in the general population. *Applied Psycholoigcal Measurement.* 1977;1:385-401.
61. Glaser R, Maccallum RC, Laskowski BF, Malarkey WB, Sheridan JF, Kiecolt-Glaser JK. Evidence for a shift in the Th-1 to Th-2 cytokine response associated with chronic stress and aging *J Gerontol A Biol Sci Med Sci.* 2001;56(M):477-482.
62. Carter PA. Family caregivers' sleep loss and depression over time. *Cancer Nursing26(4):253-9.* 2003.
63. Grunfeld E, Whelan TJ, Zitzelsberger L, Willan AR, Montesanto B, Evans WK. Cancer care workers in Ontario: prevalence of burnout, job stress and job satisfaction. *CanMed AssnJ.* 2000;163:166-169.
64. Zich JM, Attkisson CC, Greenfield TK. Screening for Depression in Primary Care Clinics: The CES-D and the BDI. *The International Journal of Psychiatry in Medicine.* 1990;20(3):259-277.
65. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. *Manual for the State-Trait Anxiety Inventory* Palo Alto: Consulting Psychologists Press; 1983.
66. Brown RT, Wiener L, Kupst MJ, et al. Single parents of children with chronic illness: an understudied phenomenon. *J Pediatr Psychol.* 2008;33(4):408-421.
67. Northouse LL, Katapodi MC, Schafenacker AM, Weiss D. The impact of caregiving on the psychological well-being of family caregivers and cancer patients. *Semin Oncol Nurs.* 2012;28(4):236-245.
68. Boyes AW, Girgis A, D'Este CA, Zucca AC, Lecathelinais C, Carey ML. Prevalence and predictors of the short-term trajectory of anxiety and depression in the first year after a cancer diagnosis: a population-based longitudinal study. *J Clin Oncol.* 2013;31(21):2724-2729.
69. Long KA, Keeley L, Reiter-Purtill J, Vannatta K, Gerhardt CA, Noll RB. Child-rearing in the context of childhood cancer: perspectives of parents and professionals. *Pediatr Blood Cancer.* 2014;61(2):326-332.

70. Devine KA, Heckler CE, Katz ER, et al. Evaluation of the psychometric properties of the Pediatric Parenting Stress Inventory (PPSI). *Health Psychol.* 2014;33(2):130-138.
71. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *Journal of Health & Social Behavior24(4):385-96.* 1983.
72. Cohen S, Williamson G. Perceived stress in a probability sample of the United States. In: Spacapan S, SE O, eds. *The social psychology of health.* Newbarry Park, CA: Sage; 1988.
73. Bradley CJ, Dahman B, Bear HD. Insurance and inpatient care: differences in length of stay and costs between surgically treated cancer patients. *Cancer.* 2012;118(20):5084-5091.
74. Juster FT, Suzman R. An overview of the Health and Retirement Study. *Journal of Human Resources.* 1995:S7-S56.
75. Neumark D, Bradley CJ, Henry-Osorio M, Dahman B. Work continuation while treated for breast cancer: The role of workplace accommodations. . *Industrial Labor Relations Review.* in press.
76. Thomas LT, Ganster DC. Impact of Family-Supportive Work Variables on Work -- Family Conflict and Strain: A Control Perspective. *Journal of Applied Psychology.* 1995;80(1):6-15.
77. Nagy MS. Using a single-item approach to measure facet job satisfaction. *Journal of Occupational & Organizational Psychology.* 2002;75(1):77-86.
78. Deeken JF, Taylor KL, Mangan P, Yabroff KR, Ingham JM. Care for the caregivers: a review of self-report instruments developed to measure the burden, needs, and quality of life of informal caregivers. *J Pain Symptom Manage.* 2003;26(4):922-953.
79. Given CW, Given B, Stommel C, Collins C, King S, Franklin S. The caregiver reaction assessment (CRA) for caregivers to persons wth chronic physical and mental impairments. *Research in Nursing and Health.* 1992;15:271-283.
80. Al-Quteimat OM, Amer AM. The Impact of the COVID-19 Pandemic on Cancer Patients. *Am J Clin Oncol.* 2020;43(6):452-455.
81. Kroenke K, Yu Z, Wu J, Kean J, Monahan PO. Operating characteristics of PROMIS four-item depression and anxiety scales in primary care patients with chronic pain. *Pain Med.* 2014;15(11):1892-1901.
82. Amtmann D, Kim J, Chung H, et al. Comparing CESD-10, PHQ-9, and PROMIS depression instruments in individuals with multiple sclerosis. *Rehabil Psychol.* 2014;59(2):220-229.
83. Tomiyama AJ, O'Donovan A, Lin J, et al. Does cellular aging relate to patterns of allostasis? An examination of basal and stress reactive HPA axis activity and telomere length. *Physiol Behav.* 2012;106(1):40-45.
84. Revesz D, Verhoeven JE, Milaneschi Y, de Geus EJ, Wolkowitz OM, Penninx BW. Dysregulated physiological stress systems and accelerated cellular aging. *Neurobiol Aging.* 2014;35(6):1422-1430.
85. Brody GH, Yu T, Beach SR. Resilience to adversity and the early origins of disease. *Dev Psychopathol.* 2016;28(4pt2):1347-1365.
86. McEwen BS. In pursuit of resilience: stress, epigenetics, and brain plasticity. *Ann N Y Acad Sci.* 2016;1373(1):56-64.
87. Prather AA, Puterman E, Lin J, et al. Shorter leukocyte telomere length in midlife women with poor sleep quality. *J Aging Res.* 2011;2011:721390.
88. Straub RH, Buttgereit F, Cutolo M. Alterations of the hypothalamic-pituitary-adrenal axis in systemic immune diseases - a role for misguided energy regulation. *Clin Exp Rheumatol.* 2011;29(5 Suppl 68):S23-31.

89. Stalder T, Steudte-Schmiedgen S, Alexander N, et al. Stress-related and basic determinants of hair cortisol in humans: A meta-analysis. *Psychoneuroendocrinology.* 2017;77:261-274.
90. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. *Diabetes Care.* 2002;25(2):275-278.
91. Davenport MD, Tiefenbacher S, Lutz CK, Novak MA, Meyer JS. Analysis of endogenous cortisol concentrations in the hair of rhesus macaques. *Gen Comp Endocrinol.* 2006;147(3):255-261.
92. Stalder T, Steudte-Schmiedgen S, Alexander N, et al. Stress-related and basic determinants of hair cortisol in humans: a meta-analysis. *Psychoneuroendocrinology.*
93. Stalder T, Tietze A, Steudte S, Alexander N, Dettenborn L, Kirschbaum C. Elevated hair cortisol levels in chronically stressed dementia caregivers. *Psychoneuroendocrinology.* 2014;47:26-30.
94. Herr RM, Almer C, Loerbroks A, et al. Associations of work stress with hair cortisol concentrations - initial findings from a prospective study. *Psychoneuroendocrinology.* 2018;89:134-137.
95. Janssens H, Clays E, Fiers T, Verstraete AG, de Bacquer D, Braeckman L. Hair cortisol in relation to job stress and depressive symptoms. *Occup Med (Oxf).* 2017;67(2):114-120.
96. Dajani R, Hadfield K, van Uum S, Greff M, Panter-Brick C. Hair cortisol concentrations in war-affected adolescents: A prospective intervention trial. *Psychoneuroendocrinology.* 2018;89:138-146.
97. Lehrer HM, Dubois SK, Maslowsky J, Laudenslager ML, Steinhardt MA. Hair cortisol concentration and glycated hemoglobin in African American adults. *Psychoneuroendocrinology.* 2016;72:212-218.
98. Hoffman MC, Mazzoni SE, Wagner BD, Laudenslager ML, Ross RG. Measures of Maternal Stress and Mood in Relation to Preterm Birth. *Obstet Gynecol.* 2016;127(3):545-552.
99. Hoffman MC, D'Anna-Hernandez K, Benitez P, Ross RG, Laudenslager ML. Cortisol during human fetal life: Characterization of a method for processing small quantities of newborn hair from 20 to 42 weeks gestation. *Dev Psychobiol.* in press.
100. Russell E, Kirschbaum C, Laudenslager ML, et al. Toward standardization of hair cortisol measurement: results of the first international interlaboratory round robin. *Ther Drug Monit.* 2015;37(1):71-75.
101. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer.* 2000;89(7):1634-1646.
102. Cleeland CS. THe M.D. Anderson Symptom Inventory. In: Center UoTMAC, ed. Verson 1 ed. Houston, TX2009.
103. Rosenthal DI, Mendoza TR, Chambers MS, et al. The M. D. Anderson symptom inventory-head and neck module, a patient-reported outcome instrument, accurately predicts the severity of radiation-induced mucositis. *Int J Radiat Oncol Biol Phys.* 2008;72(5):1355-1361.
104. Aktas A, Walsh D, Kirkova J. The psychometric properties of cancer multisymptom assessment instruments: a clinical review. *Support Care Cancer.* 2015;23(7):2189-2202.
105. Mendoza TR, Zhao F, Cleeland CS, Wagner LI, Patrick-Miller LJ, Fisch MJ. The validity and utility of the M. D. Anderson Symptom Inventory in patients with breast cancer: evidence from the symptom outcomes and practice patterns data from the eastern cooperative oncology group. *Clin Breast Cancer.* 2013;13(5):325-334.