Project Title: Improved behavioral outcome in allogeneic hematopoietic stem cell transplant patients by reducing caregiver distress: Behavioral and physiological evidence

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I. Hypotheses and Specific Aims:

Patients receiving an allogeneic hematopoietic stem cell transplant (HSCT) undergo a demanding conditioning protocol. In contrast to cancer treatments using standard-dose chemotherapy, radiation, and/or surgery, treatment protocols for HSCT are more intense and life threatening. Following transplantation, patients are at increased risk for graft versus host disease (GvHD). To ensure adequate support, monitoring and safety, allogeneic HSCT patients are required to have a caregiver available 24/7 for at least the first 100 days following transplantation and occasionally longer if complications arise. Allogeneic caregivers assist with a complicated medical procedure with 70% patient survival. The patient's quality of life (QOL) is dependent on the quality of care provided by their caregiver. Caregiver distress impacts the quality of care they provide and thus patient QOL.

We showed that a behavioral intervention for caregivers of allogeneic HSCT patients reduced caregiver distress. *A gap remains with regard to evaluating intervention impact on patient QOL*. During the first 100 days, patients may be poor targets for behavioral intervention due to significant fatigue and debilitation. Carry over to patients as improved care may derive from caregivers participating in supportive programs. Patient and caregiver dyads will be randomized to either treatment as usual (TAU) or "**f**one" **P**sycho**E**ducation and **R**elaxation (**fPER**) which provides a combination of face to face sessions and Smartphone video chat when a caregiver is unable access the clinic to meet with an interventionist. **fPER** caregivers will receive a biofeedback device for stress management. 225 dyads will be randomized from 2 sites (private and university based) and followed for 6 mo. following transplantation. Specific aims are:

Hypotheses:
Primary hypotheses: Patients whose caregivers receive fPER will have improvements in FACT-BMT compared to TAU.
Secondary hypotheses: Caregivers who receive fPER will have reduced distress compared to TAU.

Specific Aims:
Aim 1: Create a *Community Advisory Board* (CAB) consisting of allogeneic HSCT patients, caregivers, blood cancer oncologists, support staff and study investigators to provide input.

Aim 2: Assess *patient QOL* following an allogeneic HSCT using the FACT-BMT as the primary patient outcome. Patients whose caregivers receive **fPER** will have improved QOL compared to caregivers assigned to TAU.
Aim 3: Test the impact of **fPER** on a *caregiver composite distress score* (encompasses depression, anxiety, and stress) as the primary caregiver outcome. Caregivers receiving **fPER** will have reduced distress.

Aim 4: Assess *biomarkers* of allostatic load in patients prior to transplant and caregivers during the transplant process using novel biomarkers (hair cortisol and telomeres). **fPER** will be associated with reduced allostatic load in caregivers compared to TAU. Patient hair cortisol collected only before transplant will relate to QOL at intake.

Deliverables include 1) developing evidence supporting *improved patient QOL* associated with 2) *minimizing caregiver distress* as well as 3) *a manualized intervention*, **fPER,** based on stakeholder input and oversight available for dissemination.

II. Background and Significance:

A.1. Impact of the Condition on the Health of Individuals and Populations (Criterion 1)

Treatment protocols for patients receiving allogeneic hematopoietic stem cell transplants (HSCT) are more intense and life threatening than other forms of cancer treatment[1-4]. Following transplantation, HSCT patients are at increased risk for a variety of physical side effects, including infections and graft versus host disease (GvHD).[2,4] *Patient quality of life (QOL) is substantially reduced* following transplantation.[5-10] Allogeneic HSCT patients require a caregiver 24/7 for the first 100 days and occasionally longer following transplantation to ensure adequate support for the patient.[11,12] A primary role of the caregiver is to monitor the patient closely for infection, fevers, and features of GvHD as well as to track complex medication regimens, deliver specialized food preparation, and provide transportation to appointments or emergency room visits.[4,12] Patients and their caregivers are required to move to within 30 min. of the transplant center during the transplant recovery process. Our recent experience working with this group of patients indicated that over 23% of the transplant recipients lived out of state and 46% of all allogeneic HSCT transplant patients had to relocate to temporary housing near the clinic.[13] In addition to decreased patient QOL, the caregiver is at significant risk for a number of psychosocial problems.[14-18] *Caregiver distress, in turn, is likely to impact the quality of care that a caregiver provides for their patient.* In spite of these issues, there is a gap in interventions focused on coping with stress by the caregivers,[19-22] especially allogeneic HSCT caregivers.[13,14,23,24] Studies of caregiver interventions to mitigate distress have been plagued by small samples, lack of randomization, short follow up periods, problems with blinding, assessment limitations, failure to measure health services utilization by caregivers, absence of biomarkers of caregiver well-being, and caregiver study attrition[25-27] and *NONE* have focused on the impact on the patient's QOL. Therefore, a significant gap in the evidence base exists with regard to effective caregiver interventions and *their impact on the patients' QOL and medical outcomes*. The present application is pertinent to Criterion 1 as allogeneic HSCT patients have a high burden of chronic medical issues following transplantation with reliance on a caregiver for tangible, informational and emotional support.

Care for ill and/or disabled loved-ones has been increasingly assumed by family and close friends due in part to changes in our health care systems.[28] In 2009, roughly 42 million caregivers in the US provided an unpaid contribution to health care neighboring $450 billion dollars which exceeds Federal Medicaid spending over 8 fold[29]. This represents an estimated 40,300 million hours of care[29] most often provided by immediate family members. *Thus, caregivers are a fundamental component in cancer survivorship[30]: a large component of patients' health and welfare rests with the caregiver.* However the stress of caregiving brings *increased psychological and medical morbidity to the caregiver[30-34]*. Depression in spousal cancer caregivers may exceed depression in the patients themselves[35] raising the question of "*who is the patient?*"[36-38] There are bidirectional influences between the patient and caregiver such that the moods and health of one influence the moods and health of the other. Much like putting on your own oxygen mask first before assisting the passenger beside you, as instructed by flight attendants, caregivers need to prioritize their self-care needs in order to ensure that they can adequately care for their loved-one.

How would an efficacious caregiver intervention impact patient QOL? What would that intervention look like? Caregivers are faced with a demanding responsibility. We approach caregiver distress from a stress and coping framework.[39,40] Suggestions for caregiver interventions have included: 1) education regarding patient illness, 2) psychosocial intervention that will strengthen perceived control, and 3) promotion of enhanced self-care.[26] Former US Surgeon General, Richard H. Carmona, suggested a "Rx for caregivers" that included attending to depression and anxiety, identifying sources of support, reducing stress, taking care of one's physical health, and providing education regarding the illness.[41] To date, most caregiver interventions have not completely addressed the caregiver Rx, particularly in regard to HSCT caregivers and more specifically allogeneic caregivers.
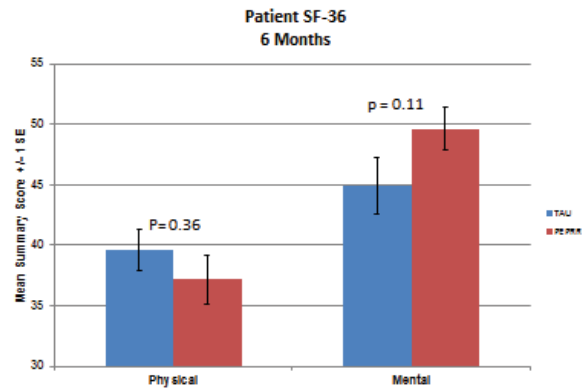
With this background, our group recently completed a randomized control trial (RCT) of an intervention for allogeneic HSCT caregivers with promising results. Our eight session, one-on-one intervention, **P**sycho**E**ducation, **P**aced **R**espiration, and **R**elaxation (**PEPRR**),[23] addressed all aspects of the Surgeon General's Rx. We found at the end of the 100 post-transplant period that caregiver perceived stress (a measure of sense of control and the primary outcome), depression, anxiety, and a summary distress score were significantly reduced in caregivers receiving **PEPRR** compared to Treatment as Usual (TAU) with effect sizes ranging from .39 - .66. However *patient* assessments were limited to medical chart reviews and the Short Form 36 health

Figure 1. Patient scores on the SF36 Physical Health scores did not differ between those whose caregivers participated in PEPRR (n=35) and TAU (n=35) six months post transplant. However there was a trend for Mental Health scores on the SF36 of the PEPRR group to exceed the TAU group as well as fall at the norms for a healthy population while the TAU group was ½ SD below that level.

questionnaire (SF36)[42] obtained 1, 3, 6 and 12 months post-transplant. Based on a completers analysis at 6 months post-transplant, there were no differences (p=.36) between TAU (n=35) and **PEPRR** (n=35) on the *SF36 physical* scale which fell below population norms in both groups. However in this small sample we noted a trend for the *patient SF36 mental score* to be slightly higher (e.g., better score, p =.11) in the **PEPRR** group compared to TAU as shown in Figure 1. One half of a standard deviation (1 SD = 10 points on the SF36) between the two groups is considered a meaningful clinical difference.[43] In spite of continued diminished physical function, the patients whose caregivers received **PEPRR** reported mental health scores in the normal range for healthy people, while those in TAU were lower. Thus our initial success with **PEPRR** for caregivers has pointed to two important paths: 1) the need for verification of changes in patient QOL and 2) extending accessibility and reach of the intervention to include caregivers who might not have been eligible for participation because they lived out of the geographic region of the transplant program.

A.2. Innovation and Potential for Improvement Based on Our Research (Criterion 2)

The initial RCT provided important insights regarding ways of enhancing the intervention based on caregiver and interventionist feedback. A caregiver intervention must be acceptable to the caregiver who may not always focus on his/her own needs and often feels quite overwhelmed. We propose to take our intervention for allogeneic HSCT caregivers,[23] **PEPRR** (pronounced "pepper"), and apply novel approaches to *enhance its reach* to stakeholders. In enhancing **PEPRR**'s *utility and usability* we drew innovatively from concepts of web design[44] to create **"fone–PER"** or **fPER (**pronounced "fepper") which will incorporate Smartphone technology to achieve part of this goal. "*Utility*" in web design refers to "does the user (e.g., caregiver) get what they want out of a system?" and "*usability*" refers to the user's perceived ease-of-use of a system.[44] We seek to optimize both dimensions. We have amassed considerable information during the initial trial of **PEPRR** regarding utility and usability from caregivers based on exit questionnaires as well as comments made during **PEPRR** sessions. Using these webpage design concepts, caregivers were essentially engaging in a User Testing Interchange regarding the utility and usability of **PEPRR** during its early testing**.** For optimal results, both utility and usability are important as *most users will not continue to use a system that does not meet their needs, no matter how easy the system is to use (utility).* Conversely, *most users will not persist with a system that is too complex*

or frustrating (usability), even if remarkable results are promised. User testing is an iterative process whereby a product (in this case the intervention) is repeatedly designed, tested, and redesigned to maximize both utility and usability. We feel this is an innovative conceptualization of developing a behavioral intervention. We asked caregivers to "think aloud" as they participated in **PEPRR**. As they learned to manage stress associated with caregiving through **PEPRR**, we simultaneously asked about their experiences and we learned from them what worked and did not work in **PEPRR**[13] while maintaining intervention fidelity. Thus *we relied heavily on caregiver input to develop fPER*. For example, we learned that a biofeedback device used in **PEPRR**, the RESPeRATE,[45] was viewed as "something more to do" and not adding an effective coping behavior. This was not our intention. Subjects found it cumbersome and simply stopped or reduced use after 4-6 weeks in the 12 week trial. An alternative biofeedback device that is less obtrusive and easier to use will be tested in **fPER** in anticipation of larger community deployment of this support program.

The initial version of **PEPRR,** based on the stress and coping model[46], sought to enhance the caregiver's perceived sense of control[47-49] of their situation by providing various approaches to coping. **PEPRR** provided education about stress and its consequences as well as means for managing stressful situations using cognitive behavioral techniques.[23] When reflecting on issues around stress and health, *caregivers often reported at the beginning of PEPRR a very limited appreciation for the consequences of stress on their personal health* and failed to utilize adaptive coping behaviors. While experiencing a special day with her loved one after completing **PEPRR**, a study caregiver wrote "… *I breathed deeply and smiled. I was grateful for a moment's peace and for a greater appreciation of the natural stress relievers that were everywhere…*" (Chicken Soup for the Soul: Say Goodbye to Stress, 2012, p.41-42.).

To increase the utility and usability of **fPER**, we plan to implement several enhancements to the intervention prior to dissemination. For example, the previously used device-guided respiration apparatus (RESPeRATE) required about 25 min/day be set aside for its use 4-5 times each week. Reported barriers to its use included finding time (26%), did not like it (6.5%), or could not make it part of their routine (10%). Subjects adhered to study requirements over the first few weeks but this declined around the time the patient was discharged from the hospital, which would be consistent with the time that caregiving duties increased. A concrete example of increasing usability based on user testing will be to exchange the RESPeRATE with a simpler device. We will substitute the RESPeRATE with an easier device, the emWave2[50-52] (HeartMath, LLC) in **fPER**. The emWave2 is a small self-contained portable platform, smaller than a cellphone, for stress management which can be readily available to the caregiver when a stressor or challenge occurs. One simply places a finger on the emWave2 for less than 5 min while pulse information is collected and translated to a light indicator (red, blue, and green) as a sign of moving from a "stressed state" to relaxation using skills learned in **fPER**. This will improve the caregiver's perceived sense of control.[14] We are fully committed to being responsive to stakeholder input which we gained during and following the first RCT to ultimately increase utility and usability of **fPER** for wide dissemination to caregivers and thereby improve their care of their loved ones.

Since most people will own Smartphones by 2025,[53] it is an opportune time for this technology to be incorporated into *fPER* in a manner that will facilitate caregiver contact and improve the likelihood of providing more *fPER* sessions. Although telephone interventions are not novel,[54-59] they are represented by only a minority (20%) of caregiver interventions based on a recent meta-analysis.[21] The advanced technology of smartphones continue to be poorly appreciated[53] including their use for reminders via text messages, prompts for medication administration, appointment reminders, data collection, and a *means to interact with support therapists visually and aurally* using concepts of telemedicine.[60-63] We propose to include the Smartphone as a new and novel enhancement to the intervention recognizing its role in the information age.[64-67]

78% of the caregivers requested additional support sessions for a variety of reasons including; a second transplant, continuing to experience high-levels of stress, or new stressors arose over time with the chronicity of their loved one's side effects. One caregiver in the prior trial commented,"… *I think a follow-up session once we left Denver would have been helpful, even by phone…*" reinforcing the need for additional support as well as developing an approach to provide support at a distance. Thus we have added

additional sessions to incorporate the requests of caregivers expressed in the initial study. The capacity for distant interventions is critical as expressed by an allogeneic HSCT caregiver:

> "...I haven't reached out to [clinic name deleted] directly for services yet because distance is a bit of an issue, especially with a small child…"

Statements specifically supportive of video chat sessions included *"... video would not be the same as in person but better than a telephone…"* and *"…I prefer face-to-face but video would be a good substitute…"*

Looking specifically at the geographic locations (See Figure 2) of the distant caregivers (representing 46% of the study group) suggests that many caregivers live a significant distance from the clinic where follow-up services can be provided using Smartphone technology.
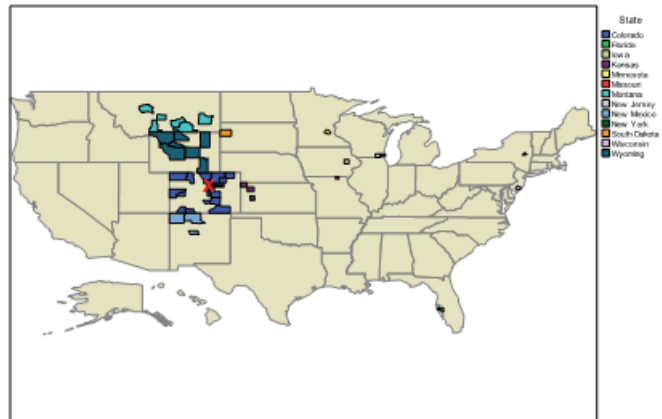

Figure 2. A distinct need for distant communication using such features as Skype or FaceTime are clearly illustrated by the geographically distant sites from which caregivers for our initial study lived prior to patient transplant at the Denver area clinic (marked with a red X). Counties from which one or more caregivers lived are illustrated.

fPER will improve patient care by providing services *previously unavailable* to families who live outside immediate clinic reach, addressing a common problem for all HSCT programs. Our own observations suggest that in the peri-transplant period, allogeneic HSCT caregivers fall above population means and clinical cut-off scores on measures of stress, depression, and anxiety.[14] Comparable stress in the patients is indicated in other studies.[68] By enhancing the caregiver's coping skills as they enter this challenge, they can better serve the patient and themselves. *In response to Criterion 2, using technology to increase utility and usability is the next step prior to multisite dissemination, implementation and wide-spread availability of this important intervention which we propose will have significant benefits on patient and caregiver mental health.* Full dissemination of our intervention requires verification that the **fPER** program will improve patient QOL and caregiver well-being while enhancing caregiver program access, participation, retention, and generalizability.

A.3. Impact on Health Care Performance (Criterion 3)

Care for an allogeneic HSCT patient is inextricably entwined with the presence of a high functioning caregiver, but this is not without cost to the caregiver.[14,15] The present study has direct relevance to Criterion 3 because *improvements in caregiver mental health* will result in *improved care for the HSCT patient* during a highly challenging experience for both stakeholders. A caregiver's comment after receiving PEPRR was "*…it should be mandatory for all caregivers…*" emphasizing this need. In support of Criterion 3 we propose that the availability of **fPER** will have a significant impact toward improving patient care and thereby their QOL by mitigating caregiver distress. In our prior research on caregivers, preliminary trends in mental health care services utilization were reduced for caregivers in the intervention group (other than care provided by the intervention). This reduction occurred during the 6 mo. period following transplantation when compared to TAU using a mixed models logistic ANOVA, month X intervention group interaction [p=0.057]. This suggests that **PEPRR** substituted for costly mental health services AND that **PEPRR** reduced perceived stress following the transplant. Furthermore, reducing potential participation barriers by improving access to the program and eliminating geographical barriers will increase the number of caregivers who can benefit from this psychosocial program which will lead to a positive impact on patient QOL.

III. **Preliminary Studies/Progress Report:**

Allogeneic hematopoietic stem cell transplant (HSCT) caregivers must be available 24/7 for the first 100 days and often longer following a transplant. However behaviorally and more importantly medically healthy caregivers are essential for the best patient outcome. Few interventions for caregivers have been tested by randomized clinical trials (RCT). Our objective is to determine if a stress management intervention for allogeneic HSCT caregivers compared to self-care relying on resources of the transplant program (treatment as usual, TAU) would be associated with lower stress. We designed a randomized control trial with intent-to-treat of an eight session manualized stress management intervention provided to caregivers following transplant. Subjective behavioral data collected longitudinally for 12 months using standardized instruments was entered blindly. The HSCT caregivers were recruited from a community transplant program between November 2008 and April 2012. The study included a consecutively approached sample of 267 caregivers of allogeneic HSCT patients. 148 (mean age=53.5 years, 75.7% female) were randomized to a manualized intervention (n=74) or TAU (n=74). 101 caregivers reached the three month follow-up with drop outs associated with patient and/or caregiver factors. The intervention included an eight session stress management program provided to caregivers by a social worker during the immediate post-transplant period that focused on learning about stress, changing role(s) of the caregiver, cognitive behavioral approach to managing stress, paced respiration with a commercial biofeedback device, and identifying resources. A panel of questionnaires and physiological markers was collected from the caregivers five times over the course of one year beginning in the peri-transplant period. The primary outcome measure was self-reported perceived stress. Secondary outcome measures included depression, anxiety, caregiver burden, physical health, sleep, trauma and composite scores of these measures. Groups did not differ at baseline. Controlling for age, the intervention resulted in significantly lower (p=0.039) caregiver perceived stress (primary outcome) at 3 months post-transplant (Mean=20.0, SD=1.0) compared to TAU (Mean=23.0, SD=1.0) with an effect size (ES) of 0.39. The intervention group showed significantly better (p=0.019) scores on a secondary composite score that includes depression, anxiety, and other distress measures (Mean=-0.22, SD=0.13) compared to TAU (Mean=0.23, SD=0.13) with an ES of 0.45. This study had limitations due to problems with low minority subject recruitment, logistics of collecting dependent measures when patients and caregivers moved out of the area, as well as missing data. While needing further study within more settings, this approach is likely to improve caregiver well-being and potentially that of patients.

IV. Research Methods

    A. Outcome Measure(s):

Patients with caregivers in **fPER** will show improved QOL and caregivers will show reduced distress as primary outcomes. Secondary outcomes will show improvements in patient comorbidities, depression and anxiety (patients and caregivers), and caregiver biomarkers of chronic stress.

    Patient QOL is the primary outcome measure in this RCT, which will be complemented by secondary behavioral and medical outcomes of the patients. The rationale for this study is that QOL and mental health factors contribute to overall outcomes in a variety of illnesses including cancer.[69-71] A variety of interventions directed towards patients have been shown to improve psychosocial and biological outcomes.[72-76] Unfortunately, during the early phases of the transplant process extensive participation by patients in psychosocial programs of any type is precluded due to physical debilitation.[68] An indirect impact may be afforded by a focus on the caregiver. Improved caregiver self-care and enhancement of coping skills may lead to improved patient QOL via indirect avenues, e.g., the caregiver is better able to focus on the patients' needs and care because the caregiver's distress is reduced. Although a bidirectional relationship between patient and caregiver is implicitly understood, there is a relative lack of evidence that family and/or caregiver interventions impact patient outcomes thus *representing a significant gap in the literature.* Improved

caregiver coping learned via fPER will have a significant impact on patients during a time of uncertainty, unpredictability and loss of control.

B. Description of Population to be Enrolled:

450 total adult subjects (225 patients and their 225 caregivers) will be randomized as pairs by permuted block into treatment as usual (TAU) or "fone" PsychoEducation and Relaxation (**fPER**). A total of 112 caregivers (distributed proportionally in relation to patient pool across the two sites and ethnic and racial category) will be randomly assigned to TAU and 113 to **fPER** after completing baseline assessments as shown in Table 1. The expected age range of caregivers and patients is expected to 18-85 years of age. It is unlikely

Table 1. Study conditions and sample sizes		
Group Condition	Site 1 - UCH	Site 2 – CBCI
TAU + Manual	37	75
fPER	38	75
Total (225 dyads)	75	150

that anyone under the age of 21 will be a caregiver for an allogeneic HSCT patient and HSCTs are not performed for children by either program. Should a younger caregiver present themselves, we will reevaluate the lower cut off. Although caregivers are expected to be generally healthy, we will exclude individuals who are taking steroidal medications for allergy or inflammatory disorders. These medications are most likely to confound the hair cortisol assessments. Medication use by caregivers will be treated as a covariate in secondary analyses. Eliminating caregivers who use any medication(s) would skew the nature of the caregiver sample so that the subjects in the intervention would be only the very healthy. Such selection would distort the potential impact of the intervention on biomarkers and behavior for the population overall.

Patients: Inclusion criteria include: 1) receiving an allogeneic HSCT, 2) able to read and speak the English language, and 3) telephone access.

Caregivers: Inclusion criteria include: 1) the person in the patient's life who is primarily responsible for care decisions, emotionally invested in the patient's care, provides instrumental care such as transportation, and available if randomized to the fPER group to participate in the majority of intervention sessions, 2) be able to read and speak the English language, 3) willingness to use a Smartphone, 4) absence of a serious medical condition likely to influence cortisol assessment in their hair, 5) alcohol consumption less than 2 drinks/day, 6) no steroid medications, and 7) at least 18 years of age.

Patient and caregiver *exclusion criteria* include a history of a psychiatric illness *unrelated to the HSCT* within the past 18 months. Children under the age of 18 do not receive HSCTs in either program.

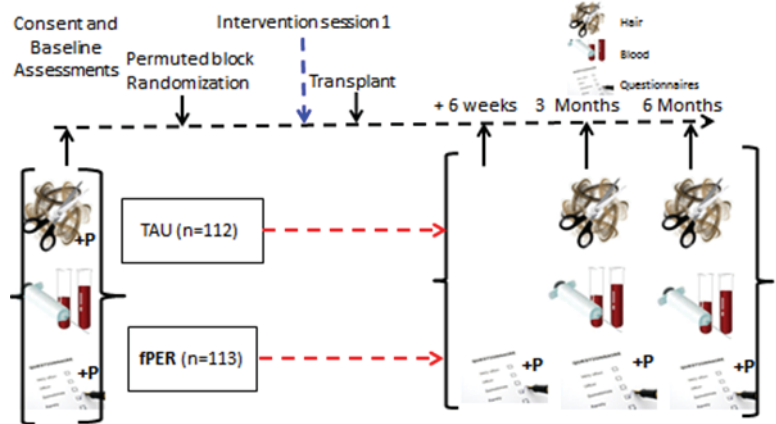**Collaborating Sites:** The two study sites include Presbyterian St. Luke's Medical Center/Colorado Blood Cancer Institute (CBCI) – Site 1 and the University of Colorado Hospital (UCH) – Site 2. There are currently no other caregiver interventions studies offered at either site that would compete or limit subject availability for the present study. Projected enrollment from each site over 27 mo. is given in the adjacent figure.
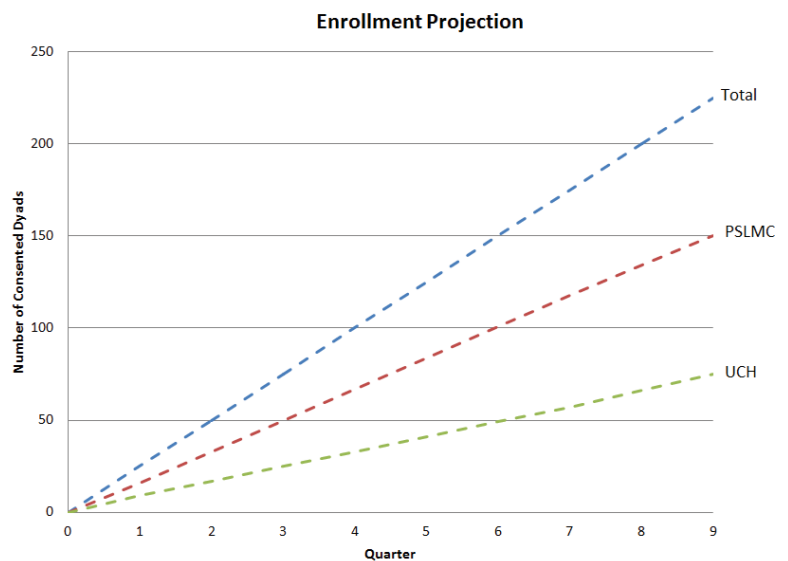
C. Study Design and Research Methods:

Subject flow for **fPER** and TAU is indicated in Figure 4. Following consent (both members of the dyad must consent), patients and caregivers will complete a panel of questionnaires and provide a baseline hair sample. Only caregivers will provide blood samples for DNA, lymphocyte and plasma banking. After completing baseline measures, subjects will be assigned to treatment group by permuted block design known only to site coordinators (Brewer and Simoneau) and interventionists. The first intervention session for **fPER** assignment will begin as soon as possible after consenting *prior to transplant*. Collection time is anchored to the day of transplant as

Figure 4. Study timeline common to CBCI (n=150) and UCH(n=75) sites with randomization by permuted block design for caregivers. Patients (indicated by +P) will provide a hair sample *only* at baseline and no blood samples beyond routine clinical assessments but they will complete questionnaire in tandem with caregivers.

day 0 for statistical analysis. The subsequent questionnaire collections for both patients and caregivers will be at approximately +6 weeks and +3 and +6 months post-transplant. Hair and blood samples will only be collected post-transplant from caregivers at 3 and 6 months. Hair will be collected from the patients pre-transplant and at +6 months post-transplant. *For those patients who have previously been on either steroid medications or chemo prior to conditioning, this information will be recorded for this exploratory study of hair cortisol in the patients.* These samples are collected for exploratory analysis only. Caregivers will provide hair samples on three occasions at baseline prior to randomization and three and six months after their patient's transplant. Hair is removed from the posterior vertex of the scalp at a proximal level using thinning shears. This region is more resistant to hair loss in male pattern baldness (e.g., one of the last areas to be lost). Cosmetically one cannot tell the hair was removed. For subjects without adequate hair this will be treated as missing data. However the Laudenslager laboratory has developed an approach that permits the assay of far less hair (1/10 of most published reports) which allows for receding hair lines and shorter hair in males.

At each phase, patients and caregivers will complete the same battery of questionnaires that includes the Center for Epidemiological Studies-Depression scale (CES-D), the perceived stress scale (PSS), Pittsburgh Sleep Quality Inventory (PSQI), and the State-Trait Anxiety Inventory (STAI). Additionally the patient will complete the FACT-BMT each time while the caregiver completes the Caregiver Reaction Assessment (CRA). Both the patient and the caregiver will additionally complete a demographic questionnaire that includes questions regard age, diagnosis, income, and other standard questions regarding nutrition, health behaviors, and health services utilization. At study completion, an exit questionnaire will address each subject's evaluation of the study and the group in which they were assigned. Each subject will be assigned a code number for de-identifying purposes at consenting and this number will be the only identifier on questionnaires. The confidential code sheet that identifies the subject's randomized treatment group based on a permuted block design, subject name, and contact information will be kept in a locked cabinet as well as in a password protected secure data base. After the randomization table is created by the biostatistician, this will be available only to Drs. Simoneau and Brewer.

Intervention groups
TAU. All patients and caregivers, regardless of randomization, are informed of what to expect during the transplant process and how to locate available support resources within each program. Patients and caregivers

are given information that is specific to their involvement in the transplantation process and recovery phase. Subjects randomized to TAU will be encouraged to participate in available support programs at their respective centers which are very similar between sites and include individual counseling as well as support groups. Due to the impact of our prior intervention on caregiver distress, we will provide each caregiver randomized to TAU a workbook prepared for someone to use without one-on-one sessions with a therapist.

fPER. Our User Testing dialogs provided a number of ideas for new approaches that will be incorporated into **fPER**. User Testing has indicated the time immediately before transplant to be a time of significant distress associated with anticipation and fear of the unknown. Many caregivers felt additional support after day 100 would also be helpful when transplant program support generally declined though they were still dealing with post-transplant issues. To address these issues, **fPER** will begin prior to transplant (unlike the previous study where the first session often did not begin until more than two weeks after the transplant). The active treatment will be increased to 10 manualized sessions (from 8 in **PEPRR**) to include two additional sessions between 4-6 months post-transplant. fPER will also include incorporation of Smartphone technology to make the interventionist available by video chat. Thus**, fPER** represents targeted modifications from the initial intervention with many enhancements and improvements that will enhance scheduling flexibility, improve retention and intervention completion rates, as well as improve outcome. Behavioral assessments will be collected prior to randomization, and at 6 weeks, 3 months and 6 months after transplant (anchored to the day of transplant as day 0). Blood samples from caregivers will be collected at the same time whereas hair samples will be collected every three months: baseline (patient and caregiver), 3 (caregiver) and 6 (patient and caregiver) months post-transplant. **fPER** sessions will be delivered either at the clinic during patient visits or via video chat.

Each **fPER** session will be devoted to a separate topic with the goal of assisting the caregiver in the development and application of stress-management coping skills including learning problem-solving skills, identifying cognitive distortions, application of relaxation techniques, use of the emWave2, coping skills training, effective use of social support, and establishing appropriate goals. The intervention meets the needs and requests identified in User Testing. All caregivers in **fPER** will be provided a Caregiver Workbook that includes information about the session topics and homework assignments.

Briefly in order, the sessions will include: 1) Overview and introduction to stress management, 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, 6) Coping with uncertainty and fear of unknown, 7) Managing changing relationships/communicating needs, and 8) Getting the support they need, modeled after a successful intervention for patient groups.[93] Manualization is crucial for successful wider implementation.[94,95] Sessions 9 and 10 will provide booster sessions in which the interventionist will assess current challenges for the caregiver, provide review, and emphasize further coping skills training that might assist the caregiver in managing current stressors such as coping with the "new normal." Intervention fidelity will be determined from DVD recordings made during sessions. Twenty percent of sessions will be randomly reviewed for adherence to an 8-11 item check list. In our prior RCT, overall fidelity (e.g., did the interventionist address each item?) was 96.4% across all sessions.

emWave2. Based on User Testing during the previous RCT, we learned that the previous biofeedback device, the RESPeRATE, was not uniformly accepted by all caregivers. Furthermore, the amount of utilization of that device was not associated with any of the behavioral outcomes at three months in the prior trial (in preparation). We will replace the previous device with a more convenient and user-friendly device, the emWave2 (Heartmath, Inc), for the **fPER** group. In brief, emWave2 is a small hand-held device on which the subject places their index finger or alternatively connects a simple sensor to their ear. Pulse information during this contact determines heart rate variability to provide visual indications of increased vagal tone or coherence (a sign of improved relaxation) using manufacturer's terminology.[52] It measures 8 X 4 X 1 cm and can be easily carried in one's pocket or purse for ready availability. The time leading to increased vagal tone has been demonstrated in a

variety of subjects to shorten while using this device.[50,51,96,97] The emWave2 is superior to the RESPeRATE on the basis of convenience associated with size and reduced burden based on set up and time required to achieve relaxation (less than 10 min versus 20-25 min.). This is not considered a medical device but rather an ancillary tool for stress reduction and personal growth according to the manufacturer and which has been commercially available for over 15 years.

Smartphone. Based on User Testing during the previous trial, we learned that flexibility in intervention scheduling was central to ensuring that caregivers participated in the majority of sessions. In the first RCT, caregivers had difficulty making appointments or did not want to leave their patient during clinic visits for a session for fear of missing a doctor's visit.[13,23] Appointments were cancelled due to patient status changes, bad weather, as well as when the interventionist was sick and avoided exposing the caregiver to an infection. The Smartphones will easily overcome these problems. Telephone interventions[59,98] as well as telemedicine are relatively new approaches to treatment but have been used successfully in rural settings.[61-63] We will incorporate this modality through the use of Smartphones for video chat with caregivers when they prefer to hold a session from a distant location. For the previous study, 46% of the caregivers and patients were required to relocate. Some of these dyads were allowed to go home early and consequently the caregiver missed the later intervention sessions which can now be provided by **fPER.** Video chat will be recorded during the session by the interventionist using BSR Screen Recorder so that these sessions can undergo reliability testing. This information will be downloaded from the interventionist's Smartphone immediately and transferred to a secure data base according to HIPPA requirements. Observations from our first trial indicate that many caregivers own a Smartphone; those who do not own a Smartphone will be provided one by the study along with a suitable Smartphone service contract for the duration of the study. They will also be provided with training on its use.

Smartphone enhancement. Smartphones will be used for sessions when the caregiver is unable to come to the transplant center. Caregivers will also receive training in the use of the Smartphone calendar app for scheduling their patient's appointments as well as their own **fPER** sessions. Interventions using a study Smartphone will send scheduled session appointments reminders via text messaging to the caregiver's Smartphone. No personal health information will be sent via text messaging. If the caregivers choose, we will upload any selected app to the subject's Smartphone that could potentially "lighten their load" such as brief affirmations each day that are positive and reinforcing.

Table 1 (Patient):

Table of Procedures Patient

	Base	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Month 6
Chart Review														X
Hair Collection	X													X
Questionnaires:														
Demographics	X													
Hormone Status (_Females Only_)	X													
General Health Questions	X						X						X	X
PSS	X						X						X	X
CES-D	X						X						X	X
STAI	X						X						X	X
PSQI	X						X						X	X
FACT-BMT	X						X						X	X
Exit Questionnaire														X

The following two tables outline the temporal sequence of procedures for the two caregiver groups.

Table 2 (Voluntary Support Services or TAU):

Table of Procedures Caregiver (Voluntary Support Services)

	Base	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Month 6
Blood collection	X												X	X
Hair Collection	X												X	X
Questionnaires:														
Demographics	X													
Hormone Status (*Females Only*)	X													
General Health Questions	X						X						X	X
PSS	X						X						X	X
CES-D	X						X						X	X
STAI	X						X						X	X
CRA	X						X						X	X
PSQI	X						X						X	X
CSNAT	X													X
Exit Questionnaire														X

Table 3 (Scheduled Individualized Training Sessions using fPER):

Table of Procedures Caregiver (Scheduled Individualized Training Sessions)

	Base	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Month 4	Month 5	Month 6
fPER Session		X	X	X	X		X		X		X		X	X	X	
emWave2		4-5X	4-5X	4-5X	4-5X	4-5X	4-5X	4-5X	4-5X	4-5X	4-5X	4-5X	4-5X			
Blood collection	X												X			X
Hair Collection	X												X			X
Questionnaires:																
Demographics	X															
Hormone Status (*Females Only*)	X															
General Health Questions	X						X						X			X
PSS	X						X						X			X
CES-D	X						X						X			X
STAI	X						X						X			X
CRA	X						X						X			X
PSQI	X						X						X			X
CSNAT	X															X
Caregiver Intervention Feedback													X			
Exit Questionnaire																X

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

Biomarkers of chronic stress

"Allostatic load" as conceptualized by McEwen and colleagues[79,111-113] represents the wear and tear on the organism associated with maintaining allostasis (physiological balance) in the presence of a challenging environment such as associated with aging[114] or created by caregiving[115]. Allostatic load markers[116-118] are quite varied. Investigators have used a number of markers of cumulative stress including inflammation,[118,119] telomere length,[90,92,120,121] and more recently the measurement of cortisol in hair.[85,87,88,122] In general, allostatic load is associated with poor health[123] including heart disease.[124] We will assess allostatic load in this study.

Blood. As indicated in Figure 4, caregivers will provide a total of 3 venous blood samples collected by trained phlebotomists through the course of the 6 month study. Each blood sample will be approximately 20 ml collected by venipuncture for lymphocyte isolation for telomere assays as well as plasma banking. Plasma will be banked at each time in the event new developments in assessing allostatic load for caregivers becomes available. Patients will not provide blood samples for the study. Blood pressure will be measured before each
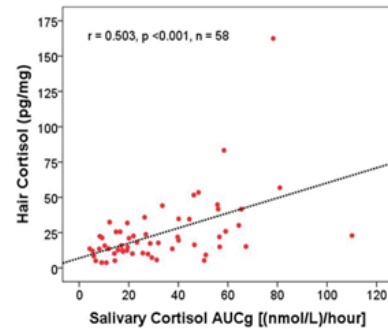
blood draw and recorded. Blood samples will be transported to the laboratory in biohazard packaging at room temperature. Plasma will be removed after centrifuging at 1800 RPM for 15 min at 25oC. Supernatants will be stored in multiple aliquots in 1.4 ml microcentrifuge tubes with o-ring seal caps at -70oC. Each tube will be labeled with a subject code number that corresponds to an Access database inventory maintained for the study. **Hair cortisol.** Repeated saliva collections as a marker of HPA activity can be taxing for subjects even when new and improved means for collection are applied.[125] Hair cortisol provides a retrospective index of HPA activity[87] (much like hemoglobin A1c reflects glucose control in diabetes[126]). Repeated collections of diurnal salivary cortisol were significantly correlated with a corresponding collection period for hair cortisol[85] as shown for a combined sample of mothers in their third
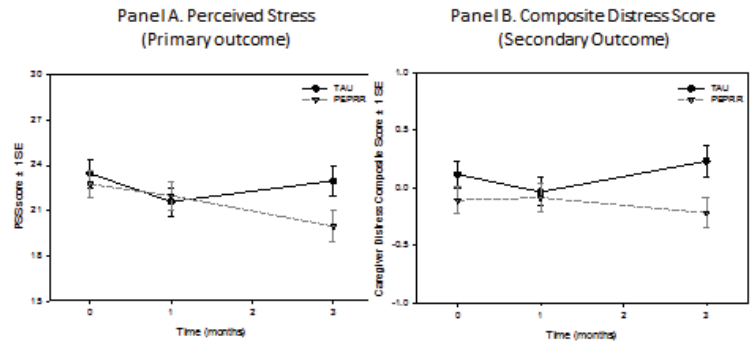
Figure 7. Hair was collected from 58 healthy women at the of the third trimester of pregnancy. Prior to hair collection (first three cm), diurnal salivary cortisol was collected four times each day on 12 "typical" days spaced over the preceding three months. Mean area under the curve for salivary cortisol was determined from these collections and found to be significantly correlated with hair cortisol (p<.001). *This provides a validation that hair cortisol is a reasonable index of retrospective cortisol release as reflected in salivary cortisol*

trimester (Figure 7). We have also found hair cortisol to be stress responsive and heritable[127] as well as associated with behavioral phenotypes.[86] We are excited about this innovative approach to objective assessment of allostatic load/retrospective stress reflected as HPA activation. As an exploratory measure, it will permit an assessment of patient *retrospective HPA activity before the transplant* and additionally continuously track HPA activity in the caregiver through the study. Patient hair will be collected twice due to the effect of transplant conditioning on hair growth. In some patients, previous treatments including steroid medications may make this not possible and as an exploratory measure this is acceptable. Cortisol will be measured as previously described[85] from hair samples collected from the posterior vertex region of the scalp using thinning shears leaving no noticeable change in appearance. Hair grows at approximately 3 cm/mo. We will assay the proximal 3 cm. by refined procedures for samples weighing less than 5 mg. In brief hair is ground, extracted, and processed by immunoassay (Salimetrics) with intra and inter-assay CVs less than 10%. We appreciate some males with balding or short hair cannot provide ideal samples but our assay allows for small samples corrected to length and the statistical approach also allows for missing data in a nonbiased manner when it occurs.

Telomere length (TL) and telomerase activity (TA). TL and TA are considered markers of aging.[90] As a stress marker, telomere length is reduced in caregivers.[90,121,128,129] However an important unanswered question is: "Are differences in telomeres reversible by behavioral interventions[92] such as *fPER* ?" Recent collaborative pilot studies have included analyses of telomere length (TL)[91,121] with Drs. Elizabeth Blackburn and Elissa Epel (UCSF) using lymphocytes collected from a subset of caregivers participating in **PEPRR** (n=20) or TAU (n=20) prior to HSCT and three months subsequently. Although caregiver TL did not change between baseline and three months after transplant, at baseline TL was negatively related to caregiver burden with a small, albeit significant, correlation (r=.31, p=.04, n=40). These observations are provocative and are substantiated by others with regard to longer term caregiving.[121,129] Telomerase data is not available but we predict it will show changes[92] over time with regard to reduced caregiver stress associated with our intervention. Lymphocytes will be recovered from heparinized whole blood using a standard protocol[130] and DNA will be extracted using a Qiagen extraction kit (Qiagen DNA blood mini kit Cat No. 51104). A portion of the isolated lymphocytes will be lysed and washed through a series of buffers according to kit protocol. The extracted DNA will be suspended, aliquoted into 2-3 O-ring sealed tubes and stored at -85°C. Lymphocytes and plasma will be stored at -85°C as well. A portion of the lymphocytes and DNA will be sent to the Blackburn lab for processing for TL and TA using routine procedures.[131] This marker is focused on caregivers as it would not be appropriate for patients due to their receipt of transplanted cells from a donor.

Behavioral measures

In the initial RCT, the primary outcome measure was the PSS and a number of secondary outcomes were further collected including measures of depression, anxiety, sleep, and overall health.[14] We extracted the first principal component from four secondary measures and PSS by principal component analysis (PCA) to produce a composite distress score[14] which was significantly affected by the PEPRR intervention as shown in Figure 5. In the present study we have reduced overall subject burden by eliminating questionnaires with replicative questions so the first principal component will be extracted from 3 (rather than 5) outcomes that had the highest loading for caregivers in the PCA of our previous study (stress, depression, and anxiety measures

Figure 5. Age-adjusted means (+SEM) for PEPPR (n=74) and TAU (n=74) groups based on a mixed model analyses for (Panel A) primary outcome PSS and (Panel B) secondary composite distress measure. On both outcomes, PEPPR was significantly less stressed at 3 months relative to TAU (p < 0.03; ES=0.39-0.45). Note that groups were not different at baseline on either outcome. Average time relative to transplant at which the intervention began was 16±10 days.

described below). This composite distress score will be the *primary outcome for the caregiver* in our conceptual model as shown in Figure 3. The main focus for patients is their quality of life so the *primary outcome measure for patients* will be the Functional Assessment of Cancer Treatment – Blood/Marrow Transplant (FACT-BMT).[8] We will collect the same stress, depression, and anxiety measures (specified below) in patients for secondary analyses as collected in caregivers.

Demographic survey. At recruitment each subject will complete a comprehensive demographic survey to establish basic facts regarding SES, age, sex, education level, relationship to the patient, caregiving hours, and employment status.

Hormone Status. At recruitment, only female subjects will complete a survey regarding their current hormone/menopausal status.

General Health Questions. This will query health habits (e.g., exercise, nutrition, physician visits) and specific medication use. At each follow up phase we will ask each caregiver *as well as patients* about changes in medication use or the presence of an individual psychotherapist or similar support groups.

Perceived Stress Scale (PSS). Stress will be assessed with the PSS[100] which measures the degree to which situations are perceived as stressful. Items on the PSS measure the degree to which the subjects feel their lives are unpredictable, uncontrollable and overwhelming on a 5 point Likert scale. It has been validated in 2,387 respondents across demographic characteristics (i.e. age, sex, SES, race)[101] with superior psychometric properties (reliability alpha of 0.84). We found PSS to be elevated above controls in caregivers of HSCT patients as well as other caregivers of patients in phase 1 trials as indicated in Figure 6. The PSS was the primary outcome measure in the initial RCT and was significantly lower than TAU at 3 mo. post-transplant as indicated in Fig. 5. *The effect size (ES) for this difference was .39.*

Center for Epidemiological Studies – depression scale (CES-D). Subjects will complete the CES-D,[102] a measure developed for the general population and with a long history of use in caregiver research.[103-105] The 20 item scale includes reference to sleep disruption, appetite disturbance, overall fatigue, and depressed affect. Scores range from 0-60 with scores over 16 viewed as reflecting significant depressive symptomatology. Test-

retest validity ranges from .51 to .67 over 2-8 weeks with an internal validity of .85 for a normal population.[102] *The ES for the difference in CES-D between TAU and PEPRR was 0.46.*

Spielberger State-Trait Anxiety Inventory (STAI). High anxiety been related to caregiver burden and stress.[106] Subject anxiety will be assessed using the State/Trait Anxiety Inventory (STAI).[107] The STAI is a 40 item scale on which the subjects will indicate how they feel "right now" (state) on a 4 point Likert scale. Internal consistency is .89 to .91. *The ES for the difference in STAI between TAU and PEPRR was 0.66.*

Pittsburgh Sleep Quality Index (PSQI). The PSQI provides information regarding sleep latency, sleep efficiency and sleep duration. The PSQI is a 26 item scale on which the subjects will rate seven domains of sleep on a 4 point Likert scale. The PSQI is a widely used questionnaire[136] that provides acceptable reliability and validity with diagnostic sensitivity of 89.6% and specificity of 86.5%. [137, 138]

FACT-BMT (*Patient only*). Patient Quality of Life (QOL) follows a time course after allogeneic HSCT[9] which is characterized by deterioration during hospitalization and as much as one year post-transplant in allogeneic HSCT.[108] Patients experiencing the greatest improvement in the first year continue to show higher QOL over subsequent years[109] with female sex being a significant negative contributor to QOL in the patient.[108] Thus the *primary outcome measure* for HSCT patient QOL is the FACT-BMT[8] which has excellent reliability (.86), validity (.89) and sensitivity to change.

Caregiver Reaction Assessment (*Caregiver only*). We will include a highly recommended[28] measure of caregiver burden, the Caregiver Reaction Assessment (CRA).[110] The 24 item CRA is scored on a 5 point Likert scale with subscales of esteem, family support, finances, schedule, and health. It has excellent test-retest reliability of .9 and responsiveness to change of .81. We noted that while distress decreased in the PEPRR group, the CRA remained similar across groups indicating that the intervention mitigates caregiver distress in spite of constant burden. This measure remains as exploratory only.

Carer Support Needs Assessment Tool (*Caregiver only*). We have included an assessment called Carer Support Needs Assessment Tool (CSNAT).[135] The instrument is comprehensive in obtaining carers' perspectives of key aspects of support needed during their time as a caregiver for an allogeneic hematopoietic stem cell transplant (HSCT).

Caregiver Intervention Feedback (*fPER Caregiver only*). We have included an assessment called Caregiver Intervention Feedback. We ask very specifically about each component of the intervention. The questionnaire allows caregivers to provide feedback about the intervention earlier than the current 6 month Exit Questionnaire. The idea with this addition is that we would provide a forum for participants to comment on the intervention in their own words.

Exit Questionnaire. Each subject will complete the Exit questionnaire at the end of study. The aim of this questionnaire is to get feedback from subjects on our designed intervention program and see what changes should be made based of their input. Also for those subjects in the fPER program, we want to get feedback on the emWave2 device verses the entrainment and learned behavior of slowed breathing. This feedback advice from subjects will be used in future clinical studies and clinical application.

Adverse Childhood Experiences (*Caregiver only*). The additional questionnaire will be sent to caregivers after they have completed the study. The ACE questionnaire was adapted and used to retrospectively assess forms of abuse, neglect, and household dysfunction. ACE will be used to learn more about early childhood experiences that may affect your response to the stress of being a caregiver.

Digital Videos

Data will be collected on digital recordings. The images of individual sessions will be viewed by the co-investigators to determine the educators' fidelity to the treatment program as outlined in the manual. In addition, we will ask participants in the fPER program to sign an additional consent for the use of video recording from sessions with the lead therapist in order to create a training DVD for new therapists and scientific conferences.

emWave2

The emWave is a device intended as a tool for stress reduction. It is not considered a medical device. The emWave has been found to be very safe. It is intended to be used for educational purposes.

Undiagnosed Psychiatric Condition

There is a risk of diagnosing a pre-existing or underlying mental health disorder that may be discovered as part of the subject's participation in this study.

E. Potential Scientific Problems:

A possible problem rests in the burden for the caregiver. We have worked hard to minimize the inconvenience to the caregiver in this project to reduce drop outs and maintain compliance. Another issue is related to patient death or subject dropout. For this reason, we use intent to treat design with the last valid measure carried forward. Subject dropouts will be considered to occur completely at random unless otherwise indicated. Caregivers are expected to be generally healthy. It is appreciated that caregiver medications might impact biomarkers. Thus medication use will treated as a covariate in the analysis. We appreciate that eliminating subjects with illnesses requiring medications would skew the caregivers to only the very healthy and least likely to have health impairments associated with caregiving. Such a strategy would distort the potential impact of the intervention on biomarkers and behavior and weaken implications for caregivers in general. It is possible that objective caregiver burden might not change as a function of treatment since in many respects the time factors and financial burden do not change regardless of the intervention. However it is expected that the subject's perception of how stressful they present themselves (subjective burden) will change and this will be seen in affect and stress measures. In summary we remain very excited about this study as it will provide empirical evidence regarding the efficacy of the **fPER** intervention for caregivers of BMT patients. Further, it will provide behavioral and biomarker corroboration regarding the efficacy of **fPER**.

Data Safety And Monitoring Plan

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 two physicians, a social worker, a member of the CAB 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. Brewer, Kilbourn, Laudenslager and Simoneau will hold monthly study review meetings with the study staff involved in the study. During these meetings, subject recruitment, subject drop-out, individual responses to the intervention, and other 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 by Dr. Laudenslager for future reference as needed. The PI, other members of the team, and the study biostatistician 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. Data will be screened for errors and outliers. Appropriate transformations will be made for non-normal outcomes. The pattern of participant dropout 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 as long as missing data is ignorable.[132,133] If this is not sufficient to minimize influences of particular observations, a sensitivity analysis will be conducted to help determine effects of missing data. Separate analyses of only those 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 baseline differences will be accounted for by randomization, but should differences remain we will co-vary variables that are both correlated with the outcome and that differ by group.

Analytic Strategy In general, outcomes will be analyzed with linear mixed models comparing intervention (**fPER**, TAU) in patients and caregivers separately. An alpha level of 0.05 will be used to evaluate significance of the a priori planned comparisons. Two-tailed tests are proposed in order to detect differences between **fPER** and TAU in either direction. The software SAS PROC MIXED will be used.[134] The analytic aims and hypotheses are briefly stated, followed by overall analytic plan for primary and secondary outcomes:

*Aim 2: Assess patient QOL following an allogeneic HSCT by the FACT-BMT as the primary patient outcome. Patients whose caregivers receive **fPER** will have improvements in FACT-BMT compared to TAU.*
*Aim 3: Test impact of **fPER** on caregiver composite distress score of depression, anxiety, and stress as the primary caregiver outcome. Caregivers who receive fPER will have reduced distress compared to TAU.*

For hypotheses addressing group differences for patients and separately for caregivers, outcomes will be evaluated with the same design: 2 groups (**fPER**, TAU) at 2 clinics (CBCI, UCH) over 4 times (prior to transplant, 6 wks., 3 mo., 6 mo.). Mixed models will specify group, clinic, time, and their interactions as fixed effects and subject as a random effect, where subject is assumed independently normally distributed with mean 0 and variance independent of the random errors. The primary caregiver model of composite distress will include caregiver age as a covariate because it related to caregiver distress in our prior study[11]; secondarily, we will investigate inclusion of patient FACT-BMT as a covariate. The primary patient model of FACT-BMT will include no covariates, but secondarily will explore inclusion of caregiver distress as a covariate.

*Aim 4: Assess biomarkers of allostatic load in patients prior to transplant and caregivers during the transplant process using novel biomarkers. Patient's hair cortisol will predict their QOL and distress at the beginning of the transplant process. **fPER** will be associated with reduced allostatic load in caregivers who receive **fPER** compared to those receiving TAU.*

Linear mixed models will similarly be used to evaluate group differences in these biomarkers separately in patients and caregivers. Caregiver age and patient FACT-BMT will be evaluated for inclusion in caregiver models. Caregiver composite distress score will be evaluated for inclusion as a covariate in patient models.

Subject sample size and power analysis. Our prior trial demonstrated medium effect sizes (0.39-0.45) for PEPRR in caregivers. We believe the proposed modifications in **fPER** will likely increase its effect for caregivers. However, the effect of **fPER** on

Table 2. Minimum detectable effect sizes with specified sample size and power

Sample Size Per Group	80% Power	85% Power	90% Power	95% Power
112 Dyads	0.19	0.20	0.22	0.24
74 Dyads	0.23	0.25	0.27	0.30
62 Dyads	0.25	0.27	0.29	0.32

patient QOL is indirect, and thus smaller effect sizes would be expected. We estimated minimum effect sizes detectable for different power specifications for a recruited sample size of 112 per treatment group and also for smaller sample sizes, allowing for increased variability due to estimated losses to follow-up of 34% at 3 mo., and 45% at 6 mo. based on our prior caregiver trial. Estimates are conservative since **fPER** has been specifically modified to reduce attrition. 112 dyads (consisting of a caregiver and patient) randomized to each group provide excellent power (>95%) for detecting the medium effect size expected for the composite distress score in caregivers and are necessary to provide adequate power (80-85%) for detecting smaller effect sizes expected for the FACT-BMT QOL measure in patients. Estimates are also conservative because mixed model analyses that include all subjects (even those with only a single observation) have been shown to provide the greatest power.[127]

G. Summarize Knowledge to be Gained:

This study will provide empirical evidence regarding both behavioral and possible physiological efficacy of a stress management psychoeducation program for caregivers and the impact on patient QOL. This is one of the few studies of its kind that promises to provide not only information regarding behavioral outcome for the patients as far as quality of life but also impact their caregivers. The results of this study will lead to the availability of a manual developed for this intervention that can be disseminated to other HSCT programs leading to improved patient QOL and reduced caregiver distress.

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