Using a Program to Lower Stress for Caregivers of Patients With Cancer Who Have Received Stem Cell Transplants

Mark L. Laudenslager, PhD1; Teresa Simoneau, PhD1; Susan Mikulich-Gilbertson, PhD3; Benjamin Brewer, PsyD1; Kristin Kilbourn, MPH, PhD2; Jon Gutman, MD1; Peter McSweeney, MD3

1University of Colorado Denver, Anschutz Medical Campus
2University of Colorado Denver
3Colorado Blood Cancer Institute

Institution Receiving Award: University of Colorado Denver, Anschutz Medical Campus
Original Project Title: Quality of Life in Allogeneic Hematopoietic Stem Cell Transplant Patients Is Improved When Their Caregiver’s Distress Is Reduced
PCORI ID: CE-1308-6208
HSRProj ID: HSRP20143506
ClinicalTrials.gov ID: NCT02037568

# Table of Contents

ABSTRACT ................................................................................................................................. 3

BACKGROUND ........................................................................................................................... 5

  Objectives/Aims ......................................................................................................................... 8

PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS .................................................... 11

METHODS ................................................................................................................................... 13

  Study Overview ......................................................................................................................... 13
  Study Design ............................................................................................................................. 13
  Participants ............................................................................................................................... 14
  Intervention ............................................................................................................................. 14
  Comparator ............................................................................................................................. 16
  Study Outcomes and Data Collection ...................................................................................... 17
  Study Setting ........................................................................................................................... 22
  Time Frame for the Study ......................................................................................................... 22
  Analytical and Statistical Approaches ..................................................................................... 23
  Protocol Changes ..................................................................................................................... 25

RESULTS .................................................................................................................................... 26

  Recruitment ............................................................................................................................ 26
  Baseline Demographics and Outcome Relationships .............................................................. 28
  Primary Outcomes .................................................................................................................. 43
  Secondary Outcomes .............................................................................................................. 47
  Adverse Events ......................................................................................................................... 48

DISCUSSION ............................................................................................................................... 48

  Context for Study Results ......................................................................................................... 48
  Generalizability of the Findings ............................................................................................... 50
  Implementation of Study Results ............................................................................................. 51
  Subpopulation Considerations ................................................................................................. 51
  Study Limitations ..................................................................................................................... 52
  Future Research ........................................................................................................................ 54

CONCLUSIONS ........................................................................................................................... 55

REFERENCES ............................................................................................................................... 56

RELATED PUBLICATIONS ............................................................................................................. 64

ACKNOWLEDGMENTS ................................................................................................................ 65

APPENDIX ................................................................................................................................. 66
ABSTRACT

Background: We have shown that our PsychoEducation, Paced Respiration, and Relaxation (PEPRR) intervention reduces caregiver psychological distress. Less distressed caregivers may contribute to better quality of life (QoL) in their patients; however, empirical evidence supporting this link is lacking.

Objective: Scientific aims included the following: (1) Assess the impact of PEPRR-2.0 on patient QoL as primary patient outcome; (2) assess the impact of PEPRR-2.0 on caregiver distress as primary caregiver outcome; and (3) assess biomarkers of chronic stress in caregivers.

Methods: We recruited patients receiving allogeneic hematopoietic stem cell transplants (Allo-HSCT) and their caregivers from a private hospital and an academic medical center. We randomized caregivers to either stress management intervention (PEPRR-2.0) or enhanced treatment as usual (eTAU; that is, they received written materials provided to PEPRR-2.0 as well as a check-in call). A master’s degree-level social worker delivered 10 one-on-one PEPRR-2.0 sessions to caregivers over 3 months. Primary outcomes were patient QoL (Functional Assessment of Cancer Therapy-Bone Marrow Transplant [FACT-BMT]) and a composite measure of caregiver distress (CG-Distress) based on the first principal component (PC) of a PC analysis (PCA) that included depression, anxiety, and stress questionnaire scores. Secondary outcomes included individual measures comprising the PCA, caregiver burden, and biomarkers of caregiver stress (hair cortisol, telomere length [TL], and telomerase activity [TA]). Hair cortisol is a retrospective measure of activity of the hypothalamic pituitary adrenal axis; TL and TA also track influences of chronic stress. We obtained outcomes at the time of transplant as well as at 6 weeks, 3 months, and 6 months following transplant. Hierarchical linear models tested intervention group, time, and interactions as fixed effects and participant as a random effect; we analyzed caregiver outcomes similarly.

Results: A total of 155 caregiver/patient dyads comprised an intent-to-treat sample. Patients and caregivers were worse than psychological norms before transplant. Randomization was effective (no baseline differences in psychological or demographic measures between groups). Patients whose caregivers were randomized to PEPRR-2.0 did not show a difference in QoL from baseline to 6 months (mean change = +3.74; 95% CI, −3.54 to 11.02) relative to patients whose caregivers were randomized to eTAU (mean change = +3.16; 95% CI, −2.88 to 9.20) based on the FACT-BMT. CG-Distress in those receiving PEPRR-2.0 decreased significantly from baseline to 6 months (mean decrease = −0.23; 95% CI, −0.448 to −0.010) compared with eTAU (mean increase = +0.27; 95% CI, 0.033, 0.504), confirming the positive effect of PEPRR-2.0 (effect size = 0.51) on CG-Distress. Biomarkers were unrelated to pretransplant distress in either caregivers or patients. We found no impact of the intervention on caregiver biomarkers.

Conclusions: PEPRR-2.0 reduced CG-Distress without influencing patient QoL. Neither distress at baseline nor intervention affected biomarkers. The short duration of intensive caregiving may have contributed to a lack of effect of caregiving on biomarkers.
**Limitations:** This study focused only on Allo-HSCT patients and caregivers. Total FACT-BMT may not have been sensitive to changes in patient psychological QoL. We also failed to meet recruitment goals in the period allowed by the PCORI contract, reducing statistical power.
BACKGROUND

Sixty-six million Americans cared for an ill person in 2015, reflecting a 49% increase in numbers of caregivers since 2008.\textsuperscript{1,2} Of this amount, 3.9 million cared for cancer patients in 2015. These numbers continue to increase. Unpaid caregiving services were valued at more than $450 billion/year in 2010.\textsuperscript{2} Yet, only 1 in 4 caregivers receive support for themselves.\textsuperscript{3} Caregiving is associated with considerable distress and hardship, affecting caregivers’ psychological and physiological well-being.\textsuperscript{4-7} This distress may affect their patients in ways yet to be determined: Would a less distressed caregiver be associated with improved patient quality of life (QoL)?

A hematopoietic stem cell transplant (HSCT) is a treatment for hematological malignancies and other conditions.\textsuperscript{8} Following chemotherapy or intensive radiation to remove the patient’s cells, hematopoietic stem cells obtained from peripheral blood or bone marrow are infused into the patient’s peripheral blood to regenerate the recipient’s marrow. Stem cells can come from either the patient (autologous, or Auto) or closely matched donors (allogeneic, or Allo). Allo-HSCT patients experience a greater risk for adverse effects, such as graft-vs-host disease (GVHD), with a poorer prognosis.\textsuperscript{9} Patients receiving an HSCT require close management by informal caregivers.\textsuperscript{10}

Allo-HSCTs have increased by 1.9-fold in the past decade (6 166 performed nationally in 2016).\textsuperscript{11} Despite Allo-HSCT transplants increasing as indications for their use broadens and procedure safety improves,\textsuperscript{11,12} HSCT patients and their caregivers\textsuperscript{13} have not been studied like those patients with other illnesses and their caregivers. A major requirement for an Allo-HSCT is having a caregiver available 24/7 for the first 100 days posttransplant.\textsuperscript{14} These caregivers contribute significantly to patient outcomes. During this 100-day period following transplant, the patient and caregiver must remain within a 30-minute patient transportation radius to the transplant facility for specialized medical care. This allows a rapid medical response for emergencies outside capabilities of the caregiver by staff prepared to care for Allo-HSCT patients; however, the caregiver assists in monitoring a complex medication regimen following
discharge, responding to emergent problems like GVHD and/or infections, attending multiple medical appointments with the patient, and maintaining an aseptic home environment. By most standards, these caregivers provide considerable supportive care. Not surprisingly, HSCT caregivers experience considerable distress in caring for their patient.\textsuperscript{10,15,16}

The overarching hypothesis of the present project is that mitigating the distress of Allo-HSCT caregivers may translate to improved QoL for their patients. However, empirical evidence is lacking for this common belief, which has been articulated for other critical illnesses.\textsuperscript{17} Reports supporting this notion are limited. For example, caregivers of patients with schizophrenia who participated in a psychoeducation program emphasizing coping skills training were more likely to have improved patient outcomes as much as 5 years later.\textsuperscript{18} Conversely, poor caregiver mental health was associated with increased mortality of patients with progressive dementia.\textsuperscript{19} However, the directionality of these observations remains unclear. For example, did the caregiver’s poor mental health decline as a function of the progressive dementia in the patient, or did the mental health of the caregiver affect his or her ability to care for the patient and thus affect patient outcome? The presumed link between caregiver and patient requires careful study to define directionality as well as possible mechanism(s) of these relations.

In a secondary analysis of caregiver and patient relationships collected from an earlier study, we noted an intriguing relationship between caregiver sleep and the patient’s time to neutrophil engraftment\textsuperscript{20} (a clinical marker of transplant recovery \textsuperscript{21}). Those caregivers reporting better sleep at the time of transplant (based on self-report as well as actigraphy) were associated with patients having a shorter time to neutrophil engraftment, after controlling for transplant-specific factors; however, caregiver sleep may be a proxy measure of patient sleep. In the present study, we assessed patient and caregiver self-reported sleep to explore this relationship further.

Observations suggest that the survival rate of patients receiving an Allo-HSCT is tied to family relationships.\textsuperscript{22} Our team has noted previously that caregivers often sleep in the hospital
room with their patient during the hospitalization phases of the transplant. An intriguing study noted that having a consistent in-hospital caregiver (a caregiver who spent 7 or more hours/day for 5 or more days/week in the hospital room) was associated with improved outcomes, accounting for 44% of the variance in patient survival after controlling for medical factors such as diagnosis or transplant type. A prospective study of caregivers planning to spend time in the hospital with their patient found that survival 4 years later with a consistent in-hospital caregiver was 42% compared with 25% in patients without a consistent in-hospital caregiver. Although the underlying mechanism(s) remain unclear, the role of caregivers in the patient’s long-term outcome seems apparent but relatively untested.

We previously demonstrated the efficacy of a stress-management intervention for Allo-HSCT caregivers, which we adapted for caregivers from a cognitive behavioral stress management program targeting medically ill patients. In brief, PsychoEducation, Paced Respiration, and Relaxation (PEPRR) consisted of 8 one-on-one sessions with a master’s-degree level social worker. Each 60-minute PEPRR session was devoted to a specific topic; the goal was assisting the caregiver in developing and applying stress-management skills including using problem solving, identifying cognitive distortions, applying relaxation techniques, using a biofeedback device for relaxation, using social support, and establishing appropriate goals. The provision of PEPRR to Allo-HSCT caregivers compared with treatment as usual (TAU) was associated with reduced perceived stress as a primary outcome (effect size [ES] = 0.39) along with reduced secondary outcomes of depression (ES = 0.46) and anxiety (ES = 0.66). We used ES to allow comparison across varying outcome measures with standardized ESs consistent with Cohen’s definitions of 0.2, 0.5, and 0.8 as representative of small, medium, and large ESs, respectively. We also noted that caregivers participating in PEPRR were less likely to seek outside psychological support services from social workers, psychologists, or support groups compared with caregivers receiving TAU.

A person’s physiology can be disrupted by caregiving. For example, telomeres are the caps of chromosomes that shorten with aging. They have been found to be shorter in...
caregivers compared with those of age-matched non-caregiver controls, suggesting accelerated aging processes.\textsuperscript{34} Other indications of disrupted physiological functioning in dementia caregivers include increased inflammation and activation of the hypothalamic pituitary adrenal axis (HPA).\textsuperscript{35-39} We have shown that a novel biomarker, hair cortisol (hCORT), may track cumulative retrospective activity of the HPA\textsuperscript{40} that is elevated in caregivers of dementia patients;\textsuperscript{41} therefore, hCORT adds another pertinent noninvasive biomarker\textsuperscript{42} for the present study in tandem with telomere length (TL) and telomerase activity (TA; rebuilds telomeres\textsuperscript{43}) as unique exploratory biomarkers. The overarching question was: Would reducing distress of caregivers mitigate changes in these markers?

**Objectives/Aims**

We provide an overarching study framework in Figure 1. Except for exploratory outcomes for the patient, we specified all relationships at ClinicalTrials.gov. The figure proposes that reduced distress in caregivers receiving PEPRR-2.0 will be associated with improved patient QoL (primary patient outcome). We derived caregiver distress (CG-Distress), primary caregiver outcome, from a composite measure used previously.\textsuperscript{4,10,20} It stipulated a single primary outcome that combined depression, anxiety, and stress. Baseline patient QoL and CG-Distress will be related (bidirectional green arrow). The exact link through which improved QoL may occur links to factors such as reduced caregiver fatigue, improved sleep, and so on, allowing the caregiver to provide better care for their patient. There were 3 scientific aims in the proposed study:

**Aim 1**

Assess patient QoL (Functional Assessment of Cancer Therapy-Bone Marrow Transplant [FACT-BMT]) following an Allo-HSCT as the primary patient outcome. We hypothesized that patients whose caregivers received PEPRR-2.0 would have an increased FACT-BMT score compared with patients whose caregivers receive enhanced TAU (eTAU).
Aim 2

Test the impact of PEPRR-2.0 on a caregiver composite distress score (includes depression, anxiety, and stress) as the primary caregiver outcome. We hypothesized that caregivers receiving PEPRR-2.0 would have reduced distress compared with caregivers receiving eTAU.

Aim 3

Assess biomarkers of chronic stress in patients and caregivers prior to transplant and follow caregivers posttransplant using novel biomarkers (hCORT and telomeres) as exploratory outcomes. We hypothesized that patient hCORT before transplant would relate to FACT-BMT. We hypothesized that caregivers receiving PEPRR-2.0 would have sustained TL and lower hCORT compared with caregivers in the eTAU group.
Figure 1. Conceptual model relating patient and caregiver

**Patient**

*Primary Outcome*
- Patient QoL
- FACT-BMT

**Patient Secondary Outcome** (Aim 3)
- Hair cortisol
- Transplant Medical Outcome
  - PSS, CESD, and STAI
  - PT-Distress

**Caregiver**

*Primary Outcome*
- CG-Distress Composite*
- CESD*
- STAI*

Covariates
- Age
- Sex
- Site

**Caregiver Secondary Outcomes** (Aim 3)
- Hair cortisol, Telomeres
- PSS, CESD, STAI, CRA, PSQI

Abbreviations: FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplant; CES-D, Center for Epidemiologic Studies—Depression; CRA, Caregiver Reaction Assessment; QoL, quality of life; PEPRR, PsychoEducation, Paced Respiration, and Relaxation; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; STAI, State-Trait Anxiety Inventory.
PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS

PEPRR-2.0 had the advantage of caregiver and patient input during earlier development of PEPRR.\textsuperscript{25} We developed PEPRR-2.0 based on feedback obtained in exit interviews during the initial trial of PEPRR.\textsuperscript{4} Focus groups and stakeholder input further assisted in formulating and improving the content execution of our one-on-one and recent web-based intervention.\textsuperscript{44,45} We learned from caregivers participating in the first trial of PEPRR that “video would not be the same as in-person but better than a telephone” and “[caregivers] prefer face-to-face, but video would be a good substitute.” We assimilated this information, adding video chat as an alternative for attending sessions when face-to-face was not possible. PEPRR-2.0 implemented digital technology not previously tested.

At the outset of this study we created a community advisory board (CAB) by recruiting representatives of patients and caregivers from both transplant sites. At the private hospital, we recruited stakeholders who had previously taken part in the first trial of PEPRR. At the university-based setting, interested participants had not been a part of the first trial. We recruited 4 individuals from each site; they represented patients and caregivers who had experienced a transplant and were now in survivorship. A total of 5 males and 3 females served as representatives of HSCT patients and caregivers. Additionally, we recruited 2 additional stakeholders (a pastor and a program director) from a community-based nonprofit program supporting individuals and families, including transportation and other activities needed by seniors and others. They joined after the second meeting and provided a community perspective on the challenges of caregiving. The CAB met twice a year, beginning before the contract was initialized. We obtained input on the handout materials, which addressed topics that the CAB believed would be useful for the intervention sessions. For example, one patient felt addressing existential issues was important; this was an issue with which his caregiver (brother) had considerable difficulty and was thus added to PEPRR-2.0.

We were limited in what we could change once the study began. Strict contract timelines required that we begin recruiting as quickly as possible and thus we needed to specify
the intervention for approval by our institutional review board (IRB) and post at ClinicalTrials.gov as early as possible. Once approved, the intervention was not changed so as to retain integrity.

Stakeholder guidance informed inclusion of the medication-reminder device. We initially provided a programmable pillbox linked to a smartphone belonging to either the caregiver, the patient, or both. The device would send text-message reminders to take medications as well as track medication adherence. There were 2 sources of stakeholder input regarding the device: nursing staff at the transplant clinics and caregivers. During a training for the device by the company, a member of the medication nursing staff at one of the study sites indicated that the idea was good but not feasible for HSCT patients due to their rapidly changing medication regimen. Foil-wrapped toxic tablets could not be included in the box. Caregivers were reluctant to use the device. Some developed other systems for medication adherence, including elaborate spreadsheets in Excel. Caregivers did not like the device due to its size (4.4” x 7” x 2.3” and 3 pounds) as well as the difficulty in programming the ever-changing medication regimen. Based on this stakeholder input and with guidance from PCORI program staff, we dropped the device from the intervention early in the study. This was the only major change during the trial as far as the intervention.

During the semiannual CAB meetings, the study team became familiar with the transplant process from perspectives of both patients and caregivers. An abstracted summary of some comments as they arose in the CAB meetings is included as Appendix 1. Some examples follow:

- **Regarding recruitment**: During an early session, 1 stakeholder indicated that caregivers are quite overwhelmed. The idea of 10 sessions may have been too much. To lighten intervention burden, the final 2 sessions were modified to “as needed” to address new problems that emerged for caregivers.

- **Regarding eTAU**: “Caregiver stated that because caregivers are so busy during early stages of transplant, those phone calls may not be very useful.” To retain fidelity in the
intervention, we had to continue calls following the delivery of each PEPRR-2.0 workbook section to the eTAU group.

- **Regarding the intervention manual**: One patient indicated, “I would never use this. I mean, it is not sold very well [while holding the manual]. It doesn’t have any pictures and is kind of boring.” *The trial had begun so we could not change it at that time.*

- **Regarding failures to complete questionnaires**: Many CAB members agreed that each caregiver–patient dyad should be approached differently by offering each method (email/iPad in room/paper questionnaires) and allowing them to choose. *We emphasized this choice to facilitate questionnaire completion.*

## METHODS

### Study Overview

We asked, “Does stress-management training for HSCT caregivers reduce CG-Distress and affect the QoL of their patient?” We hypothesized that PEPRR-2.0 provided to caregivers would reduce CG-Distress and improve patient-reported QoL compared with eTAU. See Figure 1 for the framework of this study.

### Study Design

This was a randomized control trial (RCT) with intent-to-treat analysis. Allo-HSCT patients and their caregivers were randomized by permuted block design to either PEPRR-2.0 or eTAU. The biostatistician developed a separate randomization allocation for each site to ensure balance between PEPRR-2.0 and eTAU. The study coordinator opened assignments placed in separate sequentially numbered sealed envelopes when the caregiver had completed his or her baseline psychological and physiological assessments, thus avoiding any influence of knowledge of group assignment on responses. Participant involvement began at patient screening for an Allo-HSCT at both sites. We approached every dyad (patient and his or her proposed caregiver).
Eligibility criteria included (1) both adult Allo-HSCT patient and his or her primary caregiver agreeing to participate; (2) having ability to speak and read English; (3) having telephone access; and (4) being 18 years or older. In addition, for caregivers, eligibility criteria included willingness to use a smartphone and, if randomized to the intervention group, willingness to participate in intervention sessions. Exclusion criteria included (1) uncontrolled psychiatric disorder in the patient or caregiver in the past 18 months unrelated to the patient’s illness and (2) caregiver alcohol consumption greater than 2 drinks/day. We defined the caregiver as the person in the patient’s life who was primarily responsible for care posttransplant, emotionally invested in the patient, and responsible for major decisions regarding patient care. Inclusion criteria were modified slightly (removing the exclusion of any caregiver taking prescribed steroids that could influence hCORT) during the study to improve recruitment numbers (see section on Protocol Changes).

Participants

Between March 1, 2014, and November 4, 2016, we approached every Allo-HSCT patient and his or her caregiver presenting at the 2 sites for transplant evaluation. As part of the pretransplant screening process, transplant candidates and caregivers underwent a structured psychosocial interview. Following transplant screening, we explained this study to patients and caregivers. If interested, they scheduled a separate meeting for consenting and initial assessments. We informally recorded any comments made regarding refusal when caregivers or patients volunteered them. The most frequent reasons included that they were either too busy or overwhelmed with the transplant process. “Just not interested” occurred on occasion.

Intervention

We have shown that PEPRR effectively lowers caregiver depression, anxiety, and stress.\(^4\) PEPRR was modeled after a cognitive behavioral, stress-management program for patient populations,\(^{47-49}\) which we manualized for caregivers.\(^{44}\) We provided PEPRR-2.0 over eight 60-minute sessions by 3 trained, master’s-degree level social workers during the 100-day
posttransplant period while the dyad resided within 30 minutes of the treating hospital. The intervention lasted 3 months in order to coincide with the 100-day period posttransplant, a time of great distress for the caregiver\textsuperscript{50} when the dyad might be in greatest need for this support. PEPRR-2.0 included additional cellular technology\textsuperscript{51,52} for video not used in our prior trial\textsuperscript{4} and 2 optional booster sessions. PEPRR-2.0 included video chat when caregivers could not attend one-on-one sessions. Interventionists tracked use of video chat sessions. These sessions could occur as needed after a mandatory initial one-on-one meeting with the interventionist. For the present study, 15\% of all potential intervention sessions occurred through video or audio chat. For example, video chat took place when the caregiver could not meet directly with the interventionist as during inclement weather or in rare cases after the caregiver and patient had returned early to their homes outside of the Denver area. The decision to use video chat for a session was a caregiver choice, to allow flexibility; this was not controlled. We provided smartphones and data plans at no cost to 6 caregivers without a smartphone. The first intervention session began soon after transplant. Interventionists kept clinical notes and attendance records for each participant.

Caregivers randomized to PEPRR-2.0 received a workbook including session materials and homework assignments (previously provided to PCORI). Caregivers randomized to eTAU received the same materials described under the Comparator subheading. Each PEPRR-2.0 session began with a check-in to address any new issues arising since the last meeting. Content specific to each session included (1) overview, introduction to stress management, and the biofeedback device; (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 the unknown; (7) managing changing relationships with the patient; and (8) getting needed support. Two additional open-ended booster sessions (9 and 10) were available if requested by the caregiver. Intervention fidelity was determined from video recordings made during all sessions. Three clinicians (B.B., K.K., and T.S.) randomly reviewed 20\% of session videos for adherence to a 5- to 7-item checklist for each session. Coverage of
each item in the checklist was 100% across the interventionists for more than 100 random sessions verified through the course of this study.

A biofeedback device, emWave2 (HeartMath, Inc), was introduced during the first PEPRR-2.0 session for caregiver relaxation outside the sessions. In brief, emWave2 is a small handheld device (8 x 4 x 1 cm) on which the user places his or her index finger. Pulse information during contact determines heart rate variability, with a visual color analogue representing 3 levels of vagal activity (a sign of relaxation). Using this device, the participant paces respiration in synchrony to the LED display while relaxing. The device stores usage, and the interventionist downloaded these data. Instructions were to use the device when desired for 5 to 10 minutes, 2 to 3 times each day and any time when they felt distressed. Although usage data are available, we have not addressed this aspect of adherence in this report.

Comparator

The appropriate comparator received considerable thought, taking into account published recommendations such as parallel data collection times, equivalent frequency of contact, and overlapping content in the manuals provided to both groups. Following assignment to either PEPRR-2.0 or eTAU, participants were aware of group assignment. Our prior experience has been that less than 20% of caregivers in TAU use available resources. All participants were encouraged to use the psychosocial resources available at their respective transplant site. Standard resources were similar across sites and included staff psychologists, social workers, nursing staff, support groups, and education programs at no cost. The psychologists and social workers were available at either clinic to meet directly with the patients or caregivers as needed. The services matched needs requested at the time of service. As an attention control, caregivers assigned to eTAU received each section from the workbook in the same order that it was provided to caregivers assigned to PEPRR-2.0 in their one-on-one sessions. Via email, we sent workbook sections weekly the first month, then biweekly for the next 2 months, with follow-up phone calls after sending the material. These calls occurred at the same frequency as for caregivers assigned to PEPRR-2.0. During the brief call, the staff
member asked, “How are you doing?” “Did you receive/read the materials we sent?” and “Did you use any psychosocial services (saw a psychologist, social worker, or group support about the transplant experience) since we last spoke?” If the answer was yes, the staff member asked, “What services did you use?”

**Study Outcomes and Data Collection**

Following consent and prior to stem cell infusion, patients and caregivers completed study questionnaires via a HIPAA-compliant website hosted at the University of Colorado, Denver, using REDCap or by paper format if requested (less than 25%). Patients and caregivers received identical assessment measures, except patients completed the FACT-BMT as a measure QoL and caregivers completed the Caregiver Reaction Assessment (CRA) as a measure of caregiver burden. Although several of these scales also had subscales, we based the present analysis on full-scale score results. Subscale analyses were not specified at ClinicalTrials.gov website. All psychological outcomes were self-reported measures by patients and caregivers.

**Demographic Variables**

We obtained demographic information from patients and caregivers separately. It included age, sex, race/ethnicity, patient diagnosis, income, education level, relationship to the patient or the caregiver, time of transplant, health behavior information (diet, exercise, nutrition, smoking, etc), medications, employment status, and so on.

**Patient Chart Review**

From each patient’s chart we obtained information regarding date of diagnosis, specific diagnosis, conditioning regimen, number of previous transplants, transplant cell source, transplant date, prior transplants, platelet recovery and neutrophil engraftment and platelet recovery dates, medications including steroids, GVHD dates, disease status, and number of hospital readmissions following transplant.
Questionnaires

Caregivers and patients completed the following questionnaires prior to transplant and at 6 weeks, 3 months, and 6 months following transplantation:

Center for Epidemiologic Studies–Depression

The CES-D consists of 20 items, with total scores ranging from 0 to 60 such that higher scores reflect greater depressive symptoms. Test–retest validity ranges from 0.51 to 0.67 over 2 to 8 weeks, with an internal validity of 0.85 for a normal population. Scores of 16 and above reflect depressive symptomatology and are anchored to the past week. Cronbach $\alpha$ for the present study ranged from 0.64 to 0.83 across subscales and full-scale outcomes for caregivers and patients.

State-Trait Anxiety Inventory

The STAI is a 40-item scale that asks subjects to rate how they feel “right now” (state measure; STAI-S). Internal consistency ranges from 0.89 to 0.92 and test–retest correlations range from 0.73 to 0.86. The scale has been used in both patient and caregiver populations. Total score ranges from 20 to 80; a score of 36 reflects the population norm for this scale. Higher scores reflect greater anxiety. Cronbach $\alpha$ for the present study was 0.95 and 0.94 for caregivers and patients, respectively.

Perceived Stress Scale

The 14-item PSS measures the degree to which participants have felt their lives are unpredictable, uncontrollable, and overwhelming during the past month on a 5-point Likert scale. The measure has good reliability and validity (22) with normative data available. Cronbach $\alpha$ for the present study was 0.89 and 0.86 for caregivers and patients, respectively. Total score ranges from 0 to 56; a score of 19 reflects the population norm on this scale. Higher scores reflect greater perceived stress.
Composite Distress Score

To reduce the number of comparisons and simplify the primary outcome to a single measure, we applied a PCA. This PCA extracted the first PC from caregiver summary scores from the CES-D, STAI, and PSS, and labeled CG-Distress. A similar approach that included additional measures combined into a composite score was applied in our first study. Here, we retained only CES-D, STAI, and PSS because of their high factor loadings and the demonstrated efficacy of PEPRR on these measures. We computed a composite distress score for Patient Distress (PT-Distress) similarly. By design, the composite distress scores for caregivers and for patients have a mean of 0.0 and SD of 1.0 and were computed separately for each study phase after combining both study groups. Scores are missing if any component variable is missing. Higher scores reflect greater distress on a continuous scale. There are no population norms, as the scale is unique at each assessment period. We have listed the subcomponents as secondary outcomes for the caregiver, to have a means for assessing component outcomes with known clinical ranges and thresholds.

Pittsburgh Sleep Quality Index

The PSQI provides a score that includes sleep latency, sleep efficiency, sleep duration, and other sleep quality metrics for the past month. After finding a relationship between caregiver sleep and patient time to engraftment in a previous study, we added the PSQI for the patient and caregiver as an exploratory measure. It has acceptable reliability and validity with diagnostic sensitivity of 89.6% and specificity of 86.5%. Scores ≥ 5 indicate sleep difficulty. Total scores range from 0 to 21, with higher scores reflecting greater sleep difficulty. Cronbach α for the present study was 0.72 and 0.72 for caregivers and patients, respectively.

Assessment (Patients)

Patients completed the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) consists of the FACT-G (FACT-General) with a BMT subscale to assess QoL related to HSCT during the past 7 days. The FACT-G has 27 items, and the BMT component has 10 items rated on a Likert scale from 0 (not at all) to 4 (very much). Scores range from 0 to
148, with higher scores reflecting better QoL. It has been used in other HSCT studies.\textsuperscript{72} Cronbach $\alpha$ for the FACT-BMT in the present study was 0.87 across assessments.

**Assessment (Caregivers)**

Caregivers completed the Caregiver Reaction Assessment (CRA),\textsuperscript{63} which includes 24 items scored on a 5-point Likert scale covering domains of self-esteem, family support, finances, schedule, and health, was selected as the best measure of caregiver burden compared with other measures.\textsuperscript{73} It has excellent test–retest reliability of 0.9 and responsiveness to change of 0.81\textsuperscript{63} as well as normative data for cancer caregivers.\textsuperscript{74} Total scores range from 5 to 25, with a higher score representing greater caregiver burden. Cronbach $\alpha$ for the present study was 0.73 across assessments. Higher scores indicate increased burden in the summed measure.

**Secondary Outcome Biomarkers**

Secondary outcome biomarkers that focused predominately on the caregivers included the following:

**Blood Samples**

Phlebotomists collected venous blood from the caregivers between 7 AM and 10 AM during patient clinic visits, as specified in Figure 2.

**Hair Samples**

As indicated in Figure 2 and described previously, we collected scalp hair from the posterior vertex.\textsuperscript{75-77} Individuals with balding or short hair could not provide ideal samples, but our assay allows for shorter samples, recognizing it is reflecting a shorter time. We collected hair from caregivers simultaneously with blood samples, but only at baseline and 6 months from patients to allow for hair to regrow following transplant conditioning procedures. Three-month intervals were selected to allow any cumulative impact to be expressed in the hair.\textsuperscript{40,78}
**Hair Cortisol**

As a measure of total HPA activity, we assayed hCORT in the proximal 3 cm of scalp hair samples. Hair grows at approximately 1 cm/month,\(^40,78\) and the sample was reflective of the preceding 3 months.\(^42\) In brief, hair is ground, extracted, and processed by immunoassay (Salimetrics, LLC, State College, PA) following our published methods with intra- and interassay coefficients of variation < 5 and 10%, respectively.\(^79-81\) hCORT was reported as pg/mg, independent of hair length. Our procedure is reliable.\(^82\)

**Telomere Length and Telomerase Activity**

We extracted DNA from lymphocytes with the QIAamp DNA mini kit (QIAGEN, cat no. 51306) and stored at -85°C for TL. Lymphocytes were lysed according to the TRAPEze telomerase detection kit protocol (Millipore cat no. S7700) for TA, and the lysate was stored at -85°C. Materials were processed using established protocols.\(^83-85\) Samples were processed in the Blackburn Laboratory at the University of California San Francisco.
Study Setting

This study took place at 2 sites: a university-based, NCI (National Cancer Institute)-designated Comprehensive Cancer Center and a community-based, for-profit cancer center. The patient proportion between the university and private clinic was approximately 1 to 2. These are the only HSCT programs for adults in the greater Rocky Mountain region. They reflect racial and ethnic characteristics of patients receiving Allo-HSCT in the greater Rocky Mountain region as well as national trends.86

Time Frame for the Study

Figure 2 indicates the study timeline from the participant’s perspective following consent. Patients and caregivers completed their assessments in tandem throughout the study. Outcomes included a panel of questionnaires, a blood draw from the caregivers, and hair collection, as indicated from the caregiver and patient (+P) in Figure 2. Participants completed all questionnaires and biomarkers prior to randomization for baseline samples. If randomized to the PEPRR-2.0 group, caregiver intervention sessions began immediately (first session mean = 17.4 days posttransplant; 95% CI, 10.3, 24.5, range –90 to 147, a negative day refer to days prior to transplant) and weekly for 4 weeks and then every other week to complete 4 additional sessions. Outliers reflect delays associated with tissue matching for one patient after beginning PEPRR-2.0 and scheduling difficulty with another caregiver. Patients and caregivers completed questionnaires again at 6 weeks, 3 months, and 6 months following transplantation (Figure 2). We collected biomarkers again at 3 months and 6 months (Figure 2). We selected these intervals to allow sufficient time for any effects to influence the biomarkers. The participants were involved in trial activities for approximately 6 months. We based timing decisions on our prior trial4 and known characteristics of cortisol accumulation in hair.40

Analytical and Statistical Approaches

To allow sufficient (> 85%) statistical power to detect medium ESs on CG-Distress but also to provide power to detect smaller ESs corresponding to postulated influences of a
caregiver’s participation in PEPRR-2.0 on patient QoL, we targeted 112 dyads per group, or 224 total dyads. We based small, medium, and large ESs on Cohen’s definition \(^{29,30}\) of < 0.2 as small, > 0.2 to 0.8 as medium, and > 0.8 as large ESs; however, we failed to meet overall recruitment goals within the time PCORI allowed, which reduced recruitment to 155 total dyads (caregivers and their corresponding patients) after removing 4 screen failures. With a sample size of 155 patient–caregiver pairs, we computed 80% to 95% power to detect ESs in the range of 0.23 to 0.30 (medium ESs), respectively. In designing this trial, our prior study results\(^4\) suggested that these medium ESs were reasonable to expect for caregiver outcomes (namely CG-Distress); however, we anticipated in the application that the effect size for patient QOL would be small, given the indirect effect of the intervention on patients.

We applied hierarchical linear models (HLMs)\(^{87}\) or multilevel models to allow for missing data common in longitudinal trials. HLMs are accepted approaches in the study of longitudinal data where observations nest within individuals. We used the same approach in the first efficacy trial of PEPRR.\(^4\) This approach assumes that data are missing at random, as in our previous trial. Dropouts were similar with regard to demographic characteristics across randomized groups, as were deaths. Without the ability to recruit more families to increase power, we were unable to correct for any loss. Longitudinal HLMs or growth-curve models treat time in a flexible manner that allows the modeling of change across time and accommodates unequal numbers of observations across individuals, as in the case of this study.

Intent-to-treat analyses included all randomized participants after removing 4 screen failures, where 1 patient did not receive transplant, and 3 patients could not be part of the study because their caregiver did not consent. We utilized SPSS version 24.0 (IBM Corporation, Armonk, NY) and SAS version 9.4 (SAS Institute INC, Cary, NC) software. We assessed baseline differences in demographics and other key variables between patients and caregivers in PEPRR-2.0 and eTAU and between the 2 sites using chi-square and independent \(t\) tests or nonparametric Fisher exact tests, Mann-Whitney tests, and Kruskal-Wallis tests when data were non-normal.
We analyzed primary and secondary outcomes over time in the intent-to-treat sample using linear mixed models analyses of covariance with Satterthwaite approximation for degrees of freedom, to provide group estimates at each month with fixed effects of intervention group (PEPRR-2.0, eTAU), month (baseline, Month 1.5 [6 weeks], Month 3, and Month 6) and site and their interactions. We covaried caregiver outcomes for caregiver age as in our prior study, because older age is associated with reduced distress in caregivers. We assumed repeated measures to have unstructured covariance. We removed nonsignificant interactions successively, beginning with the most nonsignificant highest-order interaction (group by site by month), and the model was re-run. The final model for each outcome included group, site, month, and the group by site interaction (regardless of significance) as well as any significant higher-order interactions; for caregiver outcomes, caregiver age was also included regardless of significance. TL, TA, and hCORT were non-normally distributed and were natural log transformed to achieve normality.

To provide some protection for multiple comparisons, we tested group effects at Month 6 only if the omnibus test of the global null hypothesis (ie, means for each group by month combination were equal) was rejected. Comparisons utilized a 2-tailed, 0.05 significance level. We calculated ESs at Month 6 as (MeTAU−MPEPRR)/SD, where MeTAU and MPEPRR represents adjusted means of eTAU and PEPRR-2.0, respectively, at Month 6 and SD as the square root of estimated variance of each outcome at Month 6.

In addition to these planned analyses, we evaluated associations between outcomes at baseline. These post hoc analyses included paired t tests between scores on psychological assessments (PSS, CES-D, STAI, PSQI) for patients and their caregivers, Pearson correlations within patients, Pearson correlations within caregivers, and Pearson correlations between caregivers and patients. Finally, we conducted a multiple linear regression of patient QoL on PT-Distress and CG-Distress to determine whether CG-Distress explained significant variance in patient QoL beyond that explained by PT-Distress score.
Aim 3 assessed biomarkers of chronic stress in patients and caregivers prior to transplant and followed caregivers during the transplant process using novel biomarkers (hCORT and telomeres) as exploratory outcomes. We hypothesized that patient hCORT before transplant would relate to FACT-BMT. We hypothesized that caregivers receiving PEPRR-2.0 would have sustained TL and lower hCORT compared with those caregivers in the eTAU group.

Protocol Changes

We made small protocol changes to caregiver inclusion criteria. We redefined the caregiver as the person in the patient’s life who is primarily responsible for his or her care posttransplant, emotionally invested in the patient’s care, and responsible for major decisions, if needed, regarding his or her care to increase potential available caregivers meeting inclusion criteria. We removed the caregiver restriction on medications containing corticosteroids. In subsequent analysis of caregiver demographics, we noted that 15 caregivers (7 before lifting the restriction) indicated a steroid medication in their general health questionnaire (some of which were cortisol related). It was the perception of the study coordinators that caregivers were often unaware of exact medical regimens. At the recommendation of PCORI program staff during a check-in call, we dropped the use of the medication-reminder device because most caregivers were opting not to use it and feedback from the CAB and nursing staff suggested it was not a good match to this setting. Although we made protocol changes to improve recruitment after consenting 67 dyads, there was no notable impact on rate of recruitment, suggesting we had saturated capacity of this population. There were no differences in demographic and psychological characteristics between the initial 67 dyads and the final dyads recruited after protocol changes.
RESULTS

We describe the present trial, beginning with recruitment and followed by baseline characteristics prior to randomization, analyses of primary outcomes for the patient and caregiver, and finally secondary analyses as specified at ClinicalTrials.gov.

Recruitment

Several problems arose that interfered with accrual; consequently, recruitment fell below projected levels. Despite recruiting from the only 2 adult transplant programs in the Rocky Mountain region covering a wide geographic range (see Figure 3), we assumed a constant rate of transplantation would occur; this did not happen. Transplantation was episodic including a seasonal decline each year during year-end and for no apparent reason at other times. At both sites we positioned an individual who was assigned to recruitment so that every transplant dyad (n = 407) was contacted prior to their transplantation. We modified inclusion criteria to accept caregivers who were responsible for caring less than 50% of the time and responsible for making major decisions regarding the patient; this assured significant emotional ties to the patient. We dropped the steroid exclusion criterion that would influence hCORT, because this was a secondary outcome, to prioritize primary outcomes. Recruitment rates did not improve. An unexpected and uncontrollable administrative reorganization took place at one of the sites, creating a staffing reduction beyond our control and setting back recruitment at that site by 6 months. The recruitment rate ultimately returned to previous levels. In retrospect, it is apparent that the transplant recruitment pool was saturated despite successfully recruiting more than 47% of eligible dyads. We simply could not meet enrollment in the time allotted by the PCORI contract.
Figure 3. Regional distribution of patients and caregivers by county within states (color reflects density based on scale)

Patient

Caregiver
Every Allo-HSCT patient–caregiver dyad (n = 407) at both sites was approached during the 32 months available for recruitment, of which 331 dyads met eligibility criteria. Of those eligible, 159 consented to participate (47.5%). All subjects provided informed consent and received financial reimbursement for participation. The Colorado Multiple IRB approved the study registered at ClinicalTrials.gov (NCT02037568) prior to first consent.

Dyads were ineligible for the following reasons: (1) did not ultimately receive an Allo-HSCT (22, 28.9%); (2) was not the primary caregiver for the transplant patient (27, 35.5%); (3) could not read or speak English (12, 15.8%); (4) alcohol consumption exceeded 2 drinks/day (1, 1.3%); (5) were younger than 18 years of age (2, 2.6%); (6) had a history of an uncontrolled psychiatric illness unrelated to their experience as a caregiver within the past 18 months (2, 2.6%); or (7) other (10, 18.4%). The CONSORT diagram is provided in Figure 4.

Baseline Demographics and Outcome Relationships

The average patient age was 53.3 years of age; most patients (64.5 %) were male. Patient cohort was predominately white (80.0%), with a college or higher education (47.7%), a diagnosis of leukemia (60.6%) as the illness for which the HSCT was required, and mean diagnosis 19.7 months prior to transplant. Baseline demographics for patients are in Table 1 and for caregivers in Table 2. Caregivers were 54.1 years of age and predominately female (80.0%) and white (83.2%), and many were college graduates or above (47.7%). Few were employed full or part time while caregiving (39.3%). Caregiving affected employment status such that full-time caregiver employment prior to transplant declined from 41.3% to 20.6%. The percentage employed part time did not change (17.4% before transplant to 18.7% after the transplant). An analysis comparing eTAU and PEPRR-2.0 assured that randomization was effective and that there were no differences between group assignments at baseline on demographic of primary and secondary outcomes (see Tables 1, 2, and 3). Caregivers came from 12 states and patients represented 9 states (see Figure 3 for counties of residence), indicating a broad geographic range of participants in this study. The patient population matches national trends for racial distribution between 2010 and 2014, as reported by the
Center for International Blood and Marrow Transplantation. Thus, our study population represents national trends in which racial disparities unfortunately exist regarding donors, access to programs, and outcome.⁸⁹
Figure 4. CONSORT diagram

Enrollment
Assessed for eligibility (n=407)
Excluded (n=248)
- Not meeting inclusion criteria (n=76)
- Declined to participate (n=166)
- Other reasons (n=6)
Consented (n=159)
Screen failure (n=4)

Enhanced TAU
Randomized (n=155)
Allocated to enhanced TAU (n=80)

PEP RR-2.0
Allocated to PEP RR-2.0 intervention (n=75)
- Received allocated intervention (n=62)
- Did not receive allocated intervention (n=13)
  - Caregiver felt overwhelmed (n=4)
  - Could not meet for sessions (n=3)
  - Interventionist did not meet with caregiver (n=2)
  - Patient's disease progression (n=2)
  - Loss to follow-up (n=1)
  - Not interested in study (n=1)

Follow-Up
Caregiver lost to follow-up (n=16)
  - Caregiver discontinued study (n=17):
    - Patient passed away (n=7)
    - Overwhelmed (n=9)
    - Patient's disease progression (n=1)
Patient lost to follow-up (n=16)
  - Patient discontinued study (n=21):
    - Caregiver withdrew from study (n=10)
    - Patient's disease progression (n=1)
    - Patient death (n=10)

Analysis

Caregiver Survey data:
Baseline: n=76
6 weeks: n=58
3 months: n=48
6 months: n=36
Hair data:
Baseline: n=75
3 months: n=49
6 months: n=39
Blood data:
Baseline: n=75
3 months: n=51
6 months: n=40

Patient Survey data:
Baseline: n=69
6 weeks: n=47
3 months: n=43
6 months: n=37
Hair data:
Baseline: n=49
6 months: n=24

Caregiver Survey data:
Baseline: n=73
6 weeks: n=57
3 months: n=44
6 months: n=36
Hair data:
Baseline: n=74
3 months: n=45
6 months: n=30
Blood data:
Baseline: n=74
3 months: n=46
6 months: n=30

Patient Survey data:
Baseline: n=70
6 weeks: n=44
3 months: n=36
6 months: n=24
Hair data:
Baseline: n=44
6 months: n=19
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristicsa</th>
<th>X (N = 155)</th>
<th>eTAU (n = 80)</th>
<th>PEPRR-2.0 (n = 75)</th>
<th>Significanceb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (95% CI), y</td>
<td>53.3 (52.0-56.3)</td>
<td>54.3 (51.1-57.5)</td>
<td>52.3 (48.8-5.7)</td>
<td>p = 0.41</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.90</td>
</tr>
<tr>
<td>Female</td>
<td>55 (35.5)</td>
<td>28 (35.0)</td>
<td>27 (36.0)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>100 (64.5)</td>
<td>52 (65.0)</td>
<td>48 (64.0)</td>
<td></td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.67</td>
</tr>
<tr>
<td>White</td>
<td>124 (80.0)</td>
<td>59 (73.8)</td>
<td>65 (86.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (0.6)</td>
<td>–</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>2 (1.3)</td>
<td>2 (2.5)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>More than one race</td>
<td>4 (2.6)</td>
<td>3 (3.8)</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Another group not listed</td>
<td>6 (3.9)</td>
<td>2 (2.5)</td>
<td>4 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, N (%)</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.23d</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>12 (7.7)</td>
<td>8 (10.0)</td>
<td>4 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic or Latino</td>
<td>119 (76.8)</td>
<td>55 (68.8)</td>
<td>64 (85.3)</td>
<td></td>
</tr>
<tr>
<td>Education, N (%)</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.55</td>
</tr>
<tr>
<td>College graduate or above</td>
<td>74 (47.7)</td>
<td>38 (47.5)</td>
<td>36 (48.0)</td>
<td></td>
</tr>
<tr>
<td>Annual income, N (%), $</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.61</td>
</tr>
<tr>
<td>&lt; 25 000</td>
<td>44 (28.4)</td>
<td>20 (25.0)</td>
<td>24 (32.0)</td>
<td></td>
</tr>
<tr>
<td>25 000-44 999</td>
<td>28 (18.1)</td>
<td>17 (21.3)</td>
<td>11 (14.7)</td>
<td></td>
</tr>
<tr>
<td>45 000-64 999</td>
<td>19 (12.3)</td>
<td>9 (11.3)</td>
<td>10 (13.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;65 000</td>
<td>30 (19.4)</td>
<td>14 (17.5)</td>
<td>16 (21.3)</td>
<td></td>
</tr>
<tr>
<td>Patient diagnosisc, N (%)</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.88</td>
</tr>
<tr>
<td>Characteristics*</td>
<td>X (N = 155)</td>
<td>eTAU (n = 80)</td>
<td>PEPRR-2.0 (n = 75)</td>
<td>Significanceb</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Leukemia</td>
<td>94 (60.6)</td>
<td>50 (62.5)</td>
<td>44 (58.7)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>20 (12.9)</td>
<td>11 (13.8)</td>
<td>9 (12.0)</td>
<td></td>
</tr>
<tr>
<td>MDS/MPS</td>
<td>35 (22.6)</td>
<td>16 (20.0)</td>
<td>19 (25.3)</td>
<td></td>
</tr>
<tr>
<td>Other (MM, SAA)</td>
<td>6 (3.9)</td>
<td>3 (3.8)</td>
<td>3 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Duration of illness, mean (95% CI), m</td>
<td>19.7 (14.2-25.1)</td>
<td>19.4 (11.0-27.8)</td>
<td>20.0 (12.9-27.0)</td>
<td>p = 0.70e</td>
</tr>
<tr>
<td>Transplant conditioning intensity, N (%)</td>
<td></td>
<td></td>
<td>p = 0.05</td>
<td></td>
</tr>
<tr>
<td>Myeloablative</td>
<td>86 (55.5)</td>
<td>42 (52.5)</td>
<td>44 (58.7)</td>
<td></td>
</tr>
<tr>
<td>Non-myeloablative</td>
<td>17 (11.0)</td>
<td>5 (6.3)</td>
<td>12 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Reduce intensity</td>
<td>39 (25.2)</td>
<td>25 (31.3)</td>
<td>14 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Donor source, N (%)</td>
<td></td>
<td></td>
<td>p = 0.10f</td>
<td></td>
</tr>
<tr>
<td>Matched related donor</td>
<td>47 (30.3)</td>
<td>20 (25.0)</td>
<td>27 (36.0)</td>
<td></td>
</tr>
<tr>
<td>Matched unrelated donor</td>
<td>55 (35.5)</td>
<td>28 (35.0)</td>
<td>27 (36.0)</td>
<td></td>
</tr>
<tr>
<td>Mismatched unrelated donor</td>
<td>8 (5.2)</td>
<td>7 (8.8)</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Cord</td>
<td>38 (24.5)</td>
<td>24 (30.0)</td>
<td>14 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (3.2)</td>
<td>1 (1.3)</td>
<td>4 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Time to engraftment, mean (95% CI), d</td>
<td>17.8 (16.8-18.7)</td>
<td>18.2 (16.8-19.7)</td>
<td>17.3 (15.9-18.6)</td>
<td>p = 0.36</td>
</tr>
</tbody>
</table>

* Patient information was not available for eTAU (enhanced treatment as usual) for the following variables: race (n = 15), ethnicity (n = 17), education (n = 11), annual income (n = 20), duration of illness (n = 2), transplant conditioning intensity (n = 8) and time to engraftment (n = 8). Patient information was not available for PEPRR (PsychoEducation, Paced Respiration, and Relaxation) for the following variables: race (n = 4), ethnicity (n = 7), education (n = 3), annual income (n = 14), duration of illness (n = 1), transplant conditioning intensity (n = 5), donor source (n = 2), and time to engraftment (n = 6).

b Significance from independent t test or Pearson chi-square test as appropriate.

Abbreviations: MDS, myelodysplastic syndrome; MPS, myeloproliferative syndrome; MM, multiple myeloma; SAA, severe aplastic anemia.

d Significance from Fisher exact test.

e Significance from Mann-Whitney Test.

f Significance from Kruskal-Wallis test.
Table 2. Caregiver Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>X (N = 155)</th>
<th>eTAU (n = 80)</th>
<th>PEPRR-2.0 (n = 75)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (95% CI), y</td>
<td>54.1 (52.0-56.3)</td>
<td>54.5 (51.7-57.4)</td>
<td>53.6 (50.2-57.0)</td>
<td>p = 0.67</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.42</td>
</tr>
<tr>
<td>Female</td>
<td>124 (80.0)</td>
<td>66 (82.5)</td>
<td>58 (77.3)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31 (20.0)</td>
<td>14 (17.5)</td>
<td>17 (22.7)</td>
<td></td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.69</td>
</tr>
<tr>
<td>White</td>
<td>129 (83.2)</td>
<td>67 (83.8)</td>
<td>62 (82.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (0.6)</td>
<td>1 (1.3)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>2 (1.3)</td>
<td>–</td>
<td>2 (2.7)</td>
<td></td>
</tr>
<tr>
<td>More than one race</td>
<td>6 (3.9)</td>
<td>3 (3.8)</td>
<td>3 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Another group not listed</td>
<td>6 (3.9)</td>
<td>3 (3.8)</td>
<td>3 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, N (%)</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.57</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>14 (9.0)</td>
<td>8 (10.0)</td>
<td>6 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic or Latino</td>
<td>128 (82.6)</td>
<td>63 (78.8)</td>
<td>65 (86.7)</td>
<td></td>
</tr>
<tr>
<td>Education, N (%)</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.51</td>
</tr>
<tr>
<td>College graduate or above</td>
<td>74 (47.7)</td>
<td>35 (43.8)</td>
<td>39 (52.0)</td>
<td></td>
</tr>
<tr>
<td>Annual income, N (%), $</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.42</td>
</tr>
<tr>
<td>&lt; 25 000</td>
<td>50 (32.3)</td>
<td>29 (36.3)</td>
<td>21 (28.0)</td>
<td></td>
</tr>
<tr>
<td>25 000-44 999</td>
<td>27 (17.4)</td>
<td>14 (17.5)</td>
<td>13 (17.3)</td>
<td></td>
</tr>
<tr>
<td>45 000-64 999</td>
<td>30 (19.4)</td>
<td>12 (15.0)</td>
<td>18 (24.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;65 000</td>
<td>29 (18.7)</td>
<td>13 (16.3)</td>
<td>16 (21.3)</td>
<td></td>
</tr>
<tr>
<td>Characteristics&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X (N = 155)</td>
<td>eTAU (n = 80)</td>
<td>PEPRR-2.0 (n = 75)</td>
<td>Significance&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Relationship, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse/partner</td>
<td>101 (65.2)</td>
<td>53 (66.3)</td>
<td>48 (64.0)</td>
<td>p = 0.34</td>
</tr>
<tr>
<td>Parent</td>
<td>20 (12.9)</td>
<td>11 (13.8)</td>
<td>9 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>29 (18.7)</td>
<td>11 (13.8)</td>
<td>18 (24.0)</td>
<td></td>
</tr>
<tr>
<td>Employment status, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before caregiving</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full time</td>
<td>64 (41.3)</td>
<td>29 (36.3)</td>
<td>35 (46.7)</td>
<td>p = 0.89</td>
</tr>
<tr>
<td>Part time</td>
<td>27 (17.4)</td>
<td>15 (18.8)</td>
<td>12 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>16 (10.3)</td>
<td>9 (11.3)</td>
<td>7 (9.3)</td>
<td></td>
</tr>
<tr>
<td>On leave</td>
<td>2 (1.3)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>40 (25.8)</td>
<td>20 (25.0)</td>
<td>20 (26.7)</td>
<td></td>
</tr>
<tr>
<td>During caregiving</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full time</td>
<td>32 (20.6)</td>
<td>14 (17.5)</td>
<td>18 (24.0)</td>
<td>p = 0.85</td>
</tr>
<tr>
<td>Part time</td>
<td>29 (18.7)</td>
<td>15 (18.8)</td>
<td>14 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>21 (13.5)</td>
<td>9 (11.3)</td>
<td>12 (16.0)</td>
<td></td>
</tr>
<tr>
<td>On leave</td>
<td>28 (18.1)</td>
<td>15 (18.8)</td>
<td>13 (17.3)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>37 (23.9)</td>
<td>20 (25.0)</td>
<td>17 (22.7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: eTAU, enhanced treatment as usual; PEPRR, PsychoEducation, Paced Respiration, and Relaxation.

<sup>a</sup> Caregiver information was not available for eTAU for the following variables: race (n = 6), ethnicity (n = 9), education (n = 5), annual income (n = 12), relationship (n = 5), employment status before caregiving (n = 6) and after caregiving (n = 7). Patient information was not available for PEPRR for the following variables: race (n = 5), ethnicity (n = 4), annual income (n = 7), and employment status after caregiving (n = 1).

<sup>b</sup> Significance from independent t test or Pearson chi-square test as appropriate.
Table 3. Means (95% CIs) for Primary and Secondary Outcomes at Baseline With Group Comparisons (N = 155)

<table>
<thead>
<tr>
<th>Characteristicsa</th>
<th>eTAU (n = 80)</th>
<th>PEPRR-2.0 (n = 75)</th>
<th>Significanceb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient FACT-BMT total</td>
<td>97.6 (93.3-102.5)</td>
<td>98.4 (94.0-102.8)</td>
<td>0.81</td>
</tr>
<tr>
<td>CG-Distress score</td>
<td>–0.07 (–0.29 to 0.14)</td>
<td>0.08 (–0.18 to 0.33)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver: CES-D</td>
<td>19.9 (18.4-21.5)</td>
<td>20.7 (19.2-22.2)</td>
<td>0.51</td>
</tr>
<tr>
<td>Caregiver: STAI</td>
<td>39.5 (36.9-42.1)</td>
<td>41.7 (38.3-45.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Caregiver: PSS</td>
<td>24.3 (22.4-26.2)</td>
<td>25.7 (23.6-27.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>Caregiver: ln hCORT</td>
<td>1.9 (1.7-2.2)</td>
<td>2.1 (1.9-2.4)</td>
<td>0.29</td>
</tr>
<tr>
<td>Caregiver: ln TL</td>
<td>0.03 (–0.03 to 0.09)</td>
<td>0.01 (–0.04 to 0.06)</td>
<td>0.66</td>
</tr>
<tr>
<td>Caregiver: ln TA</td>
<td>1.7 (1.6-1.8)</td>
<td>1.7 (1.6-1.9)</td>
<td>0.89</td>
</tr>
<tr>
<td>Caregiver: CRA total</td>
<td>10.5 (10.0-11.0)</td>
<td>10.4 (9.8-11.1)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Abbreviations: CG-Distress, Caregiver Distress; eTAU, enhanced treatment as usual; FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplant; CES-D, Center for Epidemiologic Studies–Depression; CRA, Caregiver Reaction Assessment; hCORT, hair cortisol; PEPRR, PsychoEducation, Paced Respiration, and Relaxation; PSS, Perceived Stress Scale; STAI, State-Trait Anxiety Inventory; TA, telomerase activity; TL, telomere length.

a Information was not available for eTAU for the following variables: CG-Distress (n = 8), FACT-BMT total (n = 13), CES-D (n = 5), STAI (n = 5), PSS (n = 8), hCORT (n = 7), TL (n = 5), TA (n = 6) and CRA (n = 6). Information was not available for PEPRR for the following variables: CG-Distress (n = 6), FACT-BMT total (n = 7), CES-D (n = 2), STAI (n = 3), PSS (n = 5), hCORT (n = 3), TL (n = 2), TA (n = 2), and CRA (n = 3).

b Significance from independent t test.

It is important to note that prior to transplant, 66% of patients and 74% of caregivers exceeded the mild depression threshold of the CES-D as well as the threshold for sleep difficulty (67% and 68% for patients and caregivers, respectfully), as indicated in Figure 5. Horizontal lines indicate clinical thresholds (red) or population norms (black). Scores on STAI and PSS similarly exceeded population norms by 1 standard deviation for many caregivers (58% and 65%, respectively) but to a lesser extent in patients (44% and 48%, respectively).16
Figure 5. Pretransplant box and whisker plots for patient (gray) and caregiver (open) compared with clinical cutoff or population mean.

Abbreviations: CES-D, Center for Epidemiologic Studies–Depression; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; STA, State-Trait Anxiety Inventory.
Patient and caregiver PSS, CES-D, STAI, and PSQI were significantly intercorrelated within and between patients and caregivers, as shown in Tables 4 and 5 (significance adjusted for repeated correlations). Caregivers reported greater psychological distress than did the patients for whom they care. Prior to transplant, simple paired t tests comparing patient with caregiver indicated that caregivers exceeded their patients’ score on perceived stress (PSS) by 3.4 points (95% CI, 1.63-5.14; t_{125} = 3.825; p = .0002) and anxiety (STAI) by 3.7 points (95% CI, 1.14-6.19; t_{134} = 2.892, p = .004). Patients had greater sleep difficulty (PSQI) than did their caregivers (1.1 points higher; 95% CI, 0.145-1.97; t_{120} = –2.294; p = .024). We found no differences between caregiver and patient on the CES-D pretransplant. Figure 6 indicates mean and 95% CIs (caregiver: filled bar; patient: open bar).

An overarching hypothesis was that patient and caregiver would be interrelated in psychological domains. We explored relationships between patient and caregiver pretransplant. We performed bivariate correlations between patient and caregiver on psychological measures as well as FACT-BMT and explored caregiver burden (CRA) subscales (Schedule and Health) as recommended by the scale developer (Bill Given; personal communication, May 2017). All measures revealed significant correlations between caregiver and patient, as indicated in Table 5. As expected, PT-Distress and CG-Distress were significantly correlated (r = 0.332; n = 124; p ≤ 0.001; Table 5) as were primary outcomes, patient FACT-BMT, and CG-Distress (r = –0.364; n = 127; p ≤ 0.001).

To further explore mutuality (or reciprocal influences)\textsuperscript{90} between CG-Distress and patient QoL pretransplant, an exploratory path analysis allowed existing relationships to be simultaneously specified with multiple predictors. We examined PT-Distress and CG-Distress predicting patient QoL, after accounting for the variance in dyadic distress. Following up, separate models used subscales of the FACT-BMT (general, functional, social, emotional, and physical well-being) as the dependent variable for each model. Results indicated that after controlling for patient and caregiver statistically shared distress (r = 0.33; p < .05; consistent across all models), CG-Distress significantly predicted patient QoL (beta = –.145; p = .028; total
In subscale analyses, CG-Distress remained a significant predictor of the FACT-general subscale (beta = −.139; \( p = .042 \)) as well as FACT physical well-being subscale (beta = −.175; \( p = .025 \)). Collectively, after controlling for shared distress within a patient–caregiver dyad as well as PT-Distress, CG-Distress remained a significant contributor to patient QoL before transplant, thus documenting a joint relationship.

Table 4. Pearson Correlations for Within Patient (N = 148\(^a\)) and Caregiver (N = 149\(^a\)) at Baseline

<table>
<thead>
<tr>
<th>Behavioral Measure</th>
<th>FACT-BMT</th>
<th>PSS</th>
<th>CES-D</th>
<th>STAI-S</th>
<th>PSQI</th>
<th>PT-Distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-BMT</td>
<td>1</td>
<td>−0.569**</td>
<td>−0.590**</td>
<td>−0.624**</td>
<td>−0.515**</td>
<td>−0.693**</td>
</tr>
<tr>
<td>(N)</td>
<td>(131)</td>
<td>(135)</td>
<td>(135)</td>
<td>(119)</td>
<td>(131)</td>
<td></td>
</tr>
<tr>
<td>PSS</td>
<td>1</td>
<td>0.565**</td>
<td>0.710**</td>
<td>0.483**</td>
<td>0.890**</td>
<td></td>
</tr>
<tr>
<td>(N)</td>
<td>(133)</td>
<td>(133)</td>
<td>(119)</td>
<td>(133)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES-D</td>
<td>1</td>
<td>0.531**</td>
<td>0.601**</td>
<td>0.804**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N)</td>
<td>(137)</td>
<td>(121)</td>
<td>(133)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAI-S</td>
<td></td>
<td>1</td>
<td>0.454**</td>
<td>0.878**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N)</td>
<td></td>
<td></td>
<td>(121)</td>
<td>(133)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSQI</td>
<td></td>
<td></td>
<td>1</td>
<td>0.603**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N)</td>
<td></td>
<td></td>
<td></td>
<td>(119)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT-Distress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Behavioral Measure</td>
<td>CRA Schedule</td>
<td>CRA Health</td>
<td>PSS</td>
<td>CES-D</td>
<td>STAI-S</td>
<td>PSQI</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------</td>
<td>------------</td>
<td>------</td>
<td>-------</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td>CRA Schedule</td>
<td>1</td>
<td></td>
<td>0.398**</td>
<td>0.473**</td>
<td>0.396**</td>
<td>0.459**</td>
</tr>
<tr>
<td>(N)</td>
<td>(148)</td>
<td>(143)</td>
<td>(149)</td>
<td>(148)</td>
<td>(135)</td>
<td>(142)</td>
</tr>
<tr>
<td>CRA Health</td>
<td>1</td>
<td></td>
<td>0.563**</td>
<td>0.500**</td>
<td>0.498**</td>
<td>0.437**</td>
</tr>
<tr>
<td>(N)</td>
<td>(143)</td>
<td>(148)</td>
<td>(147)</td>
<td>(135)</td>
<td>(142)</td>
<td></td>
</tr>
<tr>
<td>PSS</td>
<td>1</td>
<td></td>
<td>0.622**</td>
<td>0.737**</td>
<td>0.352**</td>
<td>0.899**</td>
</tr>
<tr>
<td>(N)</td>
<td>(143)</td>
<td>(142)</td>
<td>(130)</td>
<td>(142)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES-D</td>
<td>1</td>
<td></td>
<td>0.614**</td>
<td>0.420**</td>
<td>0.841**</td>
<td></td>
</tr>
<tr>
<td>(N)</td>
<td>(148)</td>
<td></td>
<td>(135)</td>
<td>(142)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAI-S</td>
<td>1</td>
<td></td>
<td>0.392**</td>
<td></td>
<td>0.895**</td>
<td></td>
</tr>
<tr>
<td>(N)</td>
<td></td>
<td></td>
<td>(134)</td>
<td>(142)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSQI</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.435**</td>
<td></td>
</tr>
<tr>
<td>(N)</td>
<td></td>
<td></td>
<td></td>
<td>(129)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CG-Distress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: CES-D, Center for Epidemiologic Studies–Depression; CG-Distress, Caregiver Distress Score estimated as first principal component (PC) from PC analysis of CES-D, STAI-S, and PSS; CRA, Caregiver Reaction Assessment; FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplant; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale Global Scale score; PT-Distress, Patient Distress Score estimated as first PC from PC analysis of factor analysis score of CES-D, STAI-S, and PSS; STAI-S, State-Trait Anxiety Inventory – State Anxiety.

a Complete data were not available for all patients and caregivers.

**p ≤ .001 (2-tailed).
Table 5. Pearson Correlations Between Patient and Caregiver Psychological Measures at Baseline (N = 155a)

<table>
<thead>
<tr>
<th>Psychological Measure</th>
<th>PT FACT-BMT</th>
<th>PT-PSS</th>
<th>PT-CES-D</th>
<th>PT-STA-S</th>
<th>PT-PSQI</th>
<th>PT-Distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG-PSS</td>
<td>-0.352**</td>
<td>0.286**</td>
<td>0.229</td>
<td>0.288**</td>
<td>0.248</td>
<td>0.320**</td>
</tr>
<tr>
<td>(N)</td>
<td>(128)</td>
<td>(125)</td>
<td>(129)</td>
<td>(129)</td>
<td>(115)</td>
<td>(125)</td>
</tr>
<tr>
<td>CG-CES-D</td>
<td>-0.319**</td>
<td>0.208</td>
<td>0.221</td>
<td>0.219</td>
<td>0.184</td>
<td>0.253</td>
</tr>
<tr>
<td>(N)</td>
<td>(134)</td>
<td>(131)</td>
<td>(135)</td>
<td>(135)</td>
<td>(120)</td>
<td>(131)</td>
</tr>
<tr>
<td>CG-STA-S</td>
<td>-0.309**</td>
<td>0.254</td>
<td>0.268</td>
<td>0.295**</td>
<td>0.273</td>
<td>0.328**</td>
</tr>
<tr>
<td>(N)</td>
<td>(133)</td>
<td>(130)</td>
<td>(134)</td>
<td>(134)</td>
<td>(119)</td>
<td>(130)</td>
</tr>
<tr>
<td>CG-PSQI</td>
<td>-0.273</td>
<td>0.189</td>
<td>0.111</td>
<td>0.185</td>
<td>0.258</td>
<td>0.193</td>
</tr>
<tr>
<td>(N)</td>
<td>(120)</td>
<td>(119)</td>
<td>(121)</td>
<td>(121)</td>
<td>(120)</td>
<td>(119)</td>
</tr>
<tr>
<td>CG-CRA Schedule</td>
<td>-0.175</td>
<td>0.197</td>
<td>0.029</td>
<td>0.109</td>
<td>0.073</td>
<td>0.136</td>
</tr>
<tr>
<td>(N)</td>
<td>(134)</td>
<td>(131)</td>
<td>(135)</td>
<td>(135)</td>
<td>(120)</td>
<td>(131)</td>
</tr>
<tr>
<td>CG-CRA Health</td>
<td>-0.301**</td>
<td>0.190</td>
<td>0.086</td>
<td>0.144</td>
<td>0.154</td>
<td>0.167</td>
</tr>
<tr>
<td>(N)</td>
<td>(133)</td>
<td>(130)</td>
<td>(134)</td>
<td>(134)</td>
<td>(120)</td>
<td>(130)</td>
</tr>
<tr>
<td>CG-Distress</td>
<td>-0.364**</td>
<td>0.273</td>
<td>0.260</td>
<td>0.298**</td>
<td>0.258</td>
<td>0.332**</td>
</tr>
<tr>
<td>(N)</td>
<td>(127)</td>
<td>(124)</td>
<td>(128)</td>
<td>(128)</td>
<td>(114)</td>
<td>(124)</td>
</tr>
</tbody>
</table>

Abbreviations: CES-D, Center for Epidemiologic Studies–Depression; CG-Distress, Caregiver Distress Score estimated as first principal component (PC) from PC analysis of CES-D, STAI-S, and PSS; CRA, Caregiver Reaction Assessment; FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplant; PSQI, Pittsburgh Sleep Quality Index; PSS Global, Perceived Stress Scale Global Scale Score; PT-Distress, Patient Distress Score estimated as first PC from PC analysis of CES-D, STAI-S, and PSS; STA-I-S, State-Trait Anxiety Inventory – State Anxiety.

a Complete data were not available for all dyads.

**p ≤ .001 (2-tailed).
For aim 3 prior to transplant, we did not observe relationships between caregiver psychological measures (depressive symptoms, perceived stress, anxiety, and sleep quality) and biomarkers (hCORT, TL, or TA) by bivariate correlation. Figure 7 shows the lack of relationship between hCORT and depression (CES-D), perceived stress (PSS), sleep quality (PSQI), and anxiety (STAI). Clinical thresholds (red) and population means (blue) are represented by broken
vertical lines. We noted an expected effect of age on TL ($r = -0.323; n = 147; p = 0.0007$; Figure 8), whereas TA was unrelated to age.

**Figure 7. Caregiver hCORT concentration by psychological measures**

![Graphs showing correlation between hCORT concentration and psychological measures](image)

- Depression Score: ($r = 0.09, n=139, p = ns$)
- Perceived Stress Scale: ($r = 0.02, n=133, p = ns$)
- Sleep Quality: ($r = -0.08, n=126, p = ns$)
- State Anxiety: ($r = 0.03, n=138, p = ns$)
Primary Outcomes

We specified 2 primary outcomes (one each for patient and caregiver) for this trial (NCT02037568). The patient primary outcome was total score on the FACT-BMT, and the caregiver primary outcome was composite CG-Distress based on PCA. The FACT-BMT, our proposed measure of patient QoL, was not influenced by a caregiver’s participation in PEPRR-2.0 (PEPRR-2.0 M = 101.8 [95% CI, 94.2-109.4] vs eTAU M = 101.5 [95% CI, 96.2-106.8]; group by month interaction: $F_{3,82.3} = 0.11$, $p = .96$). FACT-BMT did not differ by site but rose (improvement) following a decline at 6 weeks (PEPRR-2.0 M = 95.8 [95% CI, 90.3-101.2] and eTAU M = 95.7 [95% CI, 90.4-100.90]) with a significant main effect of month ($F_{3,82.3} = 3.47; p = .02$; see Figure 9A and Table 6 for model predictions).

CG-Distress, as hypothesized in our conceptual model (Figure 1), declined over time in PEPRR-2.0 (Figure 9B). A significant group-by-month interaction was noted ($F_{3,39.4} = 4.28; p = .007$), with an effect size of 0.51 for the change from baseline to 6 months (Table 6; PEPRR-2.0 M = –0.20 [95% CI, –0.47 to 0.07] and eTAU M = 0.14 [95% CI, –0.11 to 0.39]). CG-distress was
lower in PEPRR-2.0 compared with eTAU at 6 months. The composite CG-Distress score does not have clinical guidelines, but subscales comprising CG-Distress have norms/clinical thresholds that we tested as secondary outcomes.

Figure 9. Primary outcomes for patients (A) and caregivers (B)
B. Caregiver Distress

\[ F(3, 95.4) = 4.28, \ p = 0.007, \ ES = .51 \]

Abbreviations: ES, effect size; FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplant; PEPRR, PsychoEducation, Paced Respiration, and Relaxation; TAU, treatment as usual.
Table 6. Estimates and Test Results from Mixed Model Analyses of Covariance for Primary and Secondary Outcomes and Composite Scores

<table>
<thead>
<tr>
<th>Outcome^a</th>
<th>Intervention</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>Model Tests</th>
<th>Model Tests</th>
<th>Baseline-8 Month Group Comparison; Effect Size (ES)^e</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY OUTCOME</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient FACT BMT Total</td>
<td>PEPRR 2.0 eTAU</td>
<td>98.1 (93.6, 102.5)</td>
<td>95.8 (90.3, 101.2)</td>
<td>100.1 (94.5, 105.8)</td>
<td>101.8 (94.2, 109.4)</td>
<td>Group: F_{1.103}=0.00, p=0.100</td>
<td>Group: Month: F_{6,1017}=3.47, p=0.02</td>
<td>t_{103}=0.12, p=0.502</td>
</tr>
<tr>
<td>Caregiver Distress Score^c</td>
<td>PEPRR 2.0 eTAU</td>
<td>0.07 (-0.16, 0.30)</td>
<td>-0.06 (-0.31, 0.19)</td>
<td>0.00 (-0.27, 0.28)</td>
<td>-0.20 (-0.47, 0.07)</td>
<td>Group: F_{1.103}=0.70, p=0.40</td>
<td>Group: Month: F_{6,1017}=3.11, p=0.09</td>
<td>t_{103}=-3.07, p=0.003</td>
</tr>
</tbody>
</table>

SECONDARY OUTCOMES

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>Model Tests</th>
<th>Model Tests</th>
<th>Baseline-8 Month Group Comparison; Effect Size (ES)^e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiver: CES-D</td>
<td>PEPRR 2.0 eTAU</td>
<td>20.5 (19.9, 22.0)</td>
<td>18.3 (18.0, 19.7)</td>
<td>17.8 (16.0, 20.0)</td>
<td>18.0 (16.0, 20.0)</td>
<td>Group: F_{1.103}=2.99, p=0.09</td>
<td>Group: Month: F_{6,1017}=2.03, p=0.11</td>
<td>t_{103}=-2.78, p=0.006</td>
</tr>
<tr>
<td>Caregiver: STAI</td>
<td>PEPRR 2.0 eTAU</td>
<td>41.6 (38.8, 44.6)</td>
<td>39.6 (38.2, 42.6)</td>
<td>39.3 (38.0, 42.6)</td>
<td>36.7 (35.0, 38.2)</td>
<td>Group: F_{1.103}=0.00, p=0.0</td>
<td>Group: Month: F_{6,1017}=3.71, p=0.01</td>
<td>t_{103}=-2.53, p=0.013</td>
</tr>
<tr>
<td>Caregiver: PSS</td>
<td>PEPRR 2.0 eTAU</td>
<td>24.2 (22.3, 26.1)</td>
<td>22.9 (21.1, 24.8)</td>
<td>22.4 (20.1, 24.6)</td>
<td>20.5 (18.3, 22.7)</td>
<td>Group: F_{1.103}=0.03, p=0.88</td>
<td>Group: Month: F_{6,1017}=9.03, p&lt;0.0001</td>
<td>t_{103}=-1.93, p=0.08</td>
</tr>
<tr>
<td>Caregiver: CRA Total</td>
<td>PEPRR 2.0 eTAU</td>
<td>13.8 (11.3, 15.2)</td>
<td>10.9 (10.3, 11.6)</td>
<td>10.8 (10.2, 11.7)</td>
<td>10.5 (9.9, 11.2)</td>
<td>Group: F_{1.103}=0.99, p=0.09</td>
<td>Group: Month: F_{6,1017}=2.31, p=0.04</td>
<td>t_{103}=-0.19, p=0.92</td>
</tr>
<tr>
<td>Caregiver: In Hair Cortisol</td>
<td>PEPRR 2.0 eTAU</td>
<td>1.34 (1.32, 2.20)</td>
<td>1.30 (1.19, 2.46)</td>
<td>1.74 (1.50, 2.56)</td>
<td>2.18 (1.89, 2.50)</td>
<td>Group: F_{1.103}=0.47, p=0.69</td>
<td>Group: Month: F_{6,1017}=0.78, p=0.04</td>
<td>t_{103}=1.08, p=0.28</td>
</tr>
<tr>
<td>Caregiver: In Telomere length</td>
<td>PEPRR 2.0 eTAU</td>
<td>0.00 (-0.06, 0.00)</td>
<td>-0.00 (-0.01, 0.00)</td>
<td>0.03 (-0.02, 0.05)</td>
<td>0.00 (-0.02, 0.04)</td>
<td>Group: F_{1.103}=0.20, p=0.08</td>
<td>Group: Month: F_{6,1017}=0.04, p=0.04</td>
<td>t_{103}=-0.72, p=0.47</td>
</tr>
<tr>
<td>Caregiver: In TA</td>
<td>PEPRR 2.0 eTAU</td>
<td>1.70 (1.56, 1.85)</td>
<td>1.70 (1.60, 1.81)</td>
<td>1.70 (1.56, 1.87)</td>
<td>1.70 (1.57, 1.92)</td>
<td>Group: F_{1.103}=0.20, p=0.07</td>
<td>Group: Month: F_{6,1017}=0.04, p=0.0</td>
<td>t_{103}=-0.38, p=0.70</td>
</tr>
</tbody>
</table>

^a Abbreviations: PSS, Perceived Stress Scale; CES-D, Center for Epidemiologic Studies Depression; STAI, State-State Anxiety Inventory-State; TL, Telomere length; TA, Telomerase activity; CRA, Caregiver Reaction Assessment; In, natural logarithm.
^c Change (Baseline-6 month) post hoc t-test group comparison and corresponding estimated effect size (ES) when Group*Month interaction was significant (or 7 df test).
^e Components of Caregiver Distress score include CES-D, STAI, and PSS.
Regarding acceptability of PEPRR-2.0, participants remaining in the intervention participated in the next session at the following rates: 95% at session 2, 97% at session 3, 88% at session 4, 94% at session 5, 96% at session 6, 98% at session 7, and 93% at session 8. Optional booster sessions 9 and 10 were participated in at rates of 46% and 76%, respectively—that is, if they participated in 9, they were highly likely to participate in 10 (76%). Dropouts were often due to patient death or to feeling overwhelmed (Figure 4). Overall, video or telephone chat was used 15% of the time. An occasional use of telephone chat instead of video chat was due to technical and/or reception problems for internet links. Video chat proved useful during inclement weather or if caregivers were out of state and unable to return to the clinic. Video chat usage was unrelated to session content but used as needed to minimize inconveniences.

Secondary Outcomes

PEPRR-2.0 targeted the caregiver with several secondary outcomes (ClinicalTrials.gov). Secondary outcomes included subscales contributing to CG-Distress (depression, anxiety, and perceived stress), caregiver burden subscales, adrenal activity (natural log transformed hCORT), TL (natural log transformed TL), and TA (natural log transformed TA; see Table 6).

We assessed each psychological instrument contributing to CG-Distress to evaluate their separate contributions to the impact of PEPRR-2.0. Depression (CES-D) showed a significant group-by-month interaction ($F_{3,98.3} = 2.66; p = .05; ES = 0.61$ for the change from baseline to 6 months). For anxiety (STAI), the interaction of group with month approached significance ($F_{3,98} = 2.42; p = .07; ES = 0.44$) for the change from baseline to 6 months. For stress (PSS), the interaction of group and month also approached significance ($F_{3,97} = 2.31; p = .08; ES = 0.35$) for the change from baseline to 6 months. There was a significant effect of month on caregiver burden ($F_{3,91.7} = 2.93; p = 0.04$) but group failed to show an interaction with month. For caregiver covariates, there was a significant effect of age on CG-Distress ($p = .02$) as well as CES-D ($p = .01$), STAI ($p = .04$), PSS ($p = .02$), and TL ($p = .00003$) but not on total CRA, TA, hCORT, or study site.
Based on information collected from general health questionnaires administered at each study phase, we further noted that caregivers in eTAU were twice as likely to use supplemental psychosocial services 6 months after transplant compared with caregivers in PEPRR-2.0.

Biomarkers were secondary outcomes to determine influences of caregiving on stress physiology. We predicted (aim 3) that prior to transplant, patient hCORT would be related to FACT-BMT, which we failed to demonstrate \( (p = .77) \). The lack of hair due to transplant conditioning reduced the sample size. The intervention did not affect TL as measured by the group-by-month interaction \( (p = .74) \) and did not affect TA as measured by the group-by-month interaction \( (p = .69) \). Finally, group assignment did not significantly affect caregiver hCORT (Table 6).

**Adverse Events**

Immediate adverse events were psychological and based on reports by staff at both sites. We also collected psychological assessments from the patient and the caregiver at baseline, 6 weeks, 3 months, and 6 months for which CES-D scores were determined for questionnaires completed in the last 2 weeks. Staff members were typically aware that caregivers and patients scoring over the threshold of 16 were struggling. We did not construe depressive symptoms as related to the intervention but rather the consequence of dealing with a serious life experience. There were no other intervention-related adverse events to report.

**DISCUSSION**

**Context for Study Results**

The present study began by working with the clinical impression that patients do better with less distressed caregivers; however, the empirical evidence for this assertion is lacking. Although reviews have enumerated many successful interventions for caregivers, some analyses fail to find efficacy for cognitive behavioral therapy similar to that in PEPRR-2.0. We
replicated our previous observations on CG-Distress but failed to see an influence on patient QoL as measured by the FACT-BMT. Enhancements using a hybrid approach combining one-on-one interventions with video chat/telephone chat sessions did not affect the efficacy of PEPRR-2.0. It was important to observe that enhancements were acceptable to caregivers. The present study demonstrated efficacy across very different programs (academic vs private) as well as interventionists, suggesting it is amenable to dissemination and implementation.

The lack of effect on patient-reported FACT-BMT may be related to several factors. A compelling one is that the FACT-BMT is not sensitive to psychological changes reflecting their caregiver’s participation in PEPRR-2.0. Subscale analyses of the FACT-BMT are planned. Overall, the lack of effect on QoL could be due to inadequate power to detect a difference, due to recruitment shortfalls or to not applying a sensitive instrument. The study was initially powered in anticipation of an indirect effect of PEPRR-2.0 on patient QoL, and the recruited numbers failed to provide adequate power for the observed effect size. In reality, the ES estimate obtained with the reduced sample size for change between baseline and 6 months (ES = 0.03) was negligible for the FACT-BMT. There may have been changes that we simply did not detect with this measure of QoL. Questionnaires addressing quality of caregiver care could increase sensitivity, but we erred on keeping the patient battery short. We placed primary outcome questionnaires at the beginning of the battery, assuming initial questionnaires were more likely to be completed. However, in reviewing questionnaire completion across phases, we noted that of those patients and caregivers completing the primary outcome, only 3% failed to complete other questionnaires.

A clinical trial should select a single primary outcome on which to base success of the trial. We selected patient FACT-BMT and caregiver composite distress score as primary outcomes for each member of the dyad. We previously established combining scores by PCA to create a distress score. We selected the FACT-BMT as our primary outcome due to its frequent use in this patient population, assuming it would be responsive to CG-Distress. Items in the FACT-BMT focus on physical aspects of the transplant process (nausea, pain, vision
changes, skin changes, bowel habits, sleep quality, and fatigue), which might not be influenced by a better prepared caregiver. An exploratory analysis of individual items on the FACT-BMT that will focus on social–emotional components is presently underway. Future assessments should include a symptom burden scale such as cancer-specific self-efficacy in the patient and a focus on improvement of the patient’s relation with caregiver and family.

Combining both initial and current trials, we have provided PEPRR and PEPRR-2.0 to 157 caregivers with 150 caregivers who received TAU/eTAU by RCT. This includes 2 different sites across 3 different interventionists. We have established the efficacy of this approach for reducing CG-Distress. The composite distress score of the present study showed an ES of 0.55 for the change in CG-Distress from baseline to 6 months, with PEPRR-2.0 showing a decline, while the TAU/eTAU group showed an increase in CG-Distress. Clinically at 6 months, participants from the TAU/eTAU group reported the 5 highest scores on the CES-D, ranging from 37 to 45, which are considered serious.

**Generalizability of the Findings**

The present observations are limited to patients receiving stem cell transplants and their caregivers. To expand the reach of this program, we are developing it for caregivers of other cancers such as breast, lung, or colorectal; selection bias by race and ethnicity is less for those cancers. What is the efficacy of PEPRR-2.0 for noncancer caregiving such as Alzheimer’s, stroke recovery, cardiovascular disease, or Parkinson’s disease? These forms of caregiving are highly distressing with a longer duration of caregiving responsibility than that of HSCT. Although we predict similar efficacy, this remains to be determined. Colorado has a large Latino population; however, we have not translated the intervention into Spanish because English is the main language used in our transplant programs. Only a few participants identified as Latino (8%), which correlates with the overall underrepresentation of minorities among HSCT patients.
Implementation of Study Results

The present observations can inform best practices in stem cell transplant clinics. The number of stem cell transplants has increased nationally from 16,660 in 2010 to 19,862, or about a 19% increase, over 5 years.11 Because of the central role of the caregiver in HSCT and its stressful nature,10 providing efficacious psychological support is important in sustaining caregivers through this process.25 The provision of PEPRR-2.0 within a transplant clinic requires the presence of a social worker or nurse. Overall time required for a trained professional to implement PEPRR-2.0 in a clinic setting is 60 to 75 minutes/session and 15 to 30 minutes for record keeping, or roughly 90 to 100 minutes/patient/session. A potential problem is burnout associated with secondary trauma of staff who support caregivers.104 We addressed burnout with monthly check-ins with the interventionists in the context of clinical supervision by senior psychologists on the team, which was adequate.

Increasingly, cancer centers are providing psychosocial services for patients and families; however, actual use of one-on-one psychosocial support services by caregivers is often low31 despite a clear need.10,105 In fact, more depressed parent caregivers of children receiving an HSCT benefited the most from a program like ours.106 There are no clear approaches for facilitating use of psychological services. A consistent complaint of caregivers was lack of time to care for themselves. We developed and piloted a shortened online version of PEPRR-2.0. The website provides all essential elements of our intervention. The site includes separate videos discussing core points lasting 7 to 12 minutes. A user receives a personal login that allows tracking of use. The site includes brief exercises in relaxation and mindfulness to which the individual may return at any time for a booster. This approach has been well received45 and is undergoing testing by randomized trial. If efficacious, it will allow for wider dissemination of PEPRR-2.0, giving improved access for those unable to do a one-on-one approach.

Subpopulation Considerations

A common factor we have noted is that younger caregiver age is associated with greater distress. Younger caregivers fall into the sandwich generation107—caring for their children,
partner, and/or a parent. We have noted preliminarily that higher depressive symptoms are more likely to be associated with shorter telomeres in younger caregivers. The role of older age in resilience associated with chronic stress is an important area for further exploration.

**Study Limitations**

We began without knowledge of the magnitude of the effect of a caregiver intervention on patient QoL. We predicted a small ES, but the sample did not meet enrollment goals due to recruitment shortfalls and premature program termination of recruitment. This represents the greatest study limitation, as we can neither confirm nor deny a relationship. Caregivers also reflected relatively few males (20%). National trends suggest that female caregivers outnumber males about 2:1, and as such we fell short in representation of male caregivers. Findings of this study pertain primarily to female caregivers.

Another limitation was study dropouts overall throughout the study, which were similar across groups. Some were attributable to patient death in both study groups. Caregivers also withdrew. Despite reasonably good contact with families, we were unable to devise an effective means to maintain follow-up numbers. The time limits set by the contract prevented extension of recruitment beyond the additional 3 months we were allowed. A longer period for recruiting a greater number would have increased power.

The literature indicates disrupted physiological regulation in caregivers of dementia or stroke patients. In contrast, we did not observe significant relationships between psychological characteristics and caregiver biomarkers of hCORT or telomeres at the time of transplantation, both of which are markers of chronic stress. There are some likely explanations for this observation. First, hair collected in the most proximal 3 cm segment to the scalp is representative of the recent 3 months of HPA activity. The psychological questionnaires representing depressive symptoms, anxiety, and perceived stress were anchored to the past week, now, or past month, respectively. The psychological measures completed at the time of hair collection may not have captured distress over the full 3 months,
thereby creating a psychological questionnaire and HPA disconnect (as indicated in Figure 10). Second, as we have indicated, the duration of caregiving for an Allo-HSCT patient may be shorter in comparison with caregivers of patients with chronic cognitive disabilities. Average duration of illness for which the transplant was required was 18 months (± 33 months with a median of 5.3 months). Intensive caregiving does not begin until time of transplant. Compared with caregiving for someone with a cognitive disability, Allo-HSCT caregiving is of shorter duration, albeit quite distressing. Studies of CG-Distress rarely report caregiving duration. Based on 55 papers reviewed over a 15-year interval between 1998 and early 2013, only 15 (27%) reported the duration of caregiving that ranged from 22 to 287 months (mean = 79 months). The absence of a physiological impact could relate to the shorter duration of active caregiving. Despite this, we have noted in Allo-HSCT caregivers that diurnal cortisol variability was greater in caregivers with elevated CG-Distress at the time of transplant, a characteristic not reflected in hCORT.

Figure 10. Time anchors for hCORT and psychological outcomes

[Diagram showing time anchors for hCORT and psychological outcomes with labels for Collection, Hair cortisol (proximal 3 cm), Perceived Stress Scale, CESD- Depression, State Anxiety, and PROMIS at various time points: Past week, Past month, 3 months, and Now.]
Future Research

With the possibility of poor sensitivity of our QoL measure (FACT-BMT), patient survivorship following an Allo-HSCT might be an intriguing alternative for investigation. Both study sites as well as the Center for International Blood & Marrow Transplant Research maintain a registry of all Allo-HSCTs. These registries include follow-up data collected 6 months and yearly posttransplant. These registries include survivorship, transplant outcomes (GVHD, relapse, and neutrophil and platelet recovery), cause of death, etc. Matching study patients to these databases may provide unique insights into patient outcome over a longer period and perhaps indicate an impact of PEPRR-2.0.

Future research must expand the use of PEPRR-2.0 to a broader group of caregivers. An important direction would be other cancer caregiver groups, such as parents of children with cancer; with this group, the experience can be quite intense and longer in duration. Recently, increased attention has been directed toward supporting the needs of cancer caregivers. Other questions include the following: What is the minimal dose to produce a significant change in caregiver outcome? Is the effect of PEPRR-2.0 sustainable beyond the 6-month period?
CONCLUSIONS

The present intervention, PEPRR-2.0, was effective in reducing Allo-HSCT CG-Distress but had no remarkable influence on patient QoL, using the FACT-BMT as a measure of QoL. Encouraging caregivers to take care of themselves is important for the caregiver and may affect the patient in ways not addressed in the present study. The use of national databases of Allo-HSCT patients to follow this group over a longer time may provide important insights into other potential long-term benefits of caregiver interventions in cancer survivorship. This project further replicated the efficacy of a stress-management intervention for caregivers of transplant patients that may be useful for other caregiver groups. Improved caregiver well-being is an important outcome of PEPRR-2.0 and replicating the intervention is an important observation. The responsibility is to take PEPRR-2.0 to other caregiver groups and develop less labor-intensive approaches that incorporate the internet or social media. Because younger caregivers may require greater attention, due to their increased risk for stress-related consequences of caregiving, newer approaches that apply social media may be more acceptable. Another related issue is how to deliver these approaches to those who need them the most (eg, caregivers with high depression) but may be most likely to reject them. This project has moved caregiver science forward by providing an evidence-based intervention for caregivers, the hidden patient.\textsuperscript{133,134} That said, its impact on the patient remains unclear.
REFERENCES

1. Selected caregiver statistics. Family Caregiver Alliance website. [Link no longer active]. Published 2015.


**RELATED PUBLICATIONS**


ACKNOWLEDGMENTS

We are indebted to the patients and their caregivers who gave their time to this study. We also appreciate the support of the medical staff at the 2 study sites without whose support many aspects of this study would not have been possible.
Appendix 1: fPER Community Advisory Board Meeting Summary Highlights

We held 5 Community Advisory Board meetings. Meetings have focused, among other things, on recruitment, retention, participants’ response to the Intervention, participants’ response to technology and baseline survey development.

Recruitment:

- The study team asked the CAB members for advice on how to recruit caregivers that would say they are “too stressed” to participate in the study. The study team suspects these hard-to-reach potential participants would benefit most from the intervention.
  - An interventionist stakeholder explained that we recruit participants that are coping enough to be able to take this on, and that not everyone is able to do so.
  - A study team stakeholder says that 10 sessions sometimes scares people off during recruitment, and that most people are “apprehensive” when they start. However, many people say they want to participate in order to help others.

Intervention:

- A need was expressed to have support available beyond the first 100 days. The team indicated that the new iteration of this intervention has added two additional sessions that take place after the first 100 days.
- We discussed the use of video chat and requested feedback from the patients and caregivers. One caregiver commented on the loss of the intimacy of the one on one session in a secure private location. The team realized that specific instructions would be required for the caregiver to seek out a quiet place without distractions for a video chat. Much as we expected they thought that having face to face sessions with the interventionist BEFORE using the video chat was important to develop a personal relationship with the interventionist first. Use of the video chat was supported by one caregiver for many of the reasons we added it, that is, greater ease in scheduling and ability to not have to come in to the clinic amidst a busy schedule.
- Most CAB members agreed that the flexibility afforded by the remote session options would be advantageous.
- Existential issues were one of the last topics which was brought up by one of patients. Although this is discussed in the intervention it does not hold a prominent role. The team discussed making this a more prominent aspect in one of the sessions. The team discussed bringing this up in an early session but not in detail and then to raise it later after an alliance had developed. While discussing this, an issue of buffering the other individual (patient or caregiver) from what was happening was discussed as well. It was thought that this is a very important topic which will receive more attention as the manual is finalized.
- One former patient brainstormed about utilizing audio files for patient/caregiver education, as often there is too much information provided and patients do not always feel physically able to read all of this information. Other caregivers and former patients echoed the utility of this suggestion. In fact, it was suggested that one way to encourage caregiver self-care would be to deliver this concurrently with information relevant to patient care. This could take the form of a podcast, with separate modules for each topic (e.g., nutrition, exercise etc.). This suggestion was met with enthusiasm by the majority of the CAB.
• An interventionist stakeholder explained that people are apprehensive when they start the study. They communicate that it can be overwhelming to agree to meet with the interventionist. Although it may be overwhelming, it is helpful that we are flexible, and that we can accommodate to the participants’ schedules (e.g., “take advantage of the breaks”).

• **Booster Sessions 9 & 10:** The study team explained that caregivers seem very engaged in intervention during the first 100 days and completing Sessions 1-8; however, there is difficulty scheduling sessions 9 and 10. The study team asked the CAB stakeholders what they would hope to get out of these sessions, and if they are helpful.
  
  o One caregiver stakeholder added maybe session 9 and 10 are too close together. “This is a VERY long process,” she stated, and issues come up related to the transplant even years later. They then asked if these sessions could be after six months because so many issues are still prevalent for caregiver at that time.

• The CAB members were asked how they would feel about the study team contacting them every one or two weeks to see if they had received the material, and if they have any questions about it [as is currently conducted with this arm of the study].
  
  o One caregiver responded saying that material would be interesting and helpful. However, he said, “People want to do this on their own, on their own schedule.” It may be a good idea to leave it up to them to contact the study team if they have questions or if they want to talk. Another caregiver added that email communication might be easier for caregiver’s to respond to.
  
  o Another caregiver stated that because caregivers are so busy during early stages of transplant, that those phone calls may not be very useful. Similarly, another caregiver added, “it really depends on where [the patient] is at with transplant.”

• The study team then explained that some caregivers prefer to receive a paper version of the treatment manual versus us sending it by email because they would like to be able to write down their answers and thoughts.
  
  o One patient said that he could see the value of responding to the questions, because you would be actively writing and thinking. Although, personally he said, “I would never use this. I mean, it’s not being sold very well [while holding the manual]. It doesn’t have any pictures and is kind of boring.”
  
  o Another caregiver said that, “writing thoughts down in the manual is almost like writing in a journal,” and if you re-read your thoughts later it could help you reflect.
  
  o Another CAB member suggested that fillable fields be added to pdf’s of the treatment as usual manual, so that participants could take more notes and engage in this material to a greater degree. He then suggested that – if the goal was to increase engagement – that the material be presented via a website. The study team added that this would allow for potential monitoring of engagement by tracking whether study participants logged in and for how long. The study team agreed that this was a great idea!

**Dropouts/Retention:**

• One CAB member commented that at 6 weeks dyads are discharging from the hospital and going home, and that’s the experience that is most stressful. This is when they are settling back in, reconnecting with kids, and “life might get in the way”
• One CAB member mentioned that it is essential to remind participants about the importance of the study and why we are doing this. A member of our team added that establishing more personal relationships with our participants will also help increase motivation.

• One of our CAB members suggested scheduling intervention sessions during the beginning of the patient’s appointments when they are just getting labs might be a better time—which our interventionists try to do as best they can.

• A final idea was that we put less emphasis on the 6 week data collection if it is overwhelming the participants. Then we do not lose them for the 3 month time which is more important.

Other:

• It was agreed that everyone’s story is vastly different and we need to be flexible in that regard. The interventionist pointed out for the individuals who had not participated in the treatment group in the last trial that there was a strong attempt to be flexible in the sessions to address specific concerns that the caregiver brought up. The group thought this was important. The team began to realize that it is not the caregiving per se but the more global aspects of the challenge that the patient and caregiver were experiencing.

Participants Response to Technology

• The Medfolio© Pillbox was explained and the group was asked whether or not they would have taken advantage of this type of medication management device as caregivers. The fact that very few of the current study participants have utilized this device was also described by Study Team Members.
  o Participants agreed that this might have been helpful at the beginning of the caregiving experience. However, the majority of CAB members added that they had created their own system of medication management, alluding to a “window” (e.g., early) during the caregiving experience in which this device would be most helpful.
  o In discussing a time during caregiving that this device would have been utilized, most agreed that the “transition” from inpatient to outpatient would have been the most useful time to receive assistance with medication management. One patient described this transition as “kind of like walking out of a dark cave.”
  o When the Medfolio© feature of listing the dosages and usages was presented, one caregiver added that he had memorized all of his medications and that this feature would not have been as useful.
  o Many of the CAB members agreed that there were many changes to their respective patients’ medications during their treatment, and thus the medication management strategy was constantly changing. CAB members cited this as one reason why the current study participants
  o One CAB member asked how one would have the medications delivered to you “already in the pillbox?!” The Study PI mentioned that while this was possible through the Medfolio© company, that it was rather expensive.
  o One caregiver stakeholder stated that it may be helpful if the study team could sit down with the caregivers, and get the software up and running on their computer.
  o It’s also been a struggle to engage the nursing staff to help with this, as they often do not have time to coordinate this device into administering medications. An interventionist
stakeholder identified one nurse who recently expressed enthusiasm about incorporating this device and meeting with caregivers to do this.

- An interventionist stakeholder has handed out several of these devices and says there are different levels of interest from dyads. Some dyads already have their own systems in place, and are less interested in the device. She explained that when pitching the device there is good reception, but how much subsequent usage after is unknown at this time.
- One caregiver added that the bigger challenge through this process was the frequent medication changes, not necessarily remembering to take the medication.
- Another patient – after being handed the device – was uncertain he would have used it: “Not sure I would have wanted to deal with learning another thing.” He added that the device is large and not very appealing (“it’s grey!”). He then added that possibly having a phone app would be more accessible.

**Biofeedback devices (emwave).** The study team explained that we have received positive feedback on the emWave2 device used in the intervention.

- One caregiver stakeholder said, “anything to help relax the caregiver” would be helpful.
- We’ve received feedback from some caregivers that the emWave is not helpful in fostering relaxation. Some caregivers think that the emWave is not responding accurately (i.e. they feel relaxed, but the emWave is still red).
  - A CAB member agreed that they would like to make sure that the biofeedback device is helpful, and not just a way to collect data.
  - A caregiver also suggested that the overall intervention should include education about the transplant process (such as diet and nutrition information) to better prepare the caregiver for when the patient is discharged.

**Questionnaires**

- CAB members agreed that they were not checking emails during their transplant, thus the email method of reminders did not seem necessarily helpful. CAB members were not surprised that the response rate was delayed/lower for patients.
- One former patient described his participation in the first iteration of this study: “Completing questionnaires was not on my mind [during transplant]. I was somewhat nihilistic. I imagine that patients need more hand holding during this time.”
- A number of the CAB members agreed that each caregiver-patient dyad should be approached differently. For example, initially offering each method (email/iPad in room/paper questionnaires) and allowing the patients to choose may improve the response rate and speed with which these are returned.
- One CAB member noted that during his participation in the original study the questionnaires felt like “busy work,” and that he did not feel there was much value to the patient in completing these. Another former caregiver agreed, stating, “Those questions almost felt like a side-show; those were the 2 worst days of my wife’s life.”
One former patient mentioned that learning how to use the iPad would have been “annoying” but acknowledged that they had recently purchased a tablet and would have preferred using this method. This highlighted the individual differences in comfort level with various technology.