MSK PROTOCOL COVER SHEET

A Randomized Controlled Trial of Emotion Regulation Therapy for Cancer Caregivers: A Mechanism-Targeted Approach to Addressing Caregiver Distress

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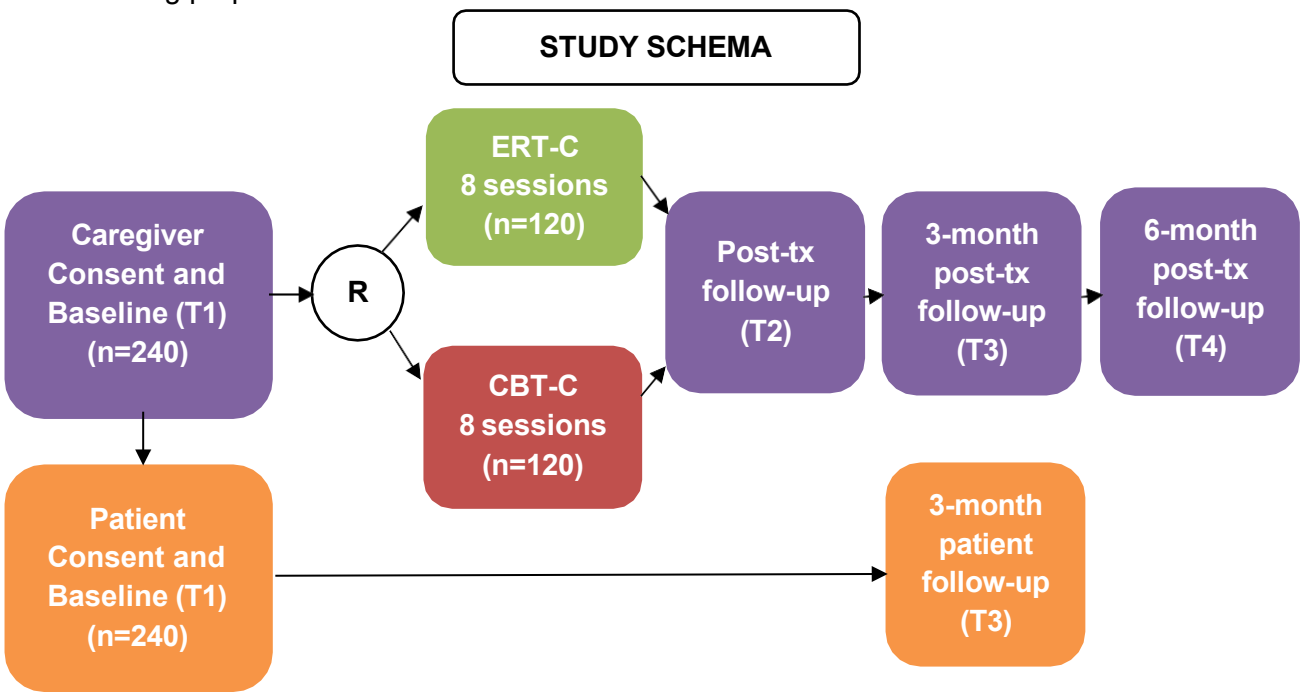
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This study will utilize a randomized, controlled, repeated measures design to investigate the efficacy of *Emotion Regulation Therapy for Cancer Caregivers* (ERT-C) vs. *Cognitive Behavioral Therapy for Cancer Caregivers* (CBT-C) in improving anxiety and depression symptoms, and caregiver and patient Quality of Life (QOL), in distressed caregivers of/and patients with varying sites and stages of cancer, evaluate whether gains in emotion regulation ability and dysfunction reflect mechanisms underlying therapeutic change, and explore whether ERT-C is associated with reductions in biological markers of stress and inflammation. The replication and extension of promising preliminary results of our earlier trials will fill a critical gap in our understanding of how to promote caregiver well-being despite increasing challenges along the caregiving trajectory. This study will enroll up to 480 participants, 240 caregiver participants and 240 patient participants from Memorial Sloan Kettering Cancer Center (MSK) and Massachusetts General Hospital (MGH). We will recruit 240 caregiver participants, 130 from MSK and 110 from MGH, with any site or stage of cancer who are currently receiving medical care of any kind (e.g., curative, palliative). Each participant will be randomized 1:1 into ERT-C or CBT-C, with randomization stratified by site. We will also strive to collect data from the 240 patients (130 from MSK and 110 from MGH) for whom caregivers provide care, though caregiver participation is not contingent on patient participation. 1-2 training cases per ERT interventionist will also be enrolled on this study for training purposes.



R = Randomization; ERT-C = Emotion Regulation Therapy for Cancer Caregivers; CBT-C = Cognitive Behavioral Therapy for Cancer Caregivers

Figure 1: Study Schema

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Aim 1: Evaluate the efficacy of ERT-C versus CBT-C in improving caregiver primary outcomes (i.e., anxiety and depression symptoms as assessed via the HADS, PSWQ and RRS), caregiver secondary outcomes (i.e., quality of life, burden), and cancer patient outcomes (i.e., patient quality of life, perceived stress, healthcare service utilization), above the effects of varying sites and stages of cancer.

- *Hypothesis 1a:* ERT-C as compared to CBT-C will result in greater improvements in caregiver primary and secondary outcomes and these gains will be maintained up to 6-months follow-up.
- *Hypothesis 1b*: ERT-C will lead to greater improvements in cancer patient outcomes as compared to CBT-C at 3-months follow-up.
- *Exploratory Hypothesis 1c:* Assess putative moderators (cancer site, cancer stage, and caregiver sociodemographic factors) of the efficacy of ERT-C versus CBT-C.

Aim 2: Evaluate the impact of gains in adaptive emotion regulation skills (e.g., attention regulation, metacognitive regulation assessed via the ACS, EQ-D and ERQ-R) in improving caregiver primary and secondary outcomes.

- *Hypothesis 2a*: Only skills that specifically target components of distress (i.e., attention regulation, metacognitive regulation) will mediate primary and secondary caregiver outcomes compared to other facets of improving the caregiving experience (i.e., reducing perceived burden, maladaptive behavioral coping).
- *Hypothesis 2b*: These gains and mediation in attention and metacognitive regulation will be more pronounced in caregivers receiving ERT-C as compared to CBT-C.

Aim 3: Examine treatment linked changes in salivary markers of stress for caregivers (e.g., diurnal cortisol) and inflammation (e.g., Interleukin 6).

- *Hypothesis 3a:* ERT-C will result in greater reductions in cortisol dysregulation and systemic inflammation as compared to CBT-C, and these gains will be maintained at 6-months follow-up.
- *Exploratory Hypothesis 3b*: Reductions in cortisol dysregulation and systemic inflammation observed with ERT-C will be most prominent in caregivers with baseline elevations in distress.

3.0 BACKGROUND AND RATIONALE

Relevant Acronyms
ERT-C: Emotion Regulation Therapy for Cancer Caregivers
CBT-C: Cognitive Behavioral Therapy for Cancer Caregivers
QOL: Quality of Life

Caregivers are Essential to the Healthcare Team. Caregivers are partners, relatives, or friends who provide assistance (i.e., physical, emotional) to a patient with often life-threatening, incurable illnesses.[29] In 2016, 40 million people in the U.S. served as caregivers for medically ill relatives, including nearly 5 million patients with cancer.[2] This number may result from the rising costs of healthcare–amplifying the role of caregivers in the care of the chronically medically ill[1]. Today's shorter hospital stays have placed a significant burden of responsibility on caregivers, many of whom have little or no preparation for this role. Rapid medical advances, including new drug and immunotherapies and more sophisticated diagnostic tools, have improved our ability to extend lives and enhance survival. With patients living longer, cancer has become a chronic, rather than abruptly life-limiting, illness and subsequently the burden on caregivers and their needs have substantially increased. Supportive caregivers are crucial to cancer care success for patients.[30] caregivers increasingly assume responsibilities once performed by medical professionals.[31] Poor caregiver functioning during cancer treatment has implications for patients' psychosocial outcomes as well:[32] higher distress among caregivers, including anxiety and depression, predicts inferior quality of care and patient health outcomes,[31,33-37] such as increased use of aggressive and unnecessary treatments during patients' end-of-life.[38-41] All told, ensuring caregiver functioning has crucial benefits for caregivers, patients, and our healthcare system.

The Devastating Impact of Cancer Caregiving. The recent AARP/National Alliance for Caregiving Report[2] highlighted that, in comparison to caregiving for other chronic or life-limiting illnesses, the cancer caregiving trajectory is particularly intense and episodic and marked by protracted, multifaceted uncertainty. For instance, marked fear of cancer recurrence, which is well documented among patients, has similarly been reported by caregivers.[42] [43,44] Further, unlike patients, caregivers bear witness to suffering on the sidelines; often feel powerless in their peripheral role in the overall medical care of patients; and struggle to concurrently maintain a balance of hope for a future with loved ones while engaging in anticipatory grief.[45] As such, repeated waves of diagnosis, treatment, remission, recurrence, and potential treatment failure contribute to psychological dysfunction. Indeed, approximately half of cancer caregivers report clinically significant symptoms of depression and anxiety, with diagnostic rates higher among caregivers than the patients for whom they provide care.[4,5,8,46,47] In our clinic, 75% of caregivers initially present with clinically significant symptoms of anxiety or depression.[48] Longitudinal studies indicate that this distress increases over time when left untreated.[3,6] Psychological dysfunction is ubiquitous across caregivers of patients with varying sites and stages of cancer and is likely more a reflection of their capacity to cope with caregiving demands, witness suffering, and live with the possibility of eventual loss, rather than the specific caregiving responsibilities and context (i.e., "burden").[49,50] Moreover, this psychological dysfunction is associated with medical complications including sleep difficulties,[51-53] fatigue,[51] cardiovascular disease,[54] increased mortality risk[54-56] and poor bereavement outcomes, such as prolonged grief disorder.[57-60]

Anxiety and depression are reliably associated with elevations in proinflammatory cytokines,[55,61-63] which in turn increase risk of physical illnesses[61] and stress-related morbidity

and mortality.[61] For instance, altered inflammatory and neuroendocrine processes underlie depression and anxiety[64] and symptoms may be driven by activation of the proinflammatory cytokine network.[65] Basic research demonstrates that proinflammatory cytokines signal the central nervous system to trigger a constellation of behavioral changes that mirror depressive-like symptoms.[66,67] In caregivers, IL-6 is has shown particular elevations in response to caregiving stress[68,69] and elevated IL-6 increases morbidity for a number of chronic illnesses including cardiovascular disease and cancer, as well as diseases and conditions related to aging (e.g., osteoporosis, Alzheimer's disease).[70] Studies show such health consequences (and their biological correlates) are only loosely related to qualities of caregiving (e.g., patient impairment) and more likely influenced by individual differences in caregivers (e.g., emotion regulatory processes).[71] Similarly, caregivers experience increased production of the proinflammatory cytokines Interleukin 6 (IL-6) and tumor necrosis factor (TNF),[72,73] which are associated with disturbed sleep, burden and mood disturbance.[74] Among cancer caregivers, increased inflammation may be affected by altered Hypothalamic-Pituitary-Adrenal Axis activity in response to caregiver burden.[63] Additionally, elderly dementia caregivers, as compared to non-caregivers,[75-77] show increased cortisol production[76,78-82] and more flattened diurnal cortisol slopes.[10] A similar pattern emerges for cancer caregivers.[83,84] The physical and emotional demands associated with caregiving show specific correlations with impaired immune system responses which may be further exacerbated by cortisol dysregulation—thereby providing strong justification to develop and refine behavioral interventions that reliably target and reduce dysregulation in these biological processes.

The Development of Interventions that Address Caregiver Distress is a Public Health Priority. The Institute of Medicine highlighted the critical role of caregivers in healthcare and the urgent need to establish programs that powerfully, quickly and effectively target their distress.[85] The majority of scientific investigations of caregivers have focused on those of frail elders or patients with varying dementias,[86] and only recently has attention been given to the needs of cancer caregivers.[87,88] Many protocols, such as brief psychoeducational interventions that seek to improve caregivers' caregiving-related skills and sense of efficacy in the role,[87,89-93] emphasize intervening in the patient-care context.[90] However, our systematic review revealed an unmet need in failing to target psychological dysfunction resulting from the caregiving experience (e.g., anxiety and depression).[87] Consequently, cognitive behavioral therapy (CBT) approaches, which have amassed the most efficacy for mood and anxiety disorders in the general population,[14,15,94] have been harnessed and adapted in hopes of better addressing caregiver distress. Several meta-analyses characterizing the state of the field of CBT interventions for caregivers, irrespective of the patient's illness, paint a mixed and disappointing picture.[95-97] Collectively, most trials exhibited low study quality and lack of rigor. Further, duration and intensity of treatment varied considerably. Most of all, effect sizes were nearly uniformly small, especially when using active comparators. In terms of CBTs for cancer caregivers, our own meta-analysis similarly demonstrated that CBTs failed to provide comparatively superior outcomes.[15] Specifically, 36 records were subjected to meta-analyses using random effects models and findings

indicated a small, statistically significant overall effect for CBTs (Hedges's *g* = 0.08) that was not significantly better than a comparator when examining RCTs alone (*g* = 0.04). Although results in aggregate reveal a mostly disappointing outcome for CBTs in resolving caregiver distress across conditions, a more careful examination of findings reveal commonalities shared by the few studies in each meta-analysis that achieved stronger effects. For instance, in dementia caregivers, CBTs combined with yoga and relaxation[98] offered comparatively greater efficacy. Similar findings emerged among caregivers for autism-spectrum patients with CBTs with mindfulness and acceptance components, which involve learning skills to maintain a present-focused attentional stance and non-judging attitude of momentary thoughts and emotions that arise.[97] Among cancer caregivers, promising but preliminary findings for an acceptance- and mindfulness-infused CBT are emerging from Co-I Jacobs's group as well.[99] Taken together, the plight of caregivers is complex and likely requires a comprehensive intervention that considers all factors inherent in the caregiver experience that may not be fully captured in traditional CBT or purely burden-focused psychoeducational approaches.

Managing Internal Distress is a Core Challenge in Caregiving. The state of caregiver treatment indicates a need to reformulate CBT interventions with a more comprehensive coverage addressing the caregiver experience and potentially the need to infuse mindfulness and acceptance components. However, integration of more components without careful consideration of what they specifically target can lead to a less parsimonious and difficult to administer protocol, that paradoxically produces worse outcomes for some recipients (e.g., Treatment of Adolescent Depression Study[100]). Recently, NIH emphasized treatment development that specifically targets biobehavioral components of distress and dysfunction (e.g., experimental therapeutics[101]). Thus, an important avenue for specifying targets and honing treatment elements of CBT is to infuse basic and translational findings from affect science to help overcome this discouraging treatment status quo.[102] In particular, emotion regulation models and research have advanced understanding of normative emotion functioning, and have helped to improve our understanding of mood and anxiety disorders,[103] medical conditions[104] and the experience of caregivers.[105] The most influential model to guide this work is Gross's process model of emotion regulation.[106] As illustrated in Figure 1, Panel A**,** this model outlines a normative emotional response trajectory with potential regulatory target processes involved in response to a stressful external or internal event. The model specifies how a response is processed internally through earlier orienting of attention and then appraised through more elaborative cognitive appraisal processes that ideally produce the most optimal behavioral response. Over time, more adaptive responses are associated with efficient biological response patterns[107] and produce more favorable learning of reward and threat contexts, which feedback to more flexible processing of new emotional events.

Considerable evidence supports the utility of this model to characterize normative emotional and behavioral responding while improving our understanding of dysfunction typified by psychiatric and health conditions.[103,108] As illustrated in Figure 1, Panel B, disruption in the caregiver context can be viewed through this regulatory framework to identify where distress

leads to maladaptive behavioral responses, which, over time can lead to biological dysregulation and dysfunctional threat and reward learning. This progression feeds back to influence more rigid processing of new emotional events in caregiving. The caregiver context is not especially modifiable, as most caregivers do not feel that they have choice over this role and often feel a concurrent sense of obligation, which together results in internal distress. Distress reflects the temporal internal processing of a situation in which the caregiver has difficulty focusing away from potential threats and losses and struggles to gain perspective to balance caregiving and everyday life (i.e., attentional rigidity[109-111]). In turn, distressed caregivers have difficulty reappraising threat and loss appraisals and often become caught in perseverative negative thinking , including worry and rumination,[16] self-criticism,[17] and loneliness.[18,19] Reliable patterns of neural activation[112] and neurophysiological systems[18,20] are associated with worry and ruminaton, and these processes exert considerable impact on cognitive functioning, role functioning,[113] and treatment prognosis.[114] Because of this internal distress, caregivers often turn towards maladaptive coping (e.g., excessive drinking, unhealthy eating) which further increases the bodily stress response and, over time, as a whole, increases markers of prolonged stress (e.g., chronic inflammation, dysregulated cortisol levels).[71,74,115-119] Serum markers of inflammation covary with adaptive and maladaptive emotion regulation strategies.[120] Evidence for these dysfunctional temporal progressions is supported by experimental and longitudinal findings in distress disorders.[121-125]

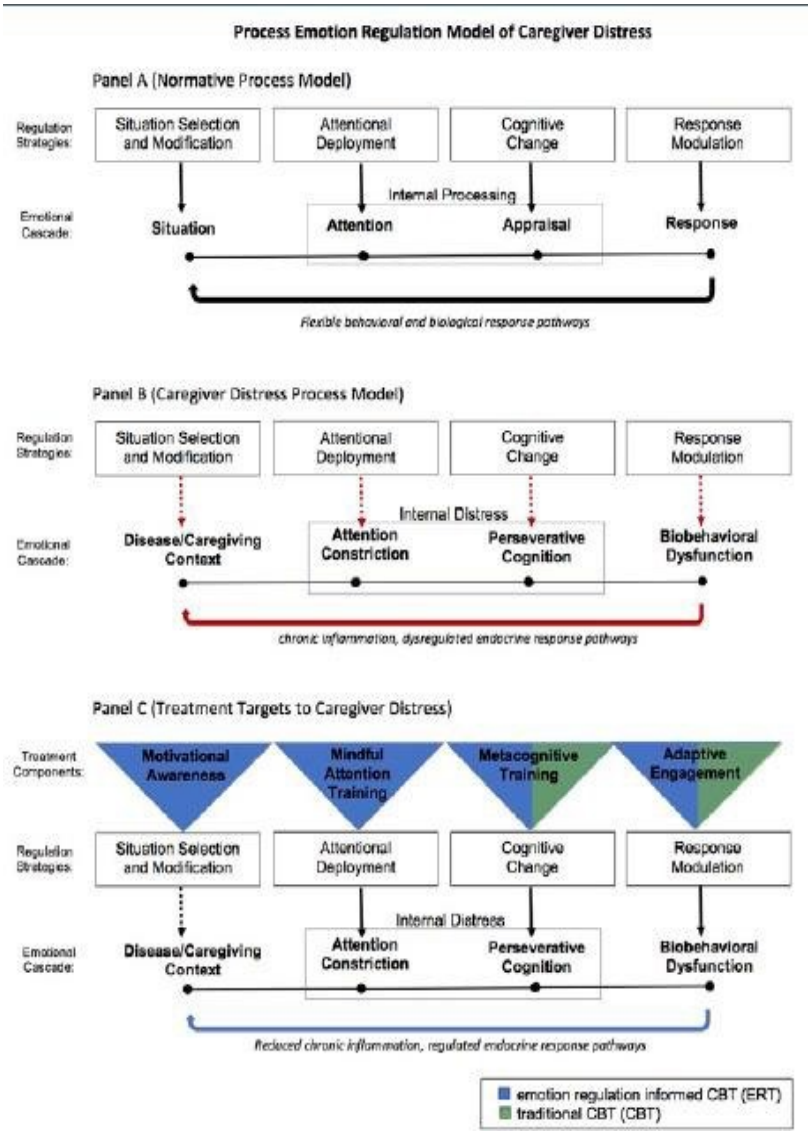


Figure 1
Emotion Regulation Therapy to Address Caregiver Distress.

With this model as a frame, treatment can be specified to target each component of the caregiver context with particular attention to internal distress (See Figure 1, Panel C). Many

psychoeducational programs that produced very small effects focused on the initial stages of caregivers' emotional response trajectory-the *situation,* its roles, and subsequent burden. A sole focus on earlier stage components misses the importance of subsequent internal distress, as recent evidence demonstrates that this distress is amenable to change and associated with improvements in function and wellbeing of caregivers.[126-129] Similarly, traditional CBT may also be limited as it is largely focused on later stages of this emotional cascade, targeting cognitive change with restructuring and behavioral elements in reward activation and threat exposure as well as instrumental control of maladaptive coping behaviors (e.g., smoking). However, this approach ignores potential targets earlier in the caregiver context emotional cascade (e.g., improved initial responding to instances of burden; training in attentional flexibility). The stronger efficacy for programs that include additional mindfulness and acceptance elements highlight this need to target all aspects of the caregiver distress trajectory.Seeking to better target internal distress, we developed a reformulated CBT (CBT-C) that systematically addresses these multiple components of the distress context.[21] Emotion Regulation Therapy (ERT) is a theoretically derived, mechanism focused treatment that integrates findings from affect science with CBT principles to target and normalize neurobehavioral deficits underlying distress through increasing motivational awareness (i.e., the ability to detect emotional intensity towards safety and/or reward"s) in emotionally evocative contexts and the training of attention (i.e., the ability to flexibly shift and sustain attention in emotional contexts) and metacognitive regulation capacities including decentering (i.e., observing items that arise in the mind with distance and perspective)[22] and reappraisal (i.e., reinterpreting the meaning to change emotional trajectory)[23] to increase more adaptive engagement of behavioral repertoires (i.e., intrinsically rewarding and goal-directed actions in the face of threat and loss). As patients become more proficient with emotion regulation skills, they are guided to confront difficult and/or desired circumstances so that effective behavioral responses can be implemented in these contexts.

Adaptation of Emotion Regulation Therapy for Cancer Caregivers (ERT-C)

ERT has been adapted for caregivers through a two-phase process.[130] First, the content and format of the ERT manual was modified to produce an 8-session intervention. Next, an abbreviated Delphi Method helped further refine the manual content; six caregivers reviewed the manual and were interviewed to provide feedback, and the revised manual was subsequently re-sent to the same six caregivers for further review and final feedback. This process produced an caregiver-focused streamlined version of ERT (ERT-C)[130,131] sensitive to caregiving demands and barriers to psychosocial service use among caregivers.[48,92,132] This consolidated version requires less intense time-commitment and integrates the key ERT approaches to addressing the components of distress (see C.2.3 for a detailed description of ERT-C). As illustrated in Figure 1, Panel C, ERT-C targets the emotional trajectory of the caregiver context through 1) increasing motivational awareness to make clearer and more intentional choices in caregiver-related situations, despite not being able to change the situation, 2) increasing attention regulation ability to promote more flexible attention in the face of increasing internal distress related to the caregiver context; 3) training in metacognitive regulation to increase perspective taking (i.e., decentering) and reframing of this internal distress towards greater courage and compassion; and 4) improved ability to respond to emotional activation

by directly impacting the bodily responses to emotions (i.e., response modulation). Over time, repeated engagement of caregiver-related emotional scenarios with this alternative approach will lead to broader and more varied learning related to meaningful rewards and a sense of safety, as well as normalization of biological stress pathways in immunological and endocrine functioning.

Empirical Support for the Efficacy and Neurobehavioral Mechanistic Findings for ERT.

ERT is Highly Efficacious. ERT has established considerable preliminary efficacy in 6 trials (4 in diagnosable distress disorders and 2 in distressed caregivers).[24-28] In an initial open trial (OT; *N* = 20; 75% women) examining symptom changes of patients diagnosed with primary generalized anxiety disorder (GAD) with and without co-occurring major depression who received 20 sessions of ERT, patients demonstrated reductions in clinician-assessed and self-reported measures of GAD and MDD severity, worry, trait anxiety, depression symptoms, and corresponding improvements in quality of life (QOL), with within subject effect sizes well exceeding conventions for large effects (*g*'s= 0.8 to 4.0). These gains were maintained 9 months following the end of treatment.[24] A subsequent randomized controlled trial (RCT; *N* = 53; 81% women) examined patients with primary GAD with and without co-occurring major depression who received immediate ERT, as compared to a modified attention control condition, evidenced significantly greater reductions in GAD and MDD severity, worry, rumination, trait anxious, and depression symptoms, and corresponding improvements in functionality and QOL, with between subject effect sizes in the medium to large range (*g*'s = 0.5 to 2.0) and gains maintained 9 months following treatment.[26] More recently, a second ERT OT was conducted among ethnically diverse and disadvantaged young adults (N = 31; 71% women) with a primary diagnosis of any anxiety or mood disorder. Results showed a comparatively more severe sample than previous trials and similarly strong ameliorative changes from pre-to-post treatment in worry, rumination, generalized anxiety, anhedonic depression, clinician rated GAD and MDD severity, social disability, and QOL (within subjects *g*'s = 1.5 to 4.0). These gains were maintained at a 3- and 9-month follow-up.[25] Most recently, we examined the efficacy of the 8- versus 16- session format of ERT compared to the 16-session version among 45 ethnically diverse and disadvantaged young adults with a primary diagnosis of any anxiety or mood disorder. No significant differences in completer status between the two arms emerged (χ^2 = 1.29, *p* = .27), highlighting that both versions were tolerable. Although both ERT formats produced significant main effect improvements, a significant group by time interaction favored 16-session ERT for most outcomes (Cohen's *f's* > .71). Beyond these indices of clinical response, these trials resulted in an impressive percent of patients achieving high end-state functioning; ERT was associated with restoration of normative symptom and functioning levels on a combination of GAD (Range = 55% to 85%) and MDD (Range = 56% to 80%) indicators that were maintained or increased into the post-treatment follow-up.[24-26,133] Together, ERT has consistently demonstrated clinical efficacy in resolving the impact of distress disorders.

ERT has subsequently been evaluated in two published cancer caregivers trials. In an initial open trial, 32 caregivers (87% women; mean age = 55; 61% partner, 19% children, and 16% parent of the patient with cancer) who endorsed significant distress and either elevated worry or rumination received 8 sessions of ERT-C, which was associated with reductions in worry, rumination, and anxiety and depression symptoms (within subject effect sizes *g*'s = 0.4 to 0.9[27]). A follow-up RCT in

81 caregivers (75% women) comparing 8 session ERT-C versus a waitlist control condition replicated and extended findings by demonstrating strong between subject reductions in psychological distress, worry, and burden post-treatment (*g*'s = 0.5 to 1.0), which were largely maintained through a 6 months follow-up. Notably, although caregiver dysfunction and distress negatively impacts functioning and well-being of cancer patients,[134-136] this trial revealed that patients of caregivers receiving ERT-C experienced a large increase in QOL as compared to patients whose caregivers were in the waitlist condition (g = 0.90).[28]

ERT Targets Mechanisms of Internal Distress. ERT has demonstrated target engagement and improvement in multiple components of internal distress, including attention and metacognition regulation ability. Further, such changes predicted or mediated changes in symptomatic and functional improvement.

Gains in attention regulation capacities predict clinical improvement. In addition to establishing strong effects for clinical outcomes, we have demonstrated significant treatment-related mechanism change from pre- to post-treatment and through follow-up in self-reported measures of target mechanisms with moderate to large within (*g*'s = 0.6 to 2.6;[24,25,27]) and between (*g*'s = 0.5-1.0) subjects effect sizes.[26,28,133] Further, utilizing more objective assessments including a modified emotional Stroop task[137] consisting of happy or fearful facial expressions with emotion words (e.g., fear, happy) overlaid on the image, ERT patients demonstrated treatment-linked improvements in attention regulation in resolving emotional conflict adaptation in trial-to-trial response gains following incongruent trials.[138] Specifically, participants evidenced pre- to mid-treatment improvements in their ability to shift attention when confronted with emotional conflict (pre- to mid-tx, *g* = 0.70) to levels comparable to healthy controls. These pre- to mid-treatment changes were associated with gains in their capacity for greater mindful observing. In a subsequent study, neural correlates of conflict adaptation were associated with reduction in activation of the dorsal medial prefrontal cortex and associated with decreases in anxiety severity and increases in self-reported attentional shifting and focusing abilities.[139] The Emotional Interference Task (EIT)[138] was also completed by a subset of trial patients to assess ERT-linked gains in attentional flexibility. This requires participants to differentiate between low- and high-pitched tones and press corresponding keys as quickly and as accurately as possible while viewing images (e.g., neutral, negative arousing, positive arousing) from the International Affective Picture System (IAPS).[138] Patients receiving ERT increased their ability to sustain attention despite emotional distraction from pre- to mid-treatment, when attention skills are specifically cultivated. Further, this attention regulation change significantly predicted reductions in anxiety and worry in addition to increases in mindful non-reactivity and social disability post-treatment. Finally, resting state functional connectivity (rsFC) analysis from our open trial[25] revealed ERT-linked changes in resting state connectivity which were associated with decreases in GAD and MDD diagnostic severity (r's = 0.4-0.6) and increases in flexible attention (r's = 0.3 -0.5).[140] Hence, a growing body of studies provide support for the role of ERT-linked gains in attention regulation related to treatment response.

Gains in metacognitive regulation capacities predict clinical improvement. In the 2018 RCT,[26] we tested a mediational model and found that measures of self-reported overall and specific attentional and metacognitive regulatory ability demonstrated indirect effects on diagnostic anxiety

severity, worry, depression, functionality, and QOL when comparing ERT to a modified attention control (MAC) condition. Further, self-reported metacognitive skills (i.e., reappraisal and decentering) assessed weekly were examined as causally preceding weekly measures of symptom change in the recent 16-session trial.[141] Findings indicated that improvements in decentering temporally preceded changes in worry and trait anxiety, while improvements in reappraisal preceded reductions in worry, trait anxiety, and generalized anxiety symptoms and were associated with increases in decentering and commensurate reductions in worry. We also examined indirect effects of regulatory skill building on outcome in our prior RCT of ERT for ICs[28] and found indices of regulatory ability, including metacognitive skills, mediated distress, worry, and burden in caregivers who received ERT-C compared to those in the waitlist control condition.[28] In another study[142] utilizing more objective assessment, we examined a commonly used explicit emotion regulation task and found increased activation in neural areas associated with regulatory ability and corresponding increases in metacognitive abilities and decreased MDD severity. Similarly, ERT-linked rsFC findings revealed pre-treatment patterns of neural activation that predicted clinical response to ERT with respect to gains in decentering and reductions in worry.[143] These ERT-linked changes in resting state connectivity were associated with decreases in GAD and MDD diagnostic severity (*r*'s = 0.4-0.6) and increases in decentering and reappraisal (*r*'s = 0.3 -0.4).[140] In all, ERT-linked gains in metacognition are associated with treatment response in patients with distress disorders.

ERT-C May Reduce Biomarkers of Stress and Inflammation in Caregivers. Consultant Hoyt found that compared to healthy controls, female caregivers of prostate cancer patients exhibited lower daily cortisol output and higher circulating levels of IL-6, which was mediated by relatively low cortisol output.[144] MPI Mennin and Consultant Hoyt[145] found that in a sample of healthy adults induced to worry followed by relaxation, IL-6 was raised following worry but then lowered following relaxation in those without depression. In comparison, those with depression increased in IL-6 with worry and did not decrease with relaxation. In a meta-analysis of psychotherapy trials for anxiety and depression that assessed serum markers of inflammation, MPI Mennin and colleagues[146] reported an overall effect of treatment on C-reactive Protein (CRP) that was more pronounced among patients with higher pretreatment levels of distress. In a subset of caregivers (N=15) from the recently published ERT-C open trial, we observed a 2% to 33% ERT-linked reduction in systemic inflammation pre- to post-treatment, depending on the pro-inflammatory marker examined. In our recently concluded RCT, caregivers receiving ERT-C evidenced a non-significant but notable decrease in IL-6 as compared to caregivers in the WLC arm (*g* = 0.36),[28] which is consistent with published findings demonstrating a stronger decrease in IL-6 for an abbreviated mindfulness-based intervention versus relaxation treatment in depressed patients.[147] Therefore, ERT shows great promise in ameliorating the PNI correlates of distress in caregivers, with significant downstream benefits on their overall health and well-being.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This study is a randomized, controlled trial to determine the efficacy of ERT-C vs. CBT-C in improving anxiety and depression symptoms, worry and rumination (primary outcomes), and caregiver and patient QOL (secondary outcomes) in distressed caregivers of/and patients with varying sites and stages of cancer (Aim 1), evaluate whether gains in emotion regulation ability and dysfunction reflect mechanisms underlying therapeutic change (Aim 2), and explore whether ERT-C is associated with reductions in biological markers of stress and inflammation (Aim 3). Participants will be 240 caregivers of patients with any site or stage of cancer who are currently receiving medical care of any kind (e.g., curative, palliative) at MSK (n=130) or MGH (n=110) who will be randomized 1:1 into ERT-C or CBT-C. We also strive to collect data from the 240 patients for whom enrolled caregivers provide care, though caregiver participation is not contingent on patient participation. 1-2 training cases per ERT interventionist will also be enrolled on this study for training purposes. Training case participants will only receive the treatment sessions and will not be asked to complete study assessments.

Potential participants will be screened for eligibility. After consenting to the study, caregiver and patient participants will complete baseline assessments (T1) (Appendix H and Appendix I). Caregivers for whom the patient does not consent to enroll are still eligible for inclusion. Caregivers will additionally provide saliva samples to measure inflammatory markers and cortisol levels (details of collection method provided below). Training case participants will not complete baseline assessments.

Caregivers will be randomly assigned to ERT-C or CBT-C and will meet with the therapist one-on-one via telepsychiatry (e.g., Webex, Zoom, Teams) for 8 individual sessions to be completed within 8 to 16 weeks from initiation of the first session. Each session is 60 minutes in length and will be audio and video recorded (e.g. Webex, Zoom, Teams) for MSK participants. Sessions will only be audio recorded (e.g. Zoom, handheld recorders) for MGH participants. With the participant's consent, session recordings may be used for academic, educational, or training purposes. This will happen when a session is particularly compelling or represents a noteworthy example of ERT-C or CBT-C in practice. Before each treatment session (but same day as treatment session), caregivers will complete a brief assessment of emotion regulation skills (weekly measures, Appendix H). After the fourth session (mid-point of intervention), caregivers will also complete a measure of therapeutic alliance.

Within 1 week of the last ERT-C or CBT-C session, caregiver participants will complete the second assessment (T2) and saliva samples to measure inflammatory markers and cortisol levels. Additionally, caregivers will complete the third assessment and saliva samples to measure inflammatory markers and cortisol levels (T3) at 3 months (+/- 1 week) following completion of the last session, and the fourth assessment and saliva samples to measure inflammatory markers and cortisol levels (T4) at 6 months (+/- 1 week) following completion of the last session. Training case participants will not complete T2, T3, or T4 assessments.

Caregiver participants who become bereaved while on study will be given the option to withdraw or remain on study. Assessments for bereaved caregivers will not include the

Caregiver Quality of Life Index-Cancer (CQOLC) or the Caregiver Reaction Assessment (CRA).Patient participants will complete baseline assessments (T1) and at 3-months following caregiver completion of ERT-C or CBT-C (T3) (Appendix I).

Participant Reimbursement: Caregiver participants will be reimbursed for their time for participating at each timepoint (e.g. electronic gift cards, gift cards, money orders, etc). Reimbursement is structured such that each subsequent timepoint is reimbursed at a higher rate to encourage continued participation:

(T1) Baseline (T1) = $5
(T2) Post-treatment assessment = $10
(T3) 3-month follow-up (after ERT-C/CBT-C last session) = $15
(T4) 6-month follow-up (after ERT-C/CBT-C last session) = $20

Caregiver participants will also receive $10 at the completion of each ERT-C or CBT-C session. Caregivers who complete the entire study (i.e., all 8 sessions and all 4 timepoints) will receive $130/participant. Patients will be compensated $25 after the completion of their T3 assessment.

The research team will give the participant a research study receipt (Appendix J) at each timepoint.

Training case participants will not receive compensation.

Biospecimen Collection:
To evaluate inflammatory markers, caregiver participants will provide an oral mucosal transudate (OMT) sample to be collected using the OraSure collection device. MSK staff will mail MSK participants an OraSure collection device, shipping materials, collection diary (Appendix K), a copy of the slides from the instructional video (Appendix N), and a cover letter (Appendix L), MGH staff mail the same materials to participants at MGH and include an intervention-specific welcome sheet at T1 collection (Appendix MGH-H, MGH-I). The research team will email participants with an expected delivery date, a link to an instructional video, and a brief summary of the contents and description of the box. At T1 collection, the package will also include a workbook corresponding to the intervention the participant was randomized to receive (Appendix C, W).

To evaluate diurnal cortisol, caregiver participants will provide saliva samples over three days at each major timepoint. Caregivers will be instructed to swab for 2 minutes and then to remove the pad from the mouth and place it directly in the vial containing an aqueous antimicrobial preservative solution. Caregivers will collect saliva samples upon awakening, 30 minutes later, 8 hours later, and at bedtime.[149] Participants will be instructed to go about their normal daily activities on data collection days and will complete a diary to assess relevant health behaviors (e.g., caffeine, tobacco, and alcohol consumption; physical activity, sleep) and daily stress. To avoid sample contamination, caregivers will be instructed to avoid brushing their teeth, eating, or drinking within 20 minutes pre-sampling (Appendix K, N).

Caregivers will be instructed to keep samples in the freezer prior to returning them to the research laboratory and to ship samples as soon as possible after the last collection day. The samples and the collection diary should be shipped using the shipping materials and return label provided to:

Michael Hoyt
Program in Public Health
215 Social Ecology II
Room 1362
Irvine, CA 92697-3954

Samples will be shipped by secured mail and are stable at standard temperatures for up to 21 days from collection. At-Home Saliva collection distribution and mailing details are included in Appendix M.

If a participant reports receiving the COVID-19 vaccine while on study, the study team will document the date of vaccination receipt. If the date of vaccination fall within 7 days of a biospecimen collection timepoint window, the participant will be instructed to not collect any samples until 7 days have passed since their vaccination. If a participant reports a COVID-19 diagnosis at any collection point, the study team will document this and instruct them not to collect biospecimens.

Training case participants will not provide biospecimen collection.

Consultant and Collaborator Roles
The research team will be led by Drs. Nelson and Mennin and brings together research leaders in Emotion Regulation Therapy (Drs. Mennin, Fresco, and O'Toole), Cognitive Behavioral Therapy (Drs. Jacobs and Applebaum), psychoneuroimmunologic correlates of distress (Dr. Hoyt), and biostatistics (Ms. Schofield). Study implementation will also rely on support roles including a Clinical Research Coordinator and Clinical Research Supervisor.

Dr. Nelson (PI) will be responsible for all aspects of the design, overall implementation, and quality assurance of the project. She will take the lead in project team meetings and will work closely with the research team to implement the recruitment and retention strategy as well as the interpretation and presentation of the data. Dr. Mennin (Columbia University) will work closely with Dr. Nelson on all aspects of the proposed study after caregivers have consented to the study, and will assist with the interpretation and presentation of the data. Drs. Mennin and Dr. Fresco (University of Michigan) are the original developers of ERT and will train and supervise the interventionists at each of the clinical sites to ensure that they deliver Emotion Regulation Therapy for Cancer Caregivers (ERT-C) with adherence and fidelity. Dr. Fresco will also be involved in the analysis and interpretation of the data. Dr. Applebaum (Mount Sinai) will support in data analysis and manuscript preparation. Dr. Jacobs will serve as the site PI for Massachusetts General Hospital and will be responsible for the implementation of this trial at MGH including data collection and analysis. She will also be responsible for

training and supervising the interventionists at each of the clinical sites to ensure that they deliver Cognitive Behavioral Therapy with adherence and fidelity. Consultant Dr. Hoyt (University of California, Irvine) will provide technical expertise and experience in the selection, performance, and interpretation of biomarker measurements, which will provide insights into the underlying inflammatory and neuroendocrine biology associated with caregiving distress and emotion regulation in this group. In addition, Dr. Hoyt will provide treatment integrity ratings for the CBT-C arm of the study and will perform with specimen analysis on the saliva samples. Finally, Consultant Dr. O'Toole (Aarhus University) will assist with data analysis and will provide treatment integrity ratings for the ERT-C arm of the study. Data will be shared between MSK and the participating sites as per Section 16.2.

4.2 Intervention

CBT-C and ERT-C are each 8-session, individual, caregiver-directed interventions delivered by a trained study therapist listed on the face page and facilitated by a manualized workbook (Appendix A and Appendix C) with between-session practice exercises (Appendix B). To accommodate caregivers and reduce compliance issues with attendance of sessions, the 8 sessions are to be completed within 8 to 16 weeks from initiation of the first session. Each session is 60 minutes in length and will be audio and video recorded for MSK participants; sessions will only be audio recorded for MGH participants. Specific modules and intervention components are described below. To accommodate as many caregivers as possible and in response to the restrictions placed on caregivers currently in the context of the COVID-19 pandemic, sessions will be offered via telepsychiatry using a platform approved by each site's respective Privacy Board (e.g. Webex, Zoom, Teams).

Cognitive Behavioral Therapy for Cancer Caregivers (CBT-C)

Cognitive Behavioral Therapy (CBT) is an evidence-based psychotherapeutic approach that is grounded in the cognitive model that purports that a person's emotional, behavioral, and physiological reactions to a situation is based on their appraisal of that situation. The focus of therapy is on changing cognitions and beliefs about a situation and altering automatic behavioral responses evoked by that perception. CBT aims to improve emotion regulation by challenging and changing unhelpful cognitions and behaviors and improving personal coping strategies. Modules incorporate skills for relaxation and information specific to the caregiving context throughout. Caregivers in this arm will practice relaxation skills using study mediation recordings as described in the CBT-C manual (Appendix C). Meditation recordings will be sent to participants via email. The CBT-C manual used in this study was specifically developed for use with cancer caregivers in previous psychotherapy trials at Massachusetts General Hospital.

The sessions are outlined as follow:

1) psychoeducation, goal-setting, and describing the rationale for CBT (Session 1);
2) coping effectiveness training (Session 2);
3) identifying unhelpful cognitions and dysfunctional beliefs (Session 3);

4) challenging and restructuring unhelpful cognitions (Session 4);
5) behavioral activation within the limitations of the caregiving context (Session 5);
6) problem-solving (Session 6);
7) communication strategies and assertiveness training (Session 7);
8) consolidating gains, maintenance, and relapse prevention (Session 8).

Emotion Regulation Therapy for Cancer Caregivers (ERT-C) Emotion Regulation Therapy for Cancer Caregivers (ERT-C) is an 8-session intervention that builds upon the foundations of CBT and addresses earlier motivational processing components of the caregiver context while targeting earlier and later components of internal distress and resultant maladaptive behavioral coping. ERT-C utilizes modules to train caregivers in: 1) cue detection and delineation of problematic motivational (i.e., threat and/or loss-based) and regulatory (i.e., worry, rumination, self-criticism, reassurance seeking, avoidance/withdrawal, and/or compulsive behaviors) responses within evocative and burdensome caregiver contexts; 2) attentional skills to increase the ability to broaden, shift, and sustain attention when distressed; 3) meta-cognitive skills to more effectively distance and reframe emotional thoughts; and 4) improving the ability to more adaptively engage contexts that are intrinsically rewarding even when accompanied by loss/threat via contextual application of learned skills.

The sessions are outlined as follow:

1) psychoeducation and motivation/dysregulation cue detection within caregiving contexts (Session 1);
2) attention regulation skills training (Sessions 1-2);
3) training in metacognitive skills (Sessions 3-4);
4) exposure to proactive living in the face of risk and loss while applying skills (Sessions 5-7);
5) consolidating gains, taking larger proactive steps, and relapse prevention (Session 8).

Selection, Training and Supervision of Study Therapists. We will carefully consider selection of therapists and provide intensive training and supervision of providers. Therapists will be drawn from disciplines of psychology, psychiatry and social work with appropriate training and knowledge of individual therapeutic dynamics. Therapists will be assigned to either the ERT-C or CBT-C arms to maximize differentiation between formats. Interventionists will include both salaried research team members and pre- and post-doctoral trainees from the Department of Psychiatry and Behavioral Sciences at MSK and the Center for Psychiatric Oncology and Behavioral Sciences at MGH Cancer Center. All interventionists will undergo extensive training in ERT-C (by Drs. Mennin and Fresco) or CBT-C (by Dr. Jacobs and Applebaum) during an initial two-day intensive training workshop during the first year of the study. Trainings will occur over Webex or Zoom so that all study therapists at both sites will be able to attend. After the first year of the study, the investigative team will conduct annual day-long training in the delivery of these interventions. These booster

trainings will also be conducted via Webex or Zoom and will serve two purposes: (1) to address and refine the therapeutic skills of existing study therapists; and (2) to provide training to any new therapists who joing the study team after the first year of the grant. Therapists will be given the treatment manual (ERT-C Manual: Appendix A; CBT-C Manual: Appendix C) for the intervention they are providing, describing in detail the philosophy, format, and techniques involved. Manuals will focus on skills acquisition in the conduct of each intervention. All therapists will receive continual training during weekly supervision sessions to maintain standardized delivery and prevent “provider drift.” Therapists without prior ERT experience will be assigned a training case patient who will be consented onto the study. Participants who are consented as training cases will not be randomized and will not complete any assessments. Data collected on training cases will be used for training and supervision purposes on this study only. These records will not be shown outside of the study supervisors, therapist in training, and staff.

Fidelity to Intervention. We will institute best practices to enhance and monitor fidelity, including: careful attention to the study design, selection, intensive training and supervision of treatment providers, delivery of treatment, receipt of treatment, and “real-life” enactment of treatment skills. In terms of study design, we will compare two intervention conditions (ERT-C and CBT-C) equivalent in the number, frequency and duration of sessions. We will monitor session attendance using a diary log with names and session dates to track percentage of attendance and account for absenteeism and reasons for missed sessions, which will be assessed with an open-ended question for enrolled participants who withdraw. To reduce likelihood of treatment contamination, each condition will be delivered by distinct treatment providers. We have developed comprehensive treatment manuals for ERT-C and CBT-C to facilitate standardized delivery. Therapists will monitor attendance and homework completion as part of their process notes. Deviations from protocol will be recorded and discussed regularly during supervision. We will also externally monitor treatment sessions and provide feedback to interventionists. To ensure providers are adhering to the treatment protocol, the manuals include a checklist/outline of intervention components for each session. We have also developed Treatment Integrity Coding Manuals for each of the two interventions (ERT-C, CBT-C). These manuals allow independent raters to evaluate each session of both interventions for treatment adherence in terms of process and content (e.g., ERT-C-specific v. CBT-C-specific content). All sessions will be audio and video recorded (MSK participants) or audio recorded (MGH participants), with prior consent of the participants. A random sample of 30% of cases (100% of audio/video taped sessions for these participants) will be evaluated and rated for treatment integrity (utilizing the Treatment Integrity Coding Manual) by consultants Drs. O’Toole and Hoyt, each of whom has considerable experience in conducting ERT-C and CBT, respectively. To prevent against therapist drift, treatment integrity ratings will be conducted regularly throughout the study. Raters will offer written feedback to individual facilitators regarding the specific individual session to enhance continued training and supervision in these individual interventions. Raters will not be blinded to the therapist, intervention arm, or the specific session within that treatment. Feedback on audio/video recorded sessions will also be incorporated into supervision sessions.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

MEASURE/ASSESSMENT	Validated	Construct/Domain Assessed
Demographic Information and Psychosocial Services Use, Preferences, and Perceived Barriers	No and not validating	Background and demographic information
Distress Thermometer (DT)	Yes	Caregiver Distress
Hospital Anxiety and Depression Scale (HADS)	Yes	Anxiety and Depression
Penn State Worry Questionnaire	Yes	Worry
Rumination-Reflection Questionnaire, Rumination subscale	Yes	Rumination
Attentional Control Scale	Yes	Attentional focus and shifting ability
Experiences Questionnaire, Decentering subscale	Yes	Disidentification with negative thinking
Emotion Regulation Questionnaire, Reappraisal subscale	Yes	Emotion regulation capacity
Caregiver Quality of Life Index-Cancer	Yes	Quality of life
Caregiver Reaction Assessment (CRA)	Yes	Caregiver burden
Self-Administered Comorbidity Questionnaire (SCQ)	Yes	Comorbid medical problems
Patient-Reported Outcomes Measurement Information System Global Health Scale (PROMIS-GH)	Yes	Global mental and physical health.
Credibility and Expectancy Questionnaire	Yes	Expectation of treatment outcome
EORTC QLQ-C30	Yes	Cancer patient quality fo life
Perceived Stress Scale	Yes	Perceived stress
National Survey on Drug Use and Health, Healthcare Utilization	Yes	Healthcare service utilization
Working Alliance Inventory-Short Form (WAI-SF189)	Yes	Therapeutic alliance

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

Caregivers

1) As per self-report, age 18 years or older.

2) As per self-report, are a current caregiver to an MSK or MGH patient with any site/stage of cancer who has received any type of treatment (e.g. curative, palliative) in the past 12 months.

3) Experience distress as evidenced by a score of 4 or greater on the Distress Thermometer (DT) **and** answer “Yes” to at least one of the follow-up questions (i.e.

reporting that their distress is related to their caregiving experience, **or** their distress started or is related to caregiving or has gotten worse since the patient was diagnosed or began treatment). (N/A for training case participants)

4) English fluent: Self-report by subject identifying English as the preferred language for healthcare, and self-reported degree of fluency as speaking English "Very well."

5) As per self-report, residing in New York or New Jersey (for MSK participants), or Massachusetts (for MGH participants), or have the ability to complete sessions while complying with current telehealth regulations.

Patients

1) Age 18 years or older as per EMR.

2) Patient of an eligible caregiver, as per self-report or the EMR.

3) English speaking as per the EMR or self report by subject identifying English as the preferred language for healthcare, and self-reported degree of fluency as speaking English "Very well.".

6.2 Participant Exclusion Criteria

Caregivers

1) As per self-report, presence of disorder that compromises comprehension of assessments or informed consent information (e.g., dementia).
2) As per the judgement of the consenting professional, clinical, PI, and/or as per the medical record, severe psychopathology or cognitive impairment which is likely to interfere with the participation or completion of the protocol or their ability to provide meaningful information.
3) As per self-report, currently engaged in regular individual psychotherapeutic support (that the participant is unable or unwilling to put on hold for the course of treatment).
4) As per self-report, a lifetime history of bipolar disorder, schizophrenia, or schizoaffective disorder.
5) As per self-report, has medical condition or medication use known to confound measures of systemic inflammation (e.g., autoimmune disorder, inflammatory disease; uncontrolled thyroid disease; active infection; myocardial infarction or stroke in the last 6 months; Type I diabetes; acute hepatitis; vaccination in the last 7 days for viral disease). (N/A for training case participants)
6) As per self-report, is a regular smoker, defined as having more than 2 cigarettes per day on most days. (N/A for training case participants)
7) As per self-report, providing care for a patient who has a caregiver currently or formerly enrolled in this study ('formerly enrolled' is N/A for training case participants).
8) As per self-report, currently enrolled in another study focused on supportive care for caregivers (MGH participants only).

Patients

1) Presence of disorder that compromises comprehension of assessments or informed consent information (e.g., dementia) as per EMR or clinician judgment.
2) As per the judgement of the consenting professional, clinical, PI, and/or as per the medical record, severe psychopathology or cognitive impairment which is likely to interfere with the participation or completion of the protocol or their ability to provide meaningful information

7.0 RECRUITMENT PLAN

A total of 480 participants (240 caregiver participants and 240 patient participants) will be enrolled at MSK and MGH. MSK will recruit 130 caregiver participants and 130 patient participants; MGH will recruit 110 caregiver participants and 110 patient participants Participants will be recruited from outpatient clinics in various departments at Memorial Sloan Kettering Cancer Center (MSK) and MGH, including the Psychiatry, Social Work, Thoracic, Gastrointestinal, Breast and Bone Marrow Transplant services. Participants will not be recruited from the Neurology Services at MSK and MGH as both sites have several competing protocols for caregivers. Participants will also be recruited from the MSK Ralph Lauren Center (RLC). Caregiver enrollment is not contingent on patient enrollment, and contact with patients is not needed in order for caregivers to be contacted, consented and enrolled.

As referenced in section 4.1, training case participants will be identified and consented onto the study for training purposes only. Training case participants will not be required to screen in with study measures (i.e. distress screening).

There will be three strategies to recruit caregiver and patient participants at MSK and MGH:

1) *Flyers and advertisements:* Flyers will be posted (either digitally or paper with the clinic's permission) in the above-named clinics with contact information for the study team (Appendix D and Appendix E). Flyers will also be posted on the MSK Caregiver website (www.mskcc.org/caregivers) and on MGH Cancer Center website pages on Supportive Care and Caregiving (www.massgeneral.org/cancer-center/patient-and-family-resources/supportive-care).

Individuals interested in learning more regarding the study will contact the research study team. If contacted over the phone, a trained consenting professional will explain the study details, verify eligibility and screen the prospective participant with the Distress Thermometer. If eligible, the individual will be consented using the verbal consent script. The study information sheet will be emailed or mailed to the caregiver. At MGH, individuals may also be consented by electronic informed consent (EIC).

2) *Remote recruitment*: The research team will provide study invitation packets for caregivers identified by the clinicians or by the study team with clinician approval in MSK and MGH clinics. Clinicians will provide the study team with the names of caregivers with the caregivers verbal permission, and the study team will be responsible for providing caregivers with the packet. This invitation packet will include an introductory letter describing the study (Appendix F), a study flyer (Appendix D), and a contact number for the PI and study team. Within approximately two weeks of mailing the invitation packet, the consenting professional will call/email potential participants to introduce the study (Appendix R). The study team will make between 3 and 5 follow-up calls/emails, varying the time of the call (morning, afternoon, evening and day of the week) and leaving no more than 3 messages and/or emails. All emails sent to prospective participants will be sent securely using secure email (i.e. MSKSecure and MGH Send Secure).

We will also utlize the MSK Facebook page in collaboration with the MSK Communications Office to circulate an advertisement for this study (Appendix U).

Caregivers will also recruited from the Counseling Center in the Department of Psychiatry and Behavioral Sciences. When caregivers who are seeking care in the Caregivers Clinic speak with the Triage Coordinator, they will first be offered a session with one of the treating psychiatrists, psychologists or APPs staffing the Clinic. They will also be told that they may be eligible for enrollment in a clinical trial focused on supporting cancer caregivers. If the caregiver is interested in learning more, the Triage Coordinator will share that caregivers' name and contact information with the study staff to determine interest and eligibility.

Interested participants will be screened and consented over the phone using the verbal consent script, or by EIC (at MGH). Once the caregiver is screened and consented, we will ask if we may contact the patient via phone to introduce the study to him/her.

3) *In-person recruitment*: The research team will screen daily clinic schedules (clinics listed above) to identify patients with upcoming oncology appointments. The treating clinician will either provide the caregiver directly with the contact information of the study team, or give verbal or written email permission to the study team to approach the patient-caregiver dyad at their visit. The timing of this approach will be based on the treating clinican's preference (i.e., before or after the clinic visit). When patients and caregivers are together at the clinic visit, once permission has been granted by the treating clinician to approach, the study CRC will approach both members of the dyad and describe the study. If the caregiver is interested, the CRC will verify eligibility and screen the prospective caregiver with the Distress Thermometer. If eligible, the individual will be consented to the study using the written consent. The CRC will then approach the patient to guage interest and if interest is expressed, proceed through the screening and enrollment process. These approaches will occur in private areas (i.e. consult rooms) of the above named clinics. If the caregiver and patient prefer to think about possible participation, the CRC will let them know that s/he will follow up with them by phone/email in the next week and will proceed with a verbal consent at that time if applicable.

When a patient is at the clinic without an caregiver, the CRC will provide him/her with information about the study and ask whether the patient has a caregiver who may be interested in taking part in the study. The CRC will provide the patient with contact information for the research team and ask that the patient give this information to the caregiver who can then reach out to the team for more information. If the caregiver consents to participate, we will then ask that caregiver if they would be willing to provide the study team with the contact information of the patient for whom the caregiver provides care to screen and potentially enroll using the verbal consent process or EIC (at MGH).

Caregiver enrollment is not contingent on patient enrollment, and this will be made clear during the consent conversation with patients. It is also not necessary to enroll patients at the same time as caregivers; however, the T1 data collection for patients must occur in advance of caregivers beginning the intervention (either ERT-C or CBT-C).

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective participant will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

The screening process for the protocol requires administration of a screening questionnaire (Appendix O and Appendix P). In following the Code of Federal Regulations Title 45, Part 46, Subpart A, which states that an IRB may waive the requirement for an investigator to obtain a signed consent form for some or all subjects if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context, a signed consent may not be required for this study. In accordance with the aforementioned regulations, we request to waive consent for identifying whether the caregiver is eligible, which includes administering the screening measures, the DT, and one or two subsequent questions as follows: 1) is this distress in any

way related to caregiving, and 2) if no, has this distress started or gotten worse since the patient for whom the caregiver provides care began treatment or was diagnosed. This waiver applies only to MSK patients and their caregivers. If a caregiver is ineligible or does not enroll for any reason following screening, identifying information stored in the screening log will be destroyed.

This limited waiver will apply only to MSK. Any participating sites that require a limited waiver must obtain it from their own local Privacy Board (PB) via a separate protocol addendum or request. It is the responsibility of the MSK staff to confirm the participating data collection site(s) have a limited waiver approved by their local IRB(s)/PBs.

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

7.2 Randomization

Participants will be randomized upon registration in CTMS through MSKCC CRDB. Randomization will be 1:1 into ERT-C or CBT-C, stratified by site (i.e., MSK or MGH), using randomly permuted blocks of random length. MSK will provide randomization for both MSK and MGH. MSK will email MGH research staff the randomization results once they are assigned. Training case participants will get assigned to an arm (rather than randomized) based on the needs of our interventionist trainings. MGH participants will be registered in both MSK CTMS and MGH OnCore per MGH policy.

8.0 INFORMED CONSENT PROCEDURES

The consent form/research authorization meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature, objectives, potential risks, and benefits of the intended study.

2. The length of study, what it entails, and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)

4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

6. How the participants' data will be protected, who will have access to their PHI, and what data will be disclosed for research purposes

Prior to inclusion in the study and before protocol-specified procedures are carried out, the consenting professionals will explain the details of the protocol as outlined in the consent and research authorization to the participants. The participant will also be informed that they are free to withdraw from the study at any time. The consent discussion may occur in person or remotely via teleconference, telephone, or videoconference.

All participants must sign an IRB/PB-approved consent form/research authorization indicating their consent to participate. Each participant and consenting professional will sign and date the consent form. The participant must receive a copy of the signed informed consent form.

The verbal informed consent/research authorization meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent/research authorization script will include the following:

1. The nature, objectives, potential risks, and benefits of the intended study.

2. The length of study, what it entails, and the likely follow-up required.

3. Alternatives to the proposed study.

4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

6. How the participants' data will be protected, who will have access to their PHI, and what data will be disclosed for research purposes.

Prior to inclusion in the study and before protocol-specified procedures are carried out, consenting professionals will explain the details of the protocol to participants/LARs. Participants/LARs will also be informed that they are free to withdraw from the study at any time. The consent discussion may occur in person or remotely via teleconference, telephone, or videoconference.

The consenting professional must sign an IRB/PB-approved consent /research authorization script to document the consent discussion and the participant's agreement.

Caregiver participants may or may not be MSK or MGH patients. If caregiver participants are patients and are consented in person, the original signed written consent form will become part of the medical record (at MSK) or research file (at MGH); if participants are consented by phone, the signature page of the verbal script will become part of their electronic medical record (at MSK) or research file (at MGH). All *patient* participant consents, written or verbal, will become part of their electronic medical record (at MSK) or research file (at MGH).

Caregiver participants who are not MSK or MGH patients and consented verbally over the phone, will be mailed a copy of the patient information sheet. Those consented in person or via the EIC process (at MGH) will receive a copy of their signed written consent form.

In following the Code of Federal Regulations Title 45, Part 46, Subpart A, the IRB is waiving the requirement for an investigator to obtain a signed consent form from the participant as the research:

- presents no more than minimal risk of harm to participants, and

- involves no procedures for which written consent is normally required outside of the research context.

In following the Code of Federal Regulations Title 45, Part 164, Subpart E, IRB/PB is waiving the requirement for the investigator to obtain signed research authorization from the participant as:

- the use or disclosure of the PHI involves no more than minimal risk to the privacy of the individuals, based on the following elements:
    - An adequate plan to protect identifiers from improper use and disclosure;
    - An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research (unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law); and
    - Adequate written assurances that the PHI will not be reused or re-disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use of disclosure of PHI would be permitted by HIPAA.
- The research could not be practicably conducted without access to and use of the PHI.
- The research could not practicably be conducted without the waiver.

9.0 PRE-TREATMENT/INTERVENTION

MEASURE/TEST	Time to complete	Screening[a]		Baseline (T1)[b]	
		Caregiver	Pt	Caregiver	Pt
Screening Questionnaire Packet	2 min	X	X		

Demographic Information and Psychosocial Services Use, Preferences, and Perceived Barriers	10 min			X	
Distress Thermometer (DT)	2 min	X		X	
Hospital Anxiety and Depression Scale (HADS)	5 min			X	
Penn State Worry Questionnaire	5 min			X	
Rumination-Reflection Questionnaire, Rumination subscale	5 min			X	
Attentional Control Scale	5 min			X	
Experiences Questionnaire, Decentering subscale	5 min			X	
Emotion Regulation Questionnaire, Reappraisal subscale	3 min			X	
Caregiver Quality of Life Index-Cancer	50 min			X	
Caregiver Reaction Assessment (CRA)	5 min			X	
Self-Administered Comorbidity Questionnaire (SCQ)	5 min			X	
Patient-Reported Outcomes Measurement Information System Global Health Scale (PROMIS-GH)	5 min			X	X
EORTC QLQ-C30	3 min				X
Perceived Stress Scale	4 min				X
National Survey on Drug Use and Health, Healthcare Utilization	2 min				X
Inflammatory Markers Assessment	5 min			X	
Diurnal Cortisol Assessment	2 min. 4x a day over 3 days			X	
Total Time		**4 min**	**2 min**	**86 min**	**14 min**

[a] Training case participants will not be required to screen in with the measures. [b] Training case participants will not complete the Baseline assessment.

The *Distress Thermometer*[150] is a single-item visual analog scale widely used to screen patients with cancer and caregivers for distress[151-155] with a 0-10 range accompanied by a 34-item problem checklist[156,157].A score of 4 or greater indicates clinically significant distress[158,159](Appendix H).

Demographic Information and Psychosocial Services Use, Preferences, and Perceived Barriers survey was designed by adapting items from a prior study from our group[160]. Demographic information, past/current psychosocial service use, support needs, intervention preferences, and perceived barriers are assessed through Likert-scale ratings and open-ended items (Appendix H).

Hospital Anxiety and Depression Scale (HADS[161]) is a 14-item questionnaire of overall psychological distress, well-tested in cancer populations[162]. Developed by Zigmond and

Snaith in 1983, the HADS produces two scales, one for anxiety (HADS–A) and one for depression (HADS–D), differentiating the two states. Items of the overall severity of anxiety and depression are rated on a five-point (0-4) severity scales (ranging from 0 = no not at all, to 3 = yes definitely), for a total score ranging from 0-21 for each subscale. A higher score indicates higher distress (Appendix H).

Penn State Worry Questionnaire is a 16-item widely used measure of future oriented trait worry[153](Appendix H).

Rumination-Reflection Questionnaire, Rumination subscale is 12-item measure of perseverative thinking about the past and loss[164](Appendix H).

Attentional Control Scale is a 20-item measure of the capacity to control attention in relation to positive and negative reactions, for which subfactors assess attentional focus and shifting ability[165](Appendix H).

Experiences Questionnaire, Decentering subscale is an 11-item measure of disidentification with content of negative thinking[22](Appendix H).

Emotion Regulation Questionnaire, *Reappraisal subscale* is a 6-item measure of cognitive reappraisal, the ability to adopt a different cognitive perspective on a current situation[166](Appendix H).

The *Caregiver Quality of Life Index-Cancer* is a 35-item measure that addresses the physical, emotional, social and financial quality of life of ICs[167](Appendix H).

The *Caregiver Reaction Assessment (CRA)* is a 24-item self-report assessment of multiple dimensions of caregiver burden, including self-esteem, family support, finances and health. The CRA has been used widely in studies with caregivers and has demonstrated good internal consistency and construct validity[168, 169](Appendix H).

Self-Administered Comorbidity Questionnaire (SCQ) is a 15-item scale that evaluates 12 defined medical problems and 3 optional conditions[170]. The maximum score is 45, and higher scores indicate greater medical severity. The SCQ has modest correlations with a widely used medical record-based comorbidity instrument and is efficient to assess comorbid conditions (Appendix H).

Patient-Reported Outcomes Measurement Information System Global Health Scale (PROMIS-GH) is an NIH-developed and well-validated item bank that captures global mental health (i.e., quality of life, mental health, satisfaction with social activities, and emotional problems) and physical health (i.e., physical health, physical function, pain, and fatigue) [203-205] (Appendix H).

EORTC QLQ-C30 is a 30-item questionnaire specifically developed to assess quality of life in cancer patients that has been used in our previous ERT-C RCT[28,174](Appendix H and Appendix I).

Perceived Stress Scale, is a widely used 9-item measure of the degree to which situations are perceived as stressful and which has demonstrated adequate validity and reliability[175,176](Appendix H and Appendix I).

The National Survey on Drug Use and Health contains 5 questions which ask patients about the frequency and nature of health service utilization over the past 12 months[177](Appendix H and Appendix I).

Inflammatory markers. We will focus on biomarkers IL-6, CRP, and sTNFαRII that indicate systemic inflammation and are associated with distress. Pro-inflammatory cytokine levels will be assessed via oral mucosal transudate (OMT), an ultrafiltrate of blood and a reflection of serum, rather than saliva. sTNFαRII collected via OMT has been validated in HIV-infected patients[178], and CRP[179] and IL-6 measured via OMT is modestly correlated with plasma levels[180]. Like markers of systemic inflammation, oral inflammatory activity increases in response to social stress[181-183] and depression[184,185] suggesting a relation between systemic and oral inflammatory activity. Because TNF-α is difficult to detect as it is quickly cleared from circulation, we will measure the type II soluble receptor for TNF-α, a more stable measure of TNF-α activity[186]. OMT will be collected using the OraSure collection device[187]. Samples will be shipped by secured mail and are stable at standard temperatures for up to 21 days from collection[187]. Upon return, samples will be centrifuged at 800g for 15 minutes to elute the sample. The eluate will be transferred into a 4 ml cryovial and frozen at -80°C until assay. Cytokine levels will be determined by immunosorbent assay (ELISA) according to assay manufacturer's protocols. Sample processing, storage, and analysis will take place under the direction of Dr. Hoyt at the Interdisciplinary Institute for Salivary Bioscience Research (IISBR) at the University of California, Irvine. Sample collection, storage, and processing instructions are detailed in the biospecimen collection instructions. All samples will be run in duplicate, and assays will be repeated on two separate days; intra-assay and interassay mean levels will be used in all analyses.

Diurnal Cortisol. Diurnal rhythm in salivary cortisol will be measured over three days at each major timepoint. Caregivers will collect saliva samples upon awakening, 30 minutes later, 8 hours later, and at bedtime [149]. Participants will be instructed to go about their normal daily activities on data collection days and will complete a diary to assess relevant health behaviors (e.g., caffeine, tobacco, and alcohol consumption; physical activity, sleep) and daily stress. To avoid sample contamination, caregivers will be instructed to avoid brushing their teeth, eating, or drinking within 20 minutes pre-sampling. Caregivers will be instructed to keep samples frozen prior to returning them to the research laboratory and returned salivettes will be stored in a -20-degree Celsius freezer until analysis. After data collection is complete, salivary cortisol will be analyzed with a time-resolved fluorescence immunoassay at the IISBR laboratory directed by Dr. Hoyt at UC Irvine. Several indices will be computed

including diurnal slope, area under the daily curve, cortisol awakening response, and total daily cortisol output.

10.0 TREATMENT/INTERVENTION PLAN

Caregivers will be randomized to ERT-C or CBT-C and will meet with the therapist one-on-one via telepsychiatry for 8 individual sessions to be completed within 8 to 16 weeks from initiation of the first session. Telepsychiatry will be conducted through a platform approved by each site's respective Privacy Board (e.g. Webex, Zoom, Teams). Caregivers and patients will complete study assessments as per the schedule of assessments in Section 11.0. Caregivers who wish to discontinue treatment before completing all 8 sessions will be given the option to remain on study to complete follow-up assessments. Those who are not interested will be withdrawn from the study and will not complete follow-up assessments. Reasons for caregiver withdrawal will be documented. Please see Section 4.2 for a full description of the study intervention, including descriptions of the ERT-C and CBT-C treatment, training and supervision of study therapists, and ensuring fidelity to intervention.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

MEASURE/TEST	**Time to complete**	**Intervetion Sessions (ERT-C or CBT-C)[a]**	**T2 (1-wk post last ERT-C or CBT-C)[b, e]**	**T3 (3-mos post ERT-C or CBT-C)[e]**		**T4 (6-ms post ERT-C or CBT-C)[e]**
		Caregiver Only	Caregiver Only	Caregiver	Pt	Caregiver Only
Distress Thermometer (DT)	2 min	X	X	X		X
Hospital Anxiety and Depression Scale (HADS)	5 min	X	X	X		X
Penn State Worry Questionnaire (PSWQ)	5 min		X	X		X
Rumination-Reflection Questionnaire, Rumination subscale (RRQ-R)	5 min		X	X		X
Attentional Control Scale (ACS)	5 min	X	X	X		X
Experiences Questionnaire, Decentering subscale (EQ-D)	5 min	X	X	X		X
Emotion Regulation Questionnaire, Reappraisal subscale (ERQ-R)	3 min	X	X	X		X

Caregiver Quality of Life Index-Cancer(CQOLC) [f]	5 min		X	X		X
Caregiver Reaction Assessment (CRA) [f]	5 min		X	X		X
Self-Administered Comorbidity Questionnaire (SCQ)	5 min		X	X		X
Patient-Reported Outcomes Measurement Information System Global Health Scale (PROMIS-GH)	4 min		X	X	X	X
Credibility and Expectancy Questionnaire (CEQ)	2 min		X			
EORTC QLQ-C30	3 min				X	
Perceived Stress Scale (PSS)	4 min				X	
National Survey on Drug Use and Health (NSDUH), Healthcare Utilization	2 min				X	
Working Alliance Inventory-Short Form (WAI-SF)	8 min	X [c]				
COPE, Active Coping Subscale	2 min.	X				
Inflammatory Markers Assessment	5 min		X	X		X
Diurnal Cortisol Assessment	2 min. 4x a day over 3 days		X[d]	X		X
Total Time		**22 min**	**80 min**	**78 min**	**13 min**	**78 min**

[a] ERT-C or CBT-C will be delivered over 8 individual sessions by a trained study therapist. The 8 sesstions must be completed within 8 to 16 weeks from initiation of the first session.[b] Questionnaires at T2 should be completed on the same day as the last session, but may be completed within 1 week. [c] The Working Alliance Inventory will be administered after the fourth intervention session.[d] Saliva collection at T2 should begin the day after the last session. [e] Training case participants will not be asked to complete follow-up assessments. [f] Bereaved caregivers who report their loved one passing away will not be asked to complete these assessments.

Most of the measures used for evaluation during treatment/intervention were also completed during Baseline (T1) and are described in Section 9.0. Before each treatment session, caregiver participants will complete a set of measures: HADS, ACS, EQ-D, ERQ-R, COPE Active Coping subscale. Additional measures during treatment/intervention are described below:

Working Alliance Inventory-Short Form (WAI-SF) assesses the perceived strength of the treatment alliance felt by patient [189,190]. After the fourth treatment (ERT-C or CBT-C) session, enrolled caregivers will complete the *Working Alliance Inventory-Short Form (WAI-*SF[189]) which assesses the perceived strength of the treatment alliance felt by patient (Appendix H).

COPE, Active Coping Subscale consists of five items describing different coping strategies used by people when responding to stress. Participants will indicate how frequently they use active coping strategies by rating statements on a scale from “1 = I usually don't do this at all” to “4 = I usually do this a lot” [188] (Appendix H).

Credibility and Expectancy Questionnaire is a 6-item measure of participants’ reactions to treatment and includes ratings of acceptability and belief about effectiveness that will be completed only at T2 [172,173]. This measure has been modified for the cancer caregiver population, has been used extensively in prior research, and has demonstrated strong psychometric properties [173] (Appendix H).

12.0 CRITERIA FOR REMOVAL FROM STUDY

Participants will be taken off study protocol under the following circumstances:

- Participating voluntarily withdraws from study.
- Caregiver experiences onset of severe cognitive difficulties that preclude participation in the study or accurate assessment in the judgment of the P.I.
- Medical illness of the caregiver that is of sufficient severity to preclude further participation in the study.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

ERT-C will be considered superior to CBT-C if at least one of the tests on the primary outcomes (i.e., HADS Anxiety, HADS Depression, PSWQ Worry, or RRQ Rumination) is statistically significant.

13.2 Criteria for Study Endpoint Evaluability

Participants need to only complete the baseline assessment for the data to be considered evaluable. If any caregiver participant withdraws consent prior to baseline assessment, they will be replaced.

Caregiver outcomes include treatment-related improvements in anxiety and depression symptoms, including worry and rumination(primary outcomes) and caregiver QOL and burden (secondary outcomes).

14.0 BIOSTATISTICS

This study is a psychotherapy RCT implemented at 2 clinical sites, with a 1:1 allocation of ERT-C to CBT-C. We propose to enroll 240 caregivers into either ERT-C or CBT-C. Caregiver participants will be assessed at pre-intervention (T1), post-intervention (T2), and at 3-months (T3) and 6-months (T4) follow-up for primary outcomes and mid-intervention at weekly therapeutic sessions for mechanistic measures and the HADS depression and anxiety outcomes. Up to 240 patients (for whom the caregiver is enrolled) will complete a short battery of assessments at T1 and T3. The four primary outcomes include caregiver depression, anxiety, worry, and rumination. Secondary outcomes include other caregiver and patient psychosocial and QOL measures. The primary analytic approach to testing the treatment efficacy in Aim 1 and change in biomarkers in Aim 3 will be Generalized Linear Mixed-Effects Model (GLIMMIX[191]), also known as Hierarchical Linear Model (HLM[192]). For Aim 2, we will use an analytic strategy known as parallel process latent growth curve modeling (PP-LGCM), which is similar to a combination of growth curve models with the Baron and Kenney[193] approach, to test mediation of ERT-C on anxiety and depression via emotion regulation skills. PP-LGCM allows tests of both direct and indirect effects of treatment on outcomes through hypothesized pathways.

The statistics for the aims are described as follows:

AIM 1: Immediate and Longer-Term Efficacy of ERT-C vs. CBT-C in Improving Symptoms of Anxiety, Depression, Rumination and Worry.

Treatment-related improvements in anxiety, depression, worry and rumination symptoms (primary outcomes) and caregiver quality of life and burden (secondary outcomes) will be assessed by comparing measures at baseline, post-treatment, and at 3- and 6-months follow-up between ERT-C and CBT-C.
Hypothesis 1a: ERT-C will result in greater improvement in caregiver primary (i.e., anxiety and depression, worry, rumination) and secondary (i.e., QOL and burden) outcomes and these gains will be maintained at 6-months follow-up.
Hypothesis 1b: ERT-C will lead to greater improvements in cancer patient outcomes as compared to CBT at 3-months follow-up.
Exploratory Hypothesis 1c: Assess putative moderators of the efficacy of ERT-C versus CBT-C.

Primary Analyses:

We will test differential effects of ERT-C versus CBT-C using separate GLIMMIX/HLM for each outcome (e.g., depression, anxiety). For HADS outcomes and for rumination and worry post-intervention outcomes, the ith caregiver, within the jth site, at the kth timepoint will be regressed on a time variable, an indicator for ERT-C arm, and time-by-arm interaction. That is, baseline assessments will be included as an outcome and not a covariate. This flexible analytic strategy will allow testing of non-linear time effects, treatment differences immediately post-treatment, and comparison of 6-month maintenance, all within the same model framework via specific contrasts. This strategy also utilizes all complete assessments, such that caregivers who miss data at a subset

of time points will still be included and analyzed in the model. Random per-caregiver and per-site intercepts will control for intraclass correlation introduced by repeated measures and cluster effects, which is an important statistical consideration in choosing GLIMMIX/HLM as our primary statistical approach. Prior to regression modeling, transformations to the outcome will be made as necessary and based on tests of parametric assumptions. A significant finding on the test of the interaction term would be evidence that there is a differential reduction in the outcome by treatment assignment. For immediate gains, data will be restricted to T1 to T2 (including the mid-intervention assessments for HADS outcomes). For 6-month maintenance, a similar model will be used, restricted to the post-intervention data. For HADS outcomes pre to post intervention, 10 assessments (T1, T2, and 8 mid-intervention timepoints) are expected; for all 4 primary outcomes, 3 timepoint assessments (T2, T3, T4) are expected for 6-month maintenance. A significant finding on the main time effect would indicate a change in outcomes during the 6-month follow-up for CBT-C participants, and a significant finding on the interaction coefficient would indicate a significantly different change in follow-up outcomes between ERT-C and CBT-C. Superiority is defined by a significant finding on post-treatment difference (T1 to T2) and either further significant differentiation post-intervention (T3 to T5) or no statistically significant differentiation if the CBT-C group converges with the ERT-C group during this time.

Rumination and Worry (Pre to Post) and Patient Outcomes: For rumination and worry pre to post intervention, only 2 assessments (T1 and T2) are collected. Patient outcomes are only collected at baseline (T1) and 3-months post-treatment (T3). Rather than test for a time-treatment interaction effect, differential change will simply be tested as the main group (ERT-C vs. CBT-C) effect in an HLM model of change scores regressed on this main effect and with a random per-site intercept, separately for each outcome (i.e., caregiver rumination, caregiver worry, patient outcomes).

Exploratory Analysis - Potential Moderators: As we move into the era of precision medicine and person-centered mental health care,[197] it is necessary to examine caregiver-specific factors that may moderate impact of ERT-C so that we may build a foundation for a targeted approach to addressing caregiver anxiety and depression. The impact of moderators of psychosocial interventions among patients with cancer has received increasing attention[198], with growing evidence for the influence of age and cancer type on various psychosocial outcomes. Therefore, putative moderators of therapeutic efficacy, including cancer site, cancer stage, and caregiver sociodemographic factors, will be assessed within this same HLM framework for Aim 1. Longitudinal change scores for each outcome at each major time point (i.e., T2, T3, T4) will first be calculated. Next, potential moderators will be included in separate HLM models, where each model regresses the change score on main effects for ERT-C and the moderator, plus an interaction of the two. The HLM structure will account for clustering effects of the sites only, as change scores are assessed individually and thus a single observation per participant.

Attrition and Missing Data. We computed sample size estimates anticipating 20% attrition. Based on previous trials at MSK and MGH with caregivers, missing data should be less than 20% by T3. Missing data rates and attrition will be compared between treatment arms, and also by pre-intervention measures.

Power and Sample Size for Aim 1. Preliminary data found ERT-C to have a pre-treatment to post-treatment effect size of g=0.49 on depression and anxiety. A recent meta-analysis found very small (g=0.08) effects of CBT on these outcomes; this implicates a differential effect size of d=0.41. Using an HLM model with up to 3 time points, a within-subject ICC of 0.2, allowing for approximately 20% attrition, and setting Type I error to the conservative value of 0.0125 to account for 4 primary outcomes, we simulate 90.4% power for the differential pre-treatment to post-treatment changes for Aim 1 if the effect size is at least *g*=0.41 and 82.8% power for a more conservative effect of *g*=0.37. Power was simulated using the simr [199] package in R. For patient outcomes, the PI anticipates at least 50% enrollment of patients associated to the caregivers, and comparable attrition between patients and caregivers. Enrollment of 120 patients, with 80% retention at the 3-month follow-up assessment will provide 80% power to detect a standardized effect of at least d=0.63 for the difference in change scores using an independent samples t-test approximation at alpha of 0.05. Similarly for rumination and worry from pre to post intervention, enrollment of 240 caregivers with 10% attrition during intervention will provide 80% power to detect a medium effect of at least d=0.50 with alpha of 0.0125 for these two primary outcomes.

AIM 2: Attention and Metacognitive Regulation Will Have Indirect Effects on the Primary and Secondary Outcomes. Growth curve models will assess overall effects of treatment on primary and secondary outcomes, and the partial mediation of primary outcomes via attention and metacognition regulation skills increases and whether this effect will be more pronounced in ERT-C compared to CBT-C.

Hypothesis 2a: Only skills that specifically target components of distress (i.e., attention regulation, metacognitive regulation) will mediate primary and secondary caregiver outcomes compared to other facets of improving the caregiving experience (i.e., reducing perceived burden, maladaptive behavioral coping).
Hypothesis 2b: These gains and mediation in attention and metacognitive regulation will be more pronounced in caregivers receiving ERT-C as compared to CBT-C.

Primary Analyses: We will assess gains in emotion regulation as well as reductions in anxiety and depressive symptoms via growth curve modeling. First, for both emotion regulation skills and outcomes, a series of traditional growth curve models will assess the effect of ERT-C (versus CBT-C) on each potential mediator from the ACS, EQ-D, ERQ-R, and COPE instruments which are assessed weekly during the intervention. Next, for each outcome, similar growth curve models will be used to assess the overall effect (direct and indirect effects) of ERT-C on outcomes both during the intervention and at major timepoints. We will employ parallel process latent growth curve modeling (PP-LGCM [200]) to assess the mediational process provided by weekly data. In PP-LGCM, changes in potential mediators and changes in outcomes are both modeled in a single measurement model. This combination of growth curve methodology with structural equation modeling efficiently utilizes the longitudinal data of both the mediators and outcome variables and is depicted for the single mediation variable case in Figure 2. Here, η_1 and η_3 represent the intercepts for the growth processes for the mediation and outcome measures, respectively; η_2 and η_4 represent the slopes for the mediation and outcome measures, respectively. Means for mediators and outcomes may be impacted by intervention and correlated. Trajectory of a mediator may be impacted by treatment and baseline outcome. Trajectory of the outcome may be impacted by treatment and with both baseline and trajectory of the mediator. The mediation hypothesis is supported if the product of α and β is significant [201], that is, if ERT-C drives change in the mediator and change in the mediator drives change in the outcome. This analysis will be conducted using M-Plus software.

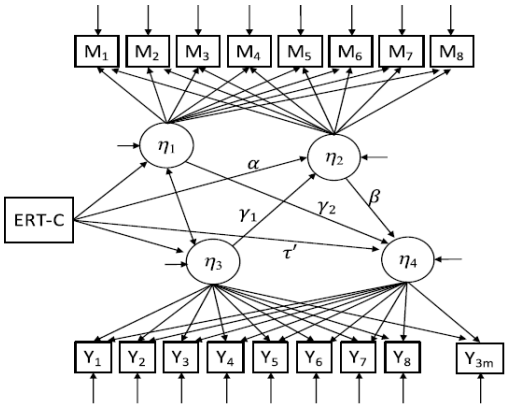


Figure 2. The parallel process latent growth curve model for mediation of ERT-C on outcomes via emotion regulation skills (measured weekly).

Power and Sample Size for Aim 2. Statistical power for mediation models was estimated from simulations by Fritz and MacKinnon, [202] which provide conservative estimates given the reduction in noise provided by our weekly assessments and growth curve modeling. Allowing for up to 20% attrition, the sample will provide at least 80% power to detect mediation using the Sobel test if one of the two paths (α or β) has a small-medium effect size (Cohen's *d*=0.39), and the other has at least a small effect (*d*=0.26).

Aim 3: Differential Effects of Treatment on Change in Biomarkers. We will describe and test differential changes in inflammation and salivary biomarkers overall and by treatment arm.

Hypothesis 3a: ERT-C will result in greater reductions in cortisol dysregulation and systemic inflammation as compared to CBT-C and gains will be maintained at 6-months follow-up.
Exploratory Hypothesis 3b: Reductions in cortisol dysregulation and systemic inflammation observed with ERT-C will be most prominent in caregivers with baseline elevations in distress.

Primary Analyses: The same HLM/GLIMMIX framework from Aim 1 will be used for Aim 3. Transformations may be needed for both biomarkers. The analysis will be similarly conducted to assess both differential pre-post change (T1 to T2) and also maintenance at 6-months follow-up (T2 to T4), using appropriate contrasts on the time variable. This same framework will allow for testing the exploratory moderation hypothesis. Specifically, for Hypothesis 3b, outcomes will be regressed on the ERT-C indicator, an indicator of elevated baseline distress, and the interaction of the two. A significant finding on the interaction term will be evidence to a moderation effect and will be followed with stratified analyses of the biomarker outcomes by baseline distress category and treatment arm.

Power and Sample Size for Aim 3. Based on previous participation rates with biological samples at our institutions, we anticipate at least 75% of the 240 enrolled caregivers to provide samples. With a conservative 20% attrition assumption, an analytic sample of n=144 would provide 80% power to detect a small-medium effect size of d=0.36 for the t-test for Hypothesis 3a.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

Participants may experience psychological distress when discussing sensitive topics during ERT-C and CBT-C sessions. We will inform potential participants prior to consenting that it is reasonable not to participate if they feel discomfort. However, we will also emphasize that the intention of this study is to assist caregivers so that we can help reduce the distress they experience. We will explain that completing the questionnaires may be emotionally distressing in advance of their consenting to participation in the study. All caregiver participants will be given information/referrals about any psychosocial support offered by their institution.

Additionally, all research staff will be trained to identify signs of psychological discomfort in participants. Study staff will report to principal investigators for assistance with evaluation, support, and/or referral as needed. These cases will be documented as a note to file in the research record.

CTCAE Version 5 will be utilized for toxicity evaluation.

15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

15.1.2 Reportable SAEs

As this is a minimal risk study, we will only report SAEs, including deaths, that are believed to be at least *possibly* related to the protocol intervention.

16.0 PROTECTION OF HUMAN PARTICIPANTS

The research staff who are also consenting professionals will outline the study and invite study participation. The purpose of the study and potential risks and benefits will be explained during the informed consent process. Prior to completing study assessments/intervention, all participants will be required to provide informed consent. Results will be presented in aggregate form with no references made to individual participants' data. Confidentiality of each participant's data will be ensured with utmost care and all survey data identified with a code number.

Through the use of password security measures, restrictions will be applied to each user commensurate with their needs to access the data. Confidential information will not be routinely available to all members of the research team but rather on a "need to know" basis. All current and new personnel will be instructed in the ethics of electronic data access, as well as receive training in both HIPAA issues and human subjects training.

In the battery of measures or questions administered, participants can choose to skip questions that they do not wish to answer.

When necessary, participants who experience psychological distress related to filling out selfreport questionnaires will be offered services from the enrolling institution's counseling center or referrals to mental health providers in their community if they do not reside near the enrolling insitution. There will be only one exception to the strict patient confidentiality policy described, which pertains to information obtained during the research assessment, which would indicate that the patient is seriously suicidal and may pose a significant and acute risk of self-harm. Participants will be informed of this exception, and will also be informed that such information will be shared with the PI of the study so that timely and appropriate psychiatric assessment and care can be provided by the enrolling institution's counseling center or local providers when geographically necessary.

Participants will be informed that information collected during their participation in this study is considered confidential. Participants will be assigned unique identification numbers, which will be used to identify all study data, including questionnaires, files from audio and video recordings of interviews and therapy sessions. No participant names will be used on any of the study data. Quantitative and qualitative data will be kept confidential, only identified by identification numbers, and only reported in aggregate form. All computer files related to study data will only be accessible by those working directly on the study.

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

A CRC will be assigned to the study. The responsibilities of the CRC include management of project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team. Minimal dataset will be entered into Clinical Research Administration (CRA) Clinical Trials Management System (CTMS).

Participants will be asked to complete assessments online using the MSK/MGH REDCap. For any communication with participants, all security precautions will be taken, including making sure to activate MSK Secure in e-mail correspondences. Participants will have the option of completing the measures via pencil and paper, over the phone, or via MSK/MGH REDCap survey link if they prefer, to reduce participant burden and ensure timely completion. If completed via pencil and paper, the CRC will enter the information into MSK/MGH REDCap.

The data collected for this study will be managed through REDCap. MSK will develop the REDCap database and provide restricted access to investigators and study staff at MGH. Investigators and research staff at MGH will have access to data for participants enrolled at MGH only. MGH will have restricted access . REDCap (Research Electronic Data Capture) is a data management software system supported by Clinical Research Administration (CRA) at Memorial Sloan Kettering Cancer Center (MSKCC). Members of the CRA supporting the REDCap software will have access to REDCap projects hosted by MSKCC's servers for the purpose of ensuring the proper functioning of the database and the overall software system. REDCap is a tool for the creation of customized, secure data management systems including web-based data entry forms, reporting tools, and a full array of security features including user and group based privileges with a full audit trail of data manipulation and export procedures. REDCap is maintained on MSKCC-owned servers that are kept in a locked server room with appropriate environmental modifications (e.g. proper ventilation, power redundancy and fault tolerance arrangement) and backed up nightly with some back-up tapes stored off-site. The MSKCC Information Systems group is responsible for applying all operating system patches and security updates to the REDCap servers. All connections to REDCap utilize encrypted (SSL-based) connections. Nationally, the REDCap software is developed, enhanced, and supported through a multi-institutional consortium led by Vanderbilt University.

MSK data will be shared with participating sites using MSKSecure email and Secure File Transfer Systems (i.e. GoAnywhere). The only data that will not be initially stored at MSK is the biospecimen data that will be stored and analyzed at UC Irvine. Data will be shared throughout the entire study period. All participants will be assigned a study identification number. During therapy sessions, the MSK participant session recordings (which are PHI by definition) will be shared with MGH, Columbia University, and the University of Michigan via GoAnywhere. The MGH participant session recordings will be captured and sent by MGH using systems approved by their Privacy Board (i.e. Zoom, handheld recorders, MGB Dropbox Business). All other data shared between these sites will be de-identified and will exclude participants' names and dates of birth but include the study identification number. The study identification number will be used to label and track biospecimen samples sent to UC Irvine. MGH participants will sign and date saliva collection logs to return to UCI.

We will share data via MSKSecure with our data analysis site at Icahn School of Medicine at Mount Sinai at the end of the study to support in endpoint analyses and publication of outcome papers. We will not share any participant identifiers or individual-level data.

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

16.3 Quality Assurance

Reports will be generated to monitor participant accruals and completeness of registration data. Data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Additionally, we will perform data and consent/eligibility audits with the first 5 participants enrolled, reviewing the questionnaires for completeness, psychological symptom levels, and accuracy of data entry. Random-sample data quality and protocol compliance audits will be conducted by the study team thereafter.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol

monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

16.5 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

Participating sites that are conducting data and/or specimen analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK. Copies of any site IRB correspondence should be forwarded to MSK.

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18.0 APPENDICES

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