1   **Study Protocol**
2
3   **Loving-Kindness Meditation and Cognitive Processing Therapy for Posttraumatic Stress Disorder**
4   **Among Veterans: A Randomized Non-Inferiority Clinical Trial**
5
6   **Contents of this protocol summary:**
7   • **Summary of protocol changes**
8   • **IRB-approved study protocol**
9

Table: Summary of Protocol Changes

Date	Description of Change
March 2014	Prior to initiation of study, refinement of measurement battery, including: • Change in frequency of administration of of pain intensity measure, adding NIH PROMIS GI distress measure, adding curiosity subscale of Toronto Mindfulness Scale, changing FFMQ to 24-item version • Refinement of safety monitoring questions to include ideation of harm to self or others
April 2014	Prior to initiation of study, refinement of measurement battery, including: • Refinement of safety monitoring to include assessment of suicidal intent • Replacement of interim cohort analyses of PTSD and depressive symptoms with individual subject monitoring for AEs • Updating AEs to include: worsening of PTSD/depressive symptoms, worsening alcohol use), refined questions about alcohol consumption • Removed exclusion criteria of prior MBSR participation and willingness to forego participation in yoga programs during study
June 2014	Revised data collection method for weekly measures: replaced Survey Monkey with paper assessments
August 2014	Revised phone screen: • Removed question about presence of thought disorder; removed question about whether veterans is 18 years old, removed question about whether they have PTSD Removed IBS-SSS from assessments and global IBS question, replaced with PROMIS GI symptom scales

October 2014	1. Added recruitment letter for veterans interested in study but cannot be reached by phone
	2. Revised MINI Psychiatric Interview
	   a. Removed sections J and K
	   b. Replaced w/ AUCIT-C at baseline
	   c. Add DAST-10 at major assessments for marijuana use
	   d. Added drug cart sort at baseline
	   e. Added 1st 3 questions of CAGE-AID at baseline

December 2014	Removed safety protocol requirement to contact a patient's provider in cases of non-imminent suicidal or homicidal ideation
January 2015	• Modified MINI Psychiatric interview question C9 to ask whether patient had made a suicide attempt within past 10 years (instead of lifetime) • Added Secure Messaging option as a

	• method of communicating reminders • Changed to administer all static assessments using Microsoft Access instead of Assessment Center • Added exclusion criterion: clinician recommendation of inpatient psychiatric admission within past 3 months • Added option of mailing paper assessments if veteran unable to attend in person
March 2016	• Offered CAPS-5 over the phone if needed for those with a barrier to in person administration
May 2016	• Added exclusion criteria: medical withdrawal from alcohol in past year (if currently drinking), or current drinking with high risk behavior or with past year history alcohol-related seizures or delirium tremens • Narrowing of criteria for an alcohol-related AE to: calculated BAC greater than 0.35.
December 2016	Permission to contact veterans by mail who completed study to inform them we are seeking additional veterans
August 2017	• Increase maximum number of patients randomized from 170 to 204

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SPECIFIC AIMS

Posttraumatic stress disorder (PTSD) is a common consequence of trauma that can persist for decades and result in a major reduction in quality of life.[1] Symptoms of PTSD occur in 21 - 31% of soldiers previously deployed to Iraq, 10-31% of Veterans who served in Vietnam, and in similar percentages of victims of assaultive violence and civilian populations exposed to war or acts of violence.[1] It is estimated that the typical person with PTSD experiences symptoms for at least two decades over the lifespan and has a significant lifetime risk of suicide.[2] PTSD often disrupts interpersonal relationships, reduces the ability to work, decreases quality of life, and increases the risk of physical illnesses, substance abuse, and affective disorders.[3]

The VA National Center for PTSD recommends evidence-based pharmacologic and behavioral interventions for PTSD, including medications (selective serotonin-reuptake inhibitors and prazosin), and psychotherapeutic approaches (cognitive therapy, exposure therapy, stress management skills training, and eye movement desensitization reprocessing-EMDR).[4] Cognitive processing therapy (CPT), has been found to be effective in the treatment of PTSD in randomized clinical trials.[5] Despite the availability of these and other interventions, many persons with PTSD continue to experience persistent PTSD symptoms, as well as anger, difficulties with interpersonal relationships, shame, and grief.[6]

Increasing evidence suggests that as many as half of Veterans seen in VA primary care settings report using Complementary and Alternative Medicine (CAM) interventions to address a variety of difficulties[7] and that many do so to limit their use of medications and to ensure that their social and spiritual needs are addressed.[8] A CAM intervention that holds promise for addressing PTSD and depression among Veterans is Loving-Kindness Meditation (LKM). Consistent with Fredrickson's broaden-and-build model of positive emotions, LKM has been shown to broaden individuals' emotional repertoires through increased positive emotions, which mediates the building of a range of personal resources (e.g., improved social support or a sense of environmental mastery), which in turn leads to improved clinical outcomes (e.g., reduced depression).[9] Pilot data from an open trial conducted in our laboratory indicate that LKM is well tolerated by Veterans and is associated with increases in positive emotions, enhanced personal resources, and reductions in PTSD and depressive symptoms.

The proposed study is a randomized, controlled non-inferiority trial that will assess whether LKM results in improvement in PTSD symptoms and depression that are not meaningfully different than Cognitive Processing Therapy—Cognitive only (CPT-C), among Veterans with current PTSD. PTSD symptoms will be measured by the Clinician Administered PTSD Scale - CAPS and depression will be measured by the NIH PROMIS measure.[10] Additional analyses will assess whether mediators of response are consistent with the mechanisms conceptualized for each intervention. One hundred seventy Veterans with PTSD will be randomized to LKM (n = 85) or CPT-C (n = 85). Comprehensive assessments will take place post-treatment and 3- and 6- months later. The following specific aims will be accomplished through the proposed clinical trial:

Aim 1: Evaluate if LKM is non-inferior to CPT-C in producing reductions in PTSD symptoms among Veterans with current PTSD.

> **Hypothesis 1:** Veterans randomized to LKM will report mean reductions in PTSD symptom severity that are not meaningfully worse than CPT-C, as indicated by a lower limit of the 95% confidence interval for difference in 6-month mean CAPS scores that is greater than -10 (corresponding to a standardized effect size of 0.5 between randomization arms). Results will also be assessed at the immediate post-test and 3-month time intervals. *(Addendum: The above description, based on CAPS-IV, was included in the original grant application. However, before the study began, the CAPS-5 became available and was used as the measure of PTSD symptom severity instead. For the CAPS-5, using the same criterion of d =0.5, the non-inferiority margin was defined as 5 points on the CAPS-5. See analysis section for additional details).*

Aim 2: Evaluate the non-inferiority of LKM and CPT-C in producing reductions in depressive symptoms among Veterans with current PTSD.

> **Hypothesis 2:** Veterans randomized to LKM will report mean reductions in depressive symptoms that are not meaningfully worse than CPT-C, as indicated by a lower limit of the 95% confidence interval for difference in 6-month mean PROMIS depression measure that is greater than -4, corresponding to a standardized effect size of approximately 0.5 between randomization arms.[11] Results will also be assessed at the immediate post-test and 3-month time intervals.

Exploratory Aim: Evaluate potential mediators of response to LKM and to CPT to provide preliminary information regarding whether they are consistent with the mechanisms of change conceptualized by each intervention to be associated with improvement in PTSD and depression.

70   **Exploratory Hypothesis 1:** Enhanced self-compassion will more strongly mediate PTSD and
71   depressive symptom improvement for those assigned to LKM than those assigned to CPT-C.
72   **Exploratory Hypothesis 2:** Reductions in posttraumatic maladaptive beliefs will more strongly mediate
73   PTSD and depressive symptom improvement for those assigned to CPT-C than those assigned to
74   LKM.

BACKGROUND AND SIGNIFICANCE

76   Posttraumatic stress disorder (PTSD) is a common consequence of trauma that can persist for decades
77 and result in a major reduction in quality of life.[1] PTSD affects approximately 8% of the general population of
78 the US. The clinical hallmarks of PTSD include recurrent, intrusive recollections or reexperiencing of a
79 traumatic event, avoidance of external or internal cues that can trigger reexperiencing, emotional numbing, and
80 hyperarousal.[12] PTSD has been shown to have a greater impact on quality of life than major depression and
81 obsessive-compulsive disorder.[13] Symptoms of PTSD occur in 21 to 31% of soldiers previously deployed to
82 Iraq,[14] 10-31%[15] of Veterans who served in Vietnam, and in similar percentages of victims of assaultive
83 violence and civilian populations exposed to war or acts of violence.[1] It is estimated that the typical person with
84 PTSD experiences active symptoms for at least two decades over the lifespan[1] and has a significant lifetime
85 risk of suicide; PTSD has a stronger association with suicidality than any other anxiety disorder.[2] PTSD often
86 disrupts interpersonal relationships, reduces the ability to work, impairs quality of life, and increases the risk of
87 physical illnesses, substance abuse, and affective disorders.[3] Among individuals seeking treatment for PTSD,
88 the rate of PTSD/depression comorbidity was found to be nearly 50% in the original national comorbidity study
89 sample.[16] Individuals suffering from both PTSD and depression have higher rates of suicidal ideation than
90 those with either disorder alone, though rates of actual suicide attempts are consistent across those with PTSD
91 only and comorbid PTSD/depression, and both groups report significantly higher rates than those with
92 depression only.[17] Comorbid PTSD and depression is also associated with greater risk of various physical
93 conditions than is PTSD alone.[3] Thus, PTSD complicated by co-occurring depression is associated with even
94 greater suffering and compromised functioning than is PTSD alone.

95   The VA National Center for PTSD recommends evidence-based pharmacologic and psychotherapeutic
96 interventions for PTSD, including medications (selective serotonin-reuptake inhibitors and prazosin), and
97 psychotherapeutic approaches (cognitive therapy, exposure therapy, stress management skills training, and
98 eye movement desensitization reprocessing-EMDR).[4] Selective serotonin reuptake inhibitors (SSRIs) produce
99 improvement in the major symptom clusters of PTSD, although the magnitude of the treatment effect is
100 modest.[18] Prazosin, an alpha-antagonist, reduces trauma-related nightmares and has also been found to have
101 a significant effect on all of the PTSD symptom clusters.[18] Despite these and other pharmacologic agents,
102 many persons with PTSD continue to experience persistent PTSD symptoms, as well as anger, difficulties with
103 interpersonal relationships, shame, and grief.[6] Psychotherapeutic techniques are often combined with
104 pharmacotherapy in the treatment of PTSD. Prolonged exposure (PE) therapy facilitates emotional processing
105 of the traumatic event, helping individuals to develop less phobic responses to internal and external trauma
106 cues.[19] However, PE is difficult for many Veterans to complete, as evidenced by a high dropout rate (38%).[20]
107 PE may also fail to address the entire realm of posttraumatic psychopathology including anger control,
108 interpersonal difficulties or grief.[6] In addition, PE and EMDR are usually administered by an individual therapist
109 rather than as a group treatment, which limits the ability to efficiently deliver these interventions to large
110 numbers of persons. Cognitive Processing Therapy (CPT) can be delivered either individually or in group
111 settings and has some initial support for efficacy in addressing PTSD among Veterans. In addition to concerns
112 about dropout for some Veterans, another potential shortcoming of current treatment for PTSD is the lack of
113 empirical data to guide treatment for persons with multiple psychiatric diagnoses. Psychiatric conditions other
114 than PTSD commonly co-occur with PTSD,[16] yet persons with multiple psychiatric diagnoses have often been
115 excluded from clinical trials. A further limitation is that many studies employed interventions delivered by expert
116 PTSD therapists with extensive experience, raising the question of whether the favorable results from these
117 clinical studies can be generalized.[20]

118   The VA has invested considerable resources to disseminate both PE and CPT through national roll-
119 outs to increase the likelihood that Veterans will have access to these empirically supported treatments.
120 Although research published in 2004 indicated that neither of these empirically supported treatments were
121 widely utilized by therapists within the VA,[21] more recent findings suggest that the roll-outs have met with initial
122 success and plans are in place to monitor future penetration of PE and CPT within the VA.[22] These efforts will
123 no doubt relieve a great deal of suffering among Veterans with PTSD. However, given the large number of
124 Veterans with PTSD, many with significant comorbidities and not all of whom will benefit from or elect to
125 participate in PE or CPT, additional cost-effective treatments suitable for broad implementation are needed.

126   Evidence indicates that about 15% of the US adult population utilizes mind-body therapies, with a
127 significantly higher rate found among persons with two or more chronic diseases.[23] Emerging evidence
128 indicates that Veterans also use various complementary and alternative medicine (CAM) interventions at high
129 rates. A large multisite study of VA outpatients found that 27% of Veterans had utilized some form of CAM in
130 the past year.[24] Another study of Veterans found that nearly 50% reported using a CAM intervention, and high
131 daily stress, chronic medical illness and a perceived negative impact of military service on mental or physical
132 health were significant predictors of CAM use.[7] Qualitative research among Veterans also suggests that
133 dissatisfaction with the reliance of conventional care on prescription medications and neglect of social and
134 spiritual aspects of health serve as motivating factors for CAM use.[8] In addition to chronic symptoms of PTSD
135 and depression, the presence of chronic illnesses associated with PTSD along with dissatisfaction with
136 reliance on prescription medications are likely to positively impact recruitment for the current study. Our past
137 experience offering meditation-based interventions as a clinical service to Veterans provides additional
138 evidence that LKM is likely to be an acceptable treatment modality among Veterans.
139   Loving-Kindness Meditation (LKM) is a CAM approach that facilitates increased positive emotions
140 through meditation exercises designed to develop feelings of warmth, kindness, and compassion for self and
141 others. A growing body of literature indicates that self-compassion is associated with healthy psychological
142 functioning (including life satisfaction and social connectedness), and negatively associated with self-criticism,
143 rumination, thought suppression, anxiety and depression.[25] Self-criticism, rumination and thought suppression
144 are phenomena frequently associated with PTSD, as is depression.[26] Therefore an intervention that increases
145 self-compassion may impact clinical manifestations of PTSD. In a study of PTSD symptoms in university
146 students, greater self-compassion significantly correlated with lower rates of avoidance symptoms, but not re-
147 experiencing or hyperarousal,[27] suggesting that individuals with higher self-compassion may engage in fewer
148 avoidance strategies. 'Compassionate mind training,' which is an intervention designed to teach self-
149 compassion, was offered to six individuals in a small pilot study by Gilbert et al. [28] The authors found significant
150 reductions in depression, self-criticism, anxiety and shame over time, and postulated that teaching techniques
151 that generate feelings of self-soothing and inner warmth may be particularly helpful for persons with a history of
152 trauma, due to pervasive feelings of shame and self-criticism coupled with the relative inability for self-soothing
153 in this population.[28] Many persons with PTSD have a long history of traumatic experiences, and have rarely felt
154 safe or reassured. Pervasive feelings of shame and guilt are common in the setting of PTSD.
155   Increasing evidence supports LKM as a technique for enhancing positive emotions and health
156 generally. Support for the efficacy of LKM to increase positive emotions was found in a study by Fredrickson
157 and colleagues.[9] This study was conducted with 139 community dwelling individuals employed by a single
158 company. The subjects were randomized to either LKM (n=67) or waitlist control (n=72). Those in the LKM
159 group reported significantly greater positive emotions and were significantly less depressed at the end-point
160 assessment than the no-LKM group, even though both groups reported a similar frequency of negative
161 emotions day-to-day. They also found that positive emotions persisted after meditation sessions ended, and
162 that over time, repeated LKM practice produced a cumulative increase in positive emotions on subsequent
163 days, regardless of whether the individual had practiced meditation on that day.[9] A pilot study of LKM for
164 chronic low back pain by Carson et al compared a group that underwent LKM (n=18) with a group receiving
165 standard care (n = 22) and found that those in the LKM group reported lower pain ratings, less anger, and less
166 psychological distress (note: positive emotions do not appear to have been assessed).[29] Another study of LKM,
167 performed in a group of community participants, indicated that a single brief session of LKM training led to
168 increased self-esteem and sense of social connectedness relative to a control condition.[30] In a report of case
169 studies in which LKM was taught to persons with schizophrenia, LKM appeared to be of potential benefit for
170 persistent negative symptoms.[31]
171   In LKM practice, a person sits quietly and calls to mind a particular person (e.g., a good friend) and
172 focuses on bringing a sense of positive regard to that individual through a series of standard phrases invoking
173 the desire for safety, happiness, health, and ease or peace for them. Classically, four phrases are used, such
174 as: "may you be safe," "may you be happy," "may you be healthy," and "may your life unfold with ease." Next,
175 the person brings positive regard to other individuals or categories of people, including themselves, neutral
176 persons, and those who have caused difficulty or harm (see Approach section), changing the phrases as
177 needed (i.e., "may you be safe" becomes "may I be safe").[32] This systematic development of kindness toward
178 self and others is intended to change the orientation to one's self, others, one's life experiences, and to result
179 in a broadening of the range of emotional responses and choices available. Loving-kindness practice has its
180 roots in the Buddhist tradition, but as described above an increasing number of studies have successfully
181 applied it as a non-religious practice. The phrase loving-kindness derives from the Pali word metta, which can

182 be translated as "love" or "unconditional friendliness," or "loving-kindness," akin to the Greek word "agape,"
183 which is typically translated as wide open unconditional love. The words loving-kindness are intended to
184 describe an emotional state that is not a sentimental love or a feeling of passion. Rather, it can be described as
185 an unconditional friendliness, benevolence, and openness toward experience – even difficult experience.
186   It can be postulated that the intentional cultivation of kindness and acceptance promoted in LKM
187 practice will positively influence multiple aspects of recovery from trauma. Although the factors described
188 below might also be developed through mindfulness practice (e.g., in MBSR through breathing meditation),
189 LKM is a distinct form of practice that is often considered more accessible and therefore more helpful to
190 persons who are in significant ongoing distress. Simply said, many persons find it easier, and more helpful, to
191 adopt and stay with a practice of LKM, which relies on the repetition of simple phrases meant to foster
192 kindness and compassion towards self and others, as compared to practicing breathing or body scan
193 meditation. This may be particularly true when an individual is in severe emotional pain. This is in agreement
194 with the recommendations of Buddhist teachers, who have been reported to recommend LKM practice instead
195 of other forms of practice when people are in significant distress.[32] The lives of persons with PTSD are marked
196 by ongoing severe emotional (and often accompanying physical) pain, including the hallmark emotion of fear.
197 In the historical Buddhist record, LKM was originally taught as a way of working with and 'staying with' the
198 strong emotion of fear, which, as noted, is the predominant emotional experience in PTSD. Indeed, one of the
199 core features of PTSD is thought to be a phobic response to reminders of a traumatic event and to the
200 memories associated with that event, which in conjunction with information processing problems, lead to
201 pervasive fear and poor functioning.[33] One aspect of LKM practice that can be hypothesized to apply to a key
202 post-trauma sequela is re-establishment of a sense of safety, or basic trust. Trauma can shatter the sense of
203 basic trust in others, oneself, and the world at large. Disruptions in basic trust, as well the tendency to avoid
204 reminders of the trauma in social situations, often result in withdrawal from close relationships.[34] The repetition
205 of LKM phrases can be hypothesized to represent a mechanism to recreate a safe 'holding environment,'
206 which in LKM is created by self-directed phrases of positive intention. This may prove particularly helpful when
207 kindness and support are lacking in the environment. Social support has been shown to be an important factor
208 in recovery from PTSD.[35] The incremental restoration of a sense of basic trust, as well as an increased ability
209 to self-modulate pervasive feelings of shame, guilt and inferiority may lead to an enhanced sense of self-
210 efficacy. Over time, enhancement of these factors might be expected to play a role in restoration of a
211 connection to the sense of self that has been lost through traumatic experiences, and may lead to a sense of
212 reconnection with the community as well. The cultivation of positive emotions through LKM might be also
213 particularly helpful for the numbing and constrictive symptoms characteristic of chronic PTSD, which can
214 present as feelings of chronic alienation and deadness. Providing a technique through which positive emotions
215 can repeatedly be enhanced, as in LKM practice, may provide an innovative pathway to address these
216 numbing and constrictive symptoms.
217   While practicing LKM, a person is asked to notice and feel the positive emotion elicited by each of the
218 phrases of positive intention, or to notice if there is a sense of reluctance, hesitation, or even aversion for the
219 self or another. The practitioner is encouraged to have compassion for these responses and to notice them
220 without judgment. More generally, during LKM, when a person becomes distracted by thoughts that arise
221 during the practice, they are instructed to notice what has distracted them with an attitude of non-judgmental,
222 mindful attention, then return to the LKM phrases and the breath without self-criticism. Walking meditation is
223 also used as a method to teach LKM. Informal LKM practices are also encouraged - participants are asked to
224 practice LKM toward themselves or others during everyday activities such as walking, eating, washing the
225 dishes, or standing in line at the grocery store.

226 **LKM and the Broaden-and-Build Theory of Positive Emotions**
227   The broaden-and-build theory of positive emotions provides a framework for understanding the
228 potential influence of LKM practice on affect, behaviors, and quality of life.[9,36] The broaden-and-build theory
229 proposes that positive emotions momentarily broaden a person's attention and thinking, and with this
230 broadened outlook they are able to build personal resources. A key postulate in the broaden-and-build theory
231 is that positive emotions broaden a person's thought-action repertoire.[36] As described by Fredrickson: "Joy
232 sparks the urge to play, interest sparks the urge to explore, contentment sparks the urge to savour and
233 integrate, and love sparks a recurring cycle of each of these urges within safe, close relationships."[36] The
234 broadened mindset associated with positive emotions is contrasted to a narrow focus often associated with
235 negative emotions, and characterized by specific, repetitious thought-action tendencies (e.g., fight or flight). A
236 second key postulate of the broaden-and-build theory is that the broadened mindset associated with positive
237 emotions leads to the building of enduring personal resources. These personal resources are thought to arise

238 through new thought-action sequences such as play, curiosity, and openness to new situations and ideas, as
239 well as new social interactions. Personal resources built may include cognitive resources (e.g., the ability to
240 mindfully attend to the present moment), psychological (e.g., a sense of purpose in life, self-acceptance or self-
241 compassion, or a sense of environmental mastery) social (e.g., improved ability to give and receive social
242 support) or physical (e.g., reduced susceptibility to stress-associated illnesses).[9] According to the broaden-
243 and-build theory, people who have developed these personal resources are more likely to successfully
244 navigate life's challenges and live happier, healthier lives.
245   There is growing evidence in support of the broaden-and-build theory. The 'broaden' hypothesis
246 predicts that positive emotions broaden a person's attention and thinking. Support for this hypothesis comes
247 from studies of experimentally-induced positive emotional states (through LKM in some cases as well as
248 through other means), which show that positive emotions broaden the scope of a person's visual attention,
249 increases one's openness to new experiences, improves ability to accept critical feedback, improves ability to
250 recognize persons of another race,[37] broadens one's repertoire of desired actions, and enhances a sense of
251 connection with others.[9] In a randomized controlled trial of LKM vs. a waitlist control (described in detail
252 above), the findings supported both the 'broaden' aspect (enhanced positive emotions) as well as the 'build'
253 part of the theory (enhanced personal resources).[9] When life satisfaction was assessed as an outcome,
254 positive emotions predicted life satisfaction only to the extent that they built personal resources.[9] In addition,
255 when depression was assessed as an outcome, LKM was found to have direct effects on depressive
256 symptoms as well as additional effects mediated by built personal resources.[9] The built cognitive,
257 psychological and social resources appear to have enhanced the ability of persons randomized to LKM to ward
258 off symptoms of depression. Similarly, in the proposed trial, we hypothesize that personal resources will be
259 built as a result of LKM practice, which will positively influence both depressive and PTSD symptoms.

260 **Mediators**
261 Identification of active components of treatments is a priority for treatment research.[38] The proposed study will
262 evaluate potential mediators of change thought to be specific to each intervention.

263 **LKM:** We will evaluate whether enhanced self-compassion mediates change in PTSD and depression for
264 LKM. Self-compassion can be considered a healthy form of self-acceptance. Neff defines self-compassion as
265 comprised of three facets: (1) treating oneself kindly and without harsh judgment in the setting of pain and
266 failure, (2) perceiving that mistakes and hardships are part of the common human experience rather than
267 isolating, and (3) maintaining mindful, non-judgmental awareness of thoughts and feelings rather than or
268 overidentifying with them.[39] Self-compassion is distinct from self-esteem, which is typically defined as an
269 evaluative process in which one's abilities and characteristics are compared to standards.[39] Self-compassion is
270 also distinct from self-centeredness, because self-compassion acknowledges the ubiquity of pain and hardship
271 among humans. LKM is considered a method to enhance self-compassion. As suggested by our pilot work
272 with LKM, we hypothesize that for those in the LKM arm of the study self-compassion will mediate improved
273 outcomes for persons with PTSD such that changes in self-compassion will both temporally precede changes
274 in PTSD and when they are statistically controlled, the changes in PTSD will be attenuated. There is initial
275 support for this hypothesis from the literature.[40,41] In an analysis of people with a history of major depression
276 randomized to a mindfulness intervention or maintenance antidepressants, enhanced self-compassion
277 mediated the relationship between participation in mindfulness training and reduced depressive symptoms at
278 follow-up.[41] The possibility of a key role for self-compassion is consistent with emerging theory and evidence
279 that self-compassion is adaptive in the setting of painful or difficult thoughts and feelings. [28,40] It is also possible
280 that changes self-compassion will mediate changes in PTSD for those in the CPT-C arm of the study, but we
281 anticipate that these effects will be less robust than for those in the LKM arm of the study.

282 **CPT-C**: We will evaluate whether reductions in posttraumatic maladaptive cognitions mediates improvement in
283 PTSD and in depression for CPT-C. CPT is hypothesized to facilitate improved emotional processing through
284 repeated practice restructuring dysfunctional beliefs and appraisals of situations that are related to the
285 individual's trauma history, which lead to painful affect and reactive behavioral choices.[42,43] Reduction of
286 posttraumatic maladaptive beliefs is postulated to be a key ingredient in CPT that will mediate improvement.
287 Indeed, recent work evaluating whether cognitive change predicts symptom reduction in the context of
288 cognitive therapy found support for this idea. Analysis of weekly measures collected during a course of
289 cognitive therapy found that changes in posttraumatic cognitions preceded and predicted changes in PTSD
290 symptom severity and that changes in PTSD symptom severity did not precede or predict changes in
291 posttraumatic cognitions.[44] Although this work was done in the context of an alternate cognitive therapy
292 intervention, Cognitive Therapy for PTSD, and not CPT, the finding suggests that CPT is also likely to result in

293 such changes in beliefs and appraisals that in turn mediate PTSD symptom reduction. The proposed project
294 would afford the opportunity to evaluate whether this is the case for Veterans who participate in group-based
295 CPT-C. [45] We will also be able to assess whether reductions in maladaptive cognitions also mediates
296 reductions in PTSD for those who receive training in LKM.

The Approach: What LKM Is and Isn't

298   Having provided an overview of what LKM is, we also believe it is important to delineate it from other
299 approaches with which it may be confused. First, although both LKM and mindfulness meditation practices
300 involve sitting meditation, typically with closed eyes and an initial focus on the breath, they differ in several
301 respects. Mindfulness meditation cultivates the ability to pay attention, without judgment in the present
302 moment, whereas LKM specifically develops the ability to experience kindness, warmth, and openheartedness
303 toward self and others. The intentionality of LKM is toward developing the ability to experience positive
304 emotions, rather than developing non-judgmental awareness. Second, LKM differs from intercessory prayer.
305 Although in LKM practice the phrases repeated express the intention of wellbeing for self and others (see
306 below), it is made clear that there is no expectation that the LKM phrases will actually benefit others. Instead, it
307 is made explicit that the goal of LKM practice is to benefit oneself, such that in developing the capacity to
308 experience kindness toward self and others, the person who holds this intention actually benefits.
309 Unfortunately the intercessory prayer literature has not evaluated whether praying for others has a salutary
310 effect on the people doing the praying, though research on spiritual involvement, including prayer activity, has
311 found that Veterans with greater spiritual involvement have better physical and mental health than those with
312 less spiritual involvement.[46] Third, although LKM involves the repetition of phrases, it is distinct from mantram
313 repetition practices, which involve bringing attention to a repeated phrase or word that facilitates
314 disengagement from difficult thoughts and feelings, and encourages relaxation. In LKM, phrases of positive
315 intention are utilized as a means to bring forth compassion for self and others, and to foster a broadened
316 emotional repertoire. Through the process of practicing LKM with different people in mind, LKM is thought to
317 reshape relationships with others, as well as to foster self-compassion. Of note, an additional effect of LKM is
318 that in the process of choosing phrases of positive intention (which carry personal meaning for a participant),
319 clarification of values and one's intentions occurs. LKM is also distinct from practices explicitly intended to
320 promote forgiveness, although forgiveness may occur through LKM practice. For the purposes of scientific
321 study, we have chosen to not include explicit forgiveness practice as part of our study. In LKM, the practice is
322 intended to develop the ability to look at others and see oneself, and in so doing, develop self-compassion and
323 compassion for others. An expanded understanding of the commonality of human experience, such that all
324 humans suffer and all desire happiness, which is fostered by LKM, is likely to lead to forgiveness. In addition,
325 LKM is also distinct from the practice of verbalizing positive affirmations. While there may be some overlap with
326 regard to the shared emphasis on positivity, affirmations tend to be stated as though they are definite personal
327 qualities and are intended to strengthen self-confidence (e.g., "I am a good, kind person"), whereas LKM is
328 usually stated as an invitation or request that is intended to tap into the intention for kindness and compassion
329 for oneself and for others (e.g., "may I be safe from harm;" "may you be happy and healthy"). Importantly,
330 another way that LKM is distinct from positive affirmations is that LKM is a meditation practice intended to
331 broaden attention and allow positive emotions to remain in awareness for sustained periods of time. Finally,
332 LKM is not intended to be used to remove painful thoughts or feelings. Rather than attempting to rid oneself of
333 these experiences, it is anticipated that individuals with PTSD can learn through LKM that pain can co-exist
334 with positive feelings because, after all, it is part of being human to experience both. This may help address the
335 phenomenon that we have frequently observed clinically wherein individuals with PTSD are afraid to
336 experience positive emotions because it is painful when they end. By re-learning (or learning for the first time)
337 that it is safe to feel good and that it is normal to have good feelings (and painful ones) that wax and wane, the
338 often profound emotional numbing typically associated with PTSD may be mitigated.[47]

Overview of Proposed Interventions
Intervention #1: Loving-Kindness Meditation (LKM)

341   The LKM course follows the instructions for LKM as described by Salzberg.[32] During the12 meetings
342 the ten to twelve group participants will receive instruction from two expert meditation teachers (who will co-
343 teach the sessions) in the practice of LKM, including both in-session practice of LKM and group discussions.
344 The intervention is designed to allow patients to adopt skills and techniques they can continue to practice
345 without the need for an ongoing relationship with a therapist. LKM is taught in a non-religious format. A class-
346 by-class outline is provided in the participant workbook (Appendix 3).
347   In order to help develop concentration, a necessary component of LKM practice, the first two sessions
348 focus on cultivating mindful attention of one's breath. The primary LKM practice begins in week 3, and involves

349 sitting in a comfortable, relaxed position with closed eyes or a neutral visual focus and then bringing to mind
350 various categories of beings – self and others. The meditator is then asked to gently repeat phrases to the
351 person who he or she has brought to mind; these phrases are intended to have meaning in terms of what is
352 wished for that person. In order to facilitate stepped learning, the class begins their LKM practice focusing on a
353 positive benefactor and over the remaining nine weeks other individuals and categories of individuals are
354 introduced, including the self and people who have caused the participant difficulty or harm.

355 **Intervention #2: Cognitive Processing Therapy (CPT).** The CPT intervention is based on Patricia Resick and
356 colleagues' manual for treating PTSD among military veterans.[48] This version of CPT highlights both combat traumas
357 and interpersonal violence and is therefore more appropriate for our population than the original version, which
358 focuses on adult rape survivors. (See CPT manual: Appendix 4) CPT evolved directly out of Social-cognitive
359 Information Processing Theory (SCIPT), which posits that deficits in emotional and cognitive processing of traumatic
360 events lead to the development of PTSD.[48] The fundamental assumption of the theory is that post-trauma
361 psychopathology occurs when there is a failure to integrate perceptions of the traumatic event with preexisting
362 beliefs.[49] SCIPT posits recovery from a traumatic event occurs when beliefs affected by the traumatic event are
363 integrated with prior beliefs.[49] Recovery happens when beliefs affected by the event are accurate and realistic and
364 negative affect about the trauma is processed. Avoidance symptoms, according to this theory, maintain the other
365 symptoms, in that they both prevent the memory of the traumatic event from being integrated with prior beliefs, and
366 prevent the examination of inaccurate beliefs affected by the traumatic event.
367   CPT combines cognitive restructuring with emotional processing of trauma related content. The therapy
368 sessions initially focus on rigid or inaccurate beliefs about the traumatic event itself, which often reflect self-
369 blame or hindsight bias. Later sessions address over-generalized beliefs about the self and others that result
370 from a traumatic event. CPT focuses on over-generalized trauma-related beliefs relevant to five key areas:
371 safety, trust, power, esteem, and intimacy. Over the course of treatment, clients learn to identify and modify
372 these beliefs in order to develop more balanced, flexible, and ultimately, more adaptive beliefs.
373   Cognitive processing therapy (CPT), has been found to be effective in the treatment of PTSD in
374 randomized clinical trials conducted by different research teams and with different trauma exposed
375 populations, including survivors of sexual and physical assault[50] and combat Veterans.[51] In these trials, CPT
376 was effective in reducing symptoms of PTSD and depression for up to 5 to ten years.[50] CPT has also been
377 found to be effective in reducing negative emotions such as grief, shame, guilt and anger.[50,51] Based on these
378 randomized clinical trials, CPT is being widely disseminated, including to the US Veterans' Administration (VA)
379 mental health system.
380   A version of CPT that does not include writing a trauma narrative has also been evaluated, CPT-C, and
381 has been found to be associated with more rapid improvement than standard CPT-C as well as comparable
382 outcomes to standard CPT.[43] The elimination of the trauma narrative makes CPT-C more conducive to a
383 group-based delivery platform as it reduces the risk that group participants will be traumatized by one another's
384 stories. CPT-C has recently been shown to be effective in a group format for Veterans, active duty military
385 personnel, and reservists with PTSD.[5] In a randomized controlled trial (N=107), group CPT-C was compared to
386 present-centered therapy (PCT) and the former found to be more effective than the latter in reducing PTSD
387 and depressive symptoms in active duty military personal with PTSD. Between group comparisons showed
388 that the CPT-C group had significantly greater improvement in PTSD symptoms than PCT with a medium
389 effect size (d=0.42; p = 0.03).[5]

390 **Importance of Study Findings to VHA**: The demand for mental health services provided by VHA has grown
391 dramatically in recent years - more than a half millions Operations Iraqi Freedom and Enduring Freedom
392 (OIF/OEF) Veterans have sought VHA care while the number of Vietnam Veterans receiving VHA mental
393 health services has doubled over the past decade.[52] PTSD is highly prevalent among Veterans, with
394 prevalence rates [13]of approximately 20 - 30% of combat Veterans.[14 15] A study of approximately 104,000
395 OIF/OEF Veterans found that 25% received a mental health diagnosis when they accessed VA health care,
396 and of these, 13% were diagnosed with PTSD.[53] To respond to the growing demand for mental health
397 services, consensus recommendations have identified the need for further research on nontraditional delivery
398 systems and group-based interventions to significantly expand the availability of cost-effective therapies.[54]
399 Given the large number of persons with PTSD, not all of whom will opt for or benefit sufficiently from PE or
400 CPT, additional cost-effective treatments suitable for broad implementation are needed that address persistent
401 symptoms and reduced QOL. Thus, if LKM is shown to be non-inferior to CPT, it would represent a novel, and
402 likely cost effective, approach to mental health care delivery.

403   A key tenet of patient-centered care is that health care practitioners listen to and honor patient and
404 family perspectives and choices. Patient and family knowledge, values, beliefs, and cultural backgrounds are
405 incorporated into the planning and delivery of care. This study would provide information to help patients
406 decide whether a contemplative practice, such as LKM meditation, presents a viable alternative to a trauma-
407 focused behavioral intervention such as CPT-C.
408

409 **APPROACH**

410 **Design Overview and Rationale**
411   The proposed study is a randomized controlled non-inferiority trial comparing Loving-Kindness Meditation
412 (LKM) with Cognitive Processing Therapy – Cognitive only (CPT-C) for treatment of PTSD and depression
413 among Veterans recruited from the VA Puget Sound Health Care System. Veterans (N = 170) with PTSD will
414 be randomized to receive 12 weeks of either LKM (n = 85) or CPT-C (n = 85). The two interventions are
415 structurally similar - Each intervention meets for 90 minutes per week for twelve weeks; the overall amount of
416 treatment time is the same across the two interventions. Both interventions will be delivered to groups of
417 Veterans by experienced leaders, and fidelity coding from audiotapes will evaluate protocol adherence.
418 Participants will complete brief take home paper assessments weekly for the 12-week duration of the active
419 treatment phase to assess key outcomes, potential mediators of change, and completion of homework
420 assignments. All participants in each study condition will complete an in-person baseline assessment, which
421 will be repeated immediately after the treatment phase as well as 3- and 6- months post-intervention. In-
422 person assessments will be performed by a blinded assessor.

423 **Use of an Active Control Arm:** The active control will account for the non-specific elements of LKM (e.g.,
424 group support, positive expectancy). The proposed control arm is CPT-C, which will provide the same amount
425 of clinician-exposure time (it is also a group-based, 12-week duration, 90-minute per session program). Similar
426 to LKM, CPT-C is taught by experienced instructors who believe in the benefit of the program; allegiance of the
427 researcher/therapist has been shown to be strong predictor of treatment outcomes.[55] CPT-C therefore
428 contains key elements of an active control – it is structurally similar to LKM (thus controlling for non-specific
429 elements of the intervention) and given that it is an accepted PTSD treatment, CPT-C will foster positive
430 expectation for intervention success by both therapists and patients. Each of these elements has been
431 described as necessary for an appropriate active control.[56]

432 **Settings, Recruitment, and Participants**
433   <u>Settings.</u> The study's clinical activities will take place at VAPSHCS; Seattle Division. In FY10 over 17,700
434 Veterans with chart diagnoses of PTSD received care at VAPSHCS and over 10,000 of them had a mental
435 health stop code, indicating that the majority were likely invested in addressing their PTSD symptoms. VA
436 Puget Sound has the nation's largest clinical program for PTSD.

437   <u>Recruitment.</u> The primary mechanism of recruitment will be letters sent to Veterans with a diagnosis of
438 PTSD (as identified using a VA database called the Corporate Data Warehouse; CDW). To illustrate the
439 effectiveness of this method, we are currently conducting a trial of MBSR for Gulf War Syndrome (see
440 preliminary studies) for which we are already successfully recruiting at the same rate as for the proposed RCT.
441 Thus, the goal of recruiting 8 Veterans per month with PTSD is feasible given the large pool of Veterans with
442 PTSD.

443   <u>Participants.</u> Based on our experiences recruiting individuals with PTSD for LKM and MBSR research, we
444 anticipate that we will need to conduct phone screens with approximately 350 individuals and in-person
445 screening. We anticipate that we will enroll at least 250 male and female Veterans over age 18 with a current
446 DSM-IV diagnosis of PTSD enrolled at VAPSHCS who will provide informed consent and undergo in-person
447 screening. Of these, we anticipate that 170 individuals with PTSD who meet study criteria will be randomized.
448 Gender and ethnic/racial distribution of the participants is expected to mirror that of our prior PTSD MBSR
449 studies in which similar recruitment strategies were used; that is 40% female, 79% Caucasian, 8% African
450 American, 6.5% Hispanic, and 6.5% other.

451   <u>Inclusion and Exclusion Criteria.</u> Inclusion criteria: current DSM-5 diagnosis of PTSD, age $\geq$ 18 years, and
452 English fluency. Participants must be willing to not participate in Mindfulness-Based Stress Reduction (MBSR)
453 or Prolonged Exposure (PE) therapy during the study period. Exclusion criteria: current substance use
454 dependence disorder other than alcohol; alcohol involvement that poses a safety concern (i.e., currently
455 drinking and has a past year history of alcohol-related seizures or delirium tremens), suicide attempt or suicidal
456 ideation with intent or plan, self-harm in the past month, a psychotic disorder, uncontrolled bipolar disorder,
457 chart diagnoses of borderline personality disorder, antisocial personality disorder, or dementia in-patient

458 admission for psychiatric reasons within the past month, prior participation in LKM, or CPT. Medication,
459 supportive individual or group counseling, case management, and self-help programs will be allowed
460 concurrently and assessed as potential covariates.

461 **Sequence of Study Visits**
462   Telephone Screen. Veterans who contact the Project Manager will be provided an overview of the study.
463 Veterans who remain interested will undergo a 15-20-minute telephone screen to ascertain basic
464 inclusion/exclusion criteria.

465   In-person Screen and Baseline Assessment. Following informed consent, participants will undergo a 2-
466 hour assessment. The Study Assessor will conduct standardized interviews for the presence of exclusionary
467 disorders (relevant subsections of the MINI International Neuropsychiatric Interview) and for diagnosing PTSD
468 (Clinician Administered PTSD Survey; CAPS).[57] Self-report measures will be administered on a VA-approved
469 computer. Those who are eligible to continue the study will receive their randomization assignment within
470 approximately one week and will begin either LKM or CPT-C within one month.

471   Weekly Paper Assessments. Participants will complete brief measures of PTSD and depressive
472 symptomatology, the hypothesized mediators of change (self-compassion and maladaptive posttraumatic
473 cognitions), and homework activity for 12 weeks during the active treatment phase.

474   Follow-up Assessments. Participants will complete a post-treatment assessment within a week of
475 completing LKM or CPT-C, and will repeat the assessment battery 3- and 6-months thereafter.

476 **Randomization**
477   We will utilize a blocked randomization approach stratified by symptom severity on PTSD because our pilot
478 studies indicate that those who score in the severe range (60 or higher)[57] on the PCL decrease their PTSD
479 symptoms more than those with less severe PTSD but are still more symptomatic at immediate post-test.
480 Baseline severity of PTSD will be dichotomized based on CAPS-5 scores $\geq$ 37 Because our pilot data did not
481 suggest that severity of depression moderated outcome, we will not include that in the randomization
482 stratification. Similarly, we chose not to stratify on gender because our pilot data indicate that this factor is not
483 predictive of PTSD symptoms at follow-up. A series of randomization tables will be constructed and will be
484 maintained by the research coordinator. Subjects will be randomized in small blocks of varying size using
485 concealed allocation, after the baseline assessment and within two weeks before the next study cohort is set to
486 begin treatment.

487 **Study Interventions:**
488 **#1 LKM Course Overview**
489   Each class meeting will begin with either a brief mindfulness meditation (weeks 1 and 2) or an LKM
490 meditation followed by an opportunity for participants to discuss their experiences integrating LKM class
491 material into their daily lives. New material will then be presented, typically introducing a new category of
492 beings (i.e., benefactor, oneself, strangers, etc.) and particular challenges associated with working with that
493 category of beings will be discussed. The class will then practice LKM incorporating the new category and then
494 discuss the experience. At the end of each class the homework for the next week will be presented and class
495 will end with another brief LKM practice. Participants will be provided with an LKM meditation CD and a
496 workbook to accompany the class. (See appendix 3, LKM manual, for additional details). An overview of the
497 class schedule is provided below:

498 Classes 1 and 2 provide an introduction to in mindfulness meditation.

499 Class 3 introduces LKM, including the LKM phrases and a description of the meaning of each phrase. Begin
500 LKM practice toward a benefactor, which is defined as a person who has been kind or helpful and for whom
501 there is gratitude, and respect. Participants will be asked to recall the ways this benefactor has helped them,
502 and the goodness within this person.

503 Class 4 introduces the theme of commitment to our own happiness as a basis for intimacy and connection with
504 self and others. Exercise: "Remembering the good within you" (Instructions: "For 10-15 minutes call to mind
505 something you have said or done that was a kind or good action"). Acknowledgement and discussion of the
506 finding that LKM toward our self is often difficult. If participant is unable to practice LKM toward self, suggestion
507 of the concept that underlying all action is a desire to be happy – this may provide a method of noticing
508 kindness toward oneself that already exists; this may act as a starting point for feeling positive emotion for
509 oneself. LKM toward benefactor and self with the 4 phrases.

510 Class 5 begins with a discussion of homework - LKM in the previous week toward a benefactor and self.
511 Introduction of walking meditation and the concept of a beloved friend (may be a person or an animal).

512 Class 6 begins with a discussion of how it is often more difficult to practice LKM toward self as compared to a
513 benefactor or beloved friend. Examination of how our life experiences up to this point may affect our
514 experience practicing LKM.

515 Class 7 introduces the concept of a neutral person – someone we do not strongly like or dislike. Perhaps this is
516 a person we do not know well. This may bring up the awareness that this may be difficult because of the
517 judgments we hold for people around us as well as pervasive fears and mistrust.

518 Class 8 begins with a discussion of homework - LKM to a neutral person. Have your feelings for that person
519 changed? Introduction of a difficult person: a person with whom we have experienced conflict and toward
520 whom we feel anger or lack of forgiveness. This could be someone who has been unsupportive or who
521 responded to us in ways that were not helpful when we needed them. At this stage, participants will be
522 instructed at this stage to not choose the person who has caused them the most pain or suffering in their lives
523 – while acknowledging that this is a suggested goal of LKM practice. Discussion of how practicing LKM does
524 not mean a sentimental love toward that person, as well as a discussion of anger – how it can serve the
525 purpose of setting boundaries and can challenge injustice, but can also cause suffering for the person who
526 holds anger as well as for the person who receives it.

527 Class 9 introduces the difficulties involved in LKM to a difficult person. Discussion: When you are feeling anger,
528 who is the person suffering from anger? Include discussion that LKM toward difficult person is actually
529 compassionate toward oneself, because it promotes letting go of this anger. Introduction of concept of difficult
530 aspects of oneself, including painful feelings, thoughts, memories, and symptoms. What aspects of ourselves
531 do we reject and feel anger or hatred toward?

532 Class 10 provides opportunity for further discussion of LKM toward difficult person. Introduction of LKM toward
533 groups. Discussion of how we often accumulate biases or prejudices toward groups or categories, and these
534 biases are often not in our conscious awareness. Practice LKM toward complementary sets of groups, with
535 discussion of whether participants feel an affinity or sense of unease practicing LKM toward one part of a
536 group. Examples of groups include: males/females, young/elderly, Veteran/civilian, all those known to me/all
537 those unknown to me, those near/those far.

538 Class 11 begins with discussion of LKM toward groups, with an emphasis on whether unconscious affinity or
539 bias was detected in the ability to practice LKM.

540 Class 12 begins with discussion of walking meditation. Introduction of LKM for all beings. Discussion of
541 different categories of beings as appropriate for each person – alive or dead, human or animal. Practice LKM
542 toward self, friend, benefactor, neutral person, difficult person, groups, toward all beings.

543 **Homework** for those randomized to LKM homework will consist of 30 minutes of sitting or walking
544 mindfulness (first two weeks) or LKM meditation facilitated by CD recordings with new categories of beings
545 added as described above. Participants will also be instructed to identify opportunities for informal LKM
546 practice each week.

547 **#2 CPT-C Course Overview.**
548 CPT-C will be led by clinicians who will be contracted by the grant to deliver this service. The group co-
549 leaders will all have completed the VA's CPT-C training and certification program or the equivalent in the
550 community. In addition, these clinicians will go through the necessary background checks and credentialing
551 procedures prior to having contact with any Veterans.
552 Those assigned to CPT-C will attend weekly 90 minute group therapy sessions for 12 weeks. Treatment
553 will be provided in groups of 10 to 12 male and female Veterans with PTSD.

554 Session 1 provides an introduction to CPT-C and education about both PTSD as a response to trauma and
555 how trauma exposure can lead to distorted thinking and beliefs. Patients are oriented to the Impact Statement
556 homework.

557 Session 2 draws from the Impact Statement homework and reviews how patients are currently framing the
558 meaning of their index trauma with regard to its impact on their lives in the following areas: safety, trust,
559 power/control, esteem, and intimacy. The concept of trauma-related cognitive "stuck points" is introduced.

560 Session 3 introduces a basic cognitive therapy overview of the relationship between thoughts and feelings
561 prompted by triggering events through the ABC sheet (A = activating event; B = beliefs; C = consequences).

562 Session 4 elaborates on the idea of "stuck points" (e.g., "I am damaged goods;" "I'm a failure because I
563 couldn't save my best buddy," etc.) that may have arisen as a result of the trauma exposure and each group
564 member is assisted in identifying their own specific "stuck points."

565 Session 5 provides a standard list of challenging questions that patients use to help themselves identify stuck
566 points.

567 Session 6 provides an overview of common patterns of problematic thinking (e.g., all/none thinking, confusing
568 feelings with facts, etc.). The Challenging Beliefs Worksheet is introduced in this session.

569 Session 7 provides further instruction on the use of the Challenging Beliefs Worksheet.

570 Session 8 reviews the safety module and patients are instructed to focus on at least one safety-related issue
571 when completing worksheets for homework.

572 Session 9 reviews the trust module and patients are instructed to focus on at least one trust-related issue when
573 completing worksheets for homework.

574 Session 10 reviews issues related to power/control and patients are instructed to focus on at least one
575 power/control-related issue when completing worksheets for homework.

576 Session 11 reviews self- and other-esteem issues and patients are instructed to focus on at least one esteem-
577 related issue when completing worksheets for homework and to write their final impact statement.

578 Session 12 reviews intimacy issues and the patients' current sense of the event's meaning.

579 **Homework** for those randomized to CPT-C will consist of 30 minutes of CPT-C-related homework 6 days a
580 week including writing an impact statement at the beginning and the end of treatment, completing CPT-C
581 worksheets, and completing exercises regarding safety, trust, power/control, esteem, and intimacy.

582 **Procedures for Maximizing Research Integrity and Patient Safety**

583 LKM Fidelity. The LKM teachers are highly experienced meditation teachers with experience teaching
584 meditation to Veterans with PTSD at VAPSHCS. These teachers currently teach LKM groups and
585 Mindfulness-Based Stress Reduction (MBSR) groups at VAPSHCS, which are offered as hospital-wide clinical
586 programs. These teachers have extensive personal experience involving LKM. LKM is also included as a
587 small component of the MBSR program, although the primary focus of MBSR is on mindfulness meditation.
588 Each of these teachers is employed as a WOC-status contract employee, and meets stringent foundational
589 teacher training requirements for MBSR, which we also apply to LKM teaching requirements: longstanding
590 practice of mindfulness and loving-kindness meditation, experience with a body-centered awareness practice,
591 attendance at silent mindfulness meditation retreats of at least 7 days duration, completion of the University of
592 MA Center for Mindfulness Residential Training/Retreat as well as a teacher practicum in MBSR. We believe
593 that these teacher training requirements and prior experience teaching MBSR will be directly applicable to
594 high-quality teaching of LKM.

595 To assure quality control, Dr. David Kearney will review at least 2 early session tapes from each LKM
596 cohort to provide supervisory feedback. Teaching responsibilities will be shared by Carolyn McManus, PT, MA
597 and Jonas Batt, MA, MHC, both of whom currently teach LKM at VAPSHCS. They will co-teach the LKM
598 courses to provide different perspectives and gender balance across the facilitators. If either of these teachers
599 becomes unavailable, there are 3 additional experienced mindfulness and loving-kindness meditation teachers
600 who are currently teaching other meditation classes at VAPSHCS who will be available to teach LKM. A subset
601 of 20% of LKM classes will be coded for protocol adherence by two independent raters (see Appendix 5).
602 Adherence and competence will be measured using treatment fidelity ratings based on the LKM curriculum.
603 Our pool of undergraduate raters will be trained by Dr. Kearney, who will provide ongoing supervision
604 regarding fidelity ratings.

605 CPT-C Fidelity. CPT-C group leaders selected to provide CPT-C will have completed either the VA's
606 national rollout dissemination training and certification process or the community equivalent, and thus will have
607 had at least 6 months of supervised experience delivering CPT-C. They will also be employed as WOC
608 contractors. The CPT-C supervisor will be Dr. Carie Rodgers is a national trainer in CPT for the VA National
609 Center for PTSD who was trained by CPT originator, Dr. Patricia Resick and has extensive experience both
610 delivering group-based CPT-C herself within VHA and supervising others.. She will provide weekly supervision
611 based on both review of session tapes and oral reports from the group co-leaders to assure real-time quality
612 control of CPT-C delivery.

613 A random subset of 20% of each group's 12 sessions will be coded for protocol adherence and
614 competence by two independent raters from our pool of undergraduate raters (see Appendix 6 for coding
615 forms). Adherence and competence will be measured using established published measures of CPT-C

616 treatment fidelity. Raters will be trained by Dr. Galovski (CPT-C) with ongoing supervision provided by Dr.
617 Rodgers.

618   <u>CAPS Interview Fidelity.</u> The Study Assessor will a be master's level clinician who will undergo training on
619 the CAPS interview by Dr. Simpson. Dr. Simpson will sit in on at least 5% of the CAPS interviews to provide
620 ongoing supervision.

621   <u>Maintaining the Assessment Blind.</u> The Study Assessor will be kept blind to participant condition:
622 participants will be reminded not to disclose treatment assignment, and other study personnel will avoid
623 communications that could provide such information.

624   <u>Procedures for Maximizing Retention.</u> Participants will update contact information at each visit and will be
625 paid $20 for baseline, post-test, $30 for the 3- and 6-month assessments, and $5 per week for the 12 online
626 assessments. Participants who complete all assessments will be eligible for an additional $20 bonus.The
627 maximum remuneration is $180 per enrollee. Frequent contact maximizes participant retention.[58]

628   <u>Project Management.</u> We will utilize web-based software to ensure coordination among study team
629 members and reliable participant tracking.

630   <u>Electronic Data Capture.</u> We will utilize the online version of Assessment Center that conforms to VHA
631 privacy and security requirements to create user friendly electronic versions of our measures that participants
632 will complete either using VA desktop computers during the in-person major assessment appointments. This
633 method of collecting data will ensure that items that are skipped are intentionally skipped, thus cutting down on
634 missing data. It will also reduce the need for manual data entry, thereby decreasing the risk of introducing
635 human error into the dataset and increasing the efficiency of moving from data collection to data cleaning and
636 analysis.

637   <u>Maintaining Participant Safety.</u> Participants will be provided a phone number to call if they require
638 psychiatric assistance, as well as the local county crisis clinic phone number. See also Appendix 7 for a full
639 description of safety procedures.

640 **Study Instruments and Materials (Table 3; see Appendix 8 for study measures)**

Study Construct/Variables	Study Phase	Measurement Scale	Purpose
Inclusion/Exclusion Criteria			
Demographic information	B		sample description, blocking (gender); moderators
MINI International Neuropsychiatric Interview V-5 (DSM-IV)[59]	B	dichotomous	sample description, exclusion
Medical history interview (seizures, DT's)	B	dichotomous	exclusion
Question assessing ideation of harm to self or others	B		exclusion
Drug Card Sort	B		exclusion
CAGE-AID	B		exclusion
Tracking			
Contact form	B,P,3,6		retention
Primary Outcomes			
Life Events Checklist[60]	B,P,3,6	dichotomous	inclusion (establish Criterion A)
Clinician-Administered PTSD Scale (CAPS)[57]	B, P,3,6	continuous	inclusion, blocking, **primary outcome**
NIH PROMIS depression measure[10]	B,P,3,6	continuous	**primary outcome**
Mediation Analyses			
Self-Compassion Scale-Short Form[61]	B, W,P,3,6	continuous	mediation analyses
Posttraumatic cognitions inventory[62]	B,W,P,3,6	continuous	mediation analyses
PTSD Checklist; Civilian Version (PCL-C)[63]	B,W,P,3,6	continuous	mediation analyses, secondary outcome measure
NIH PROMIS depression measure (static version-SF8a)[10]	W	continuous	mediation analyses, secondary outcome measure
Other			
Chronic Multisymptom Illness (CMI)	B		

Survey			
Spiritual Transcendence Index	B		
Rome III IBS Criteria	B		
TBI screening questions	B		
Cognitive Failures Questionnaire	B, P, 3, 6		
AUDIT-C	B		
DAST-10	B, P, 3, 6		
NIH PROMIS alcohol item bank: Use, Negative Consequences	B, P, 3, 6		
Alcohol Consumption (for BAC) short form	B, P, 3, 6		
Experiences Questionnaire	B, P, 3, 6		
Veterans Short Form Health Survey	B, P, 3, 6		
NIH PROMIS CAT measures: pain interference, fatigue, sleep disturbances	B, P, 3, 6		
NIH PROMIS Global Health, short form, static	B, P, 3, 6		
NIH Toolbox Emotion Battery	B, P, 3, 6		
Average daily pain intensity	B, P, 3, 6		
Curiosity subscale of Toronto Mindfulness Scale- short form	B, P, 3, 6		
PROMIS GI Symptom Scales	B, P, 3, 6		
Five Facet Mindfulness Questionnaire- short form	B, P, 3, 6		
Medication usage	B, P, 3, 6		
Qualitative Interview	3		
VA mental health care			
Corporate data warehouse mental health psychotherapy and medication management stopcodes	9-month post-baseline interval	dichotomous & continuous	check on VA mental health services received by both conditions
CPRS review for engagement in mental health treatment	9-months post-baseline	dichotomous	check on whether either PE or CPT was obtained during study

641 **Baseline (B), Post-test (P), Weekly, 3- and 6-month Assessments**

642 **Overview of Outcome Measures Chosen, and Further Description of Measures**
643   We have chosen the following measures in order to assess outcomes for the aims of this study,
644 including PTSD symptomatology, depression, and potential mediators. The weekly monitoring phase will
645 record the amount of homework practice completed (for both LKM and CPT-C), in order to provide the ability to
646 assess whether homework practice is predictive of improved outcomes.

647 PTSD Symptoms. Participants' PTSD symptomatology will be assessed using the Clinician-Administered
648 PTSD Scale (CAPS) and the PTSD checklist (PCL).
649   The **CAPS** is the primary outcome measure. The CAPS requires a clinician to rate 17 diagnostic
650 symptoms of PTSD, as defined by DSM-IV criteria. (Note: because a new version of the DSM is due out in May
651 2013, we will update our inclusion/exclusion criteria and the main outcome assessment materials once DSM-V
652 is made available). The CAPS gives both a continuous measure of PTSD severity and a dichotomous
653 diagnosis of PTSD. The psychometric properties of the CAPS have been evaluated in several studies and
654 have been found to be excellent.[57] The CAPS takes approximately 45 minutes to complete and will be
655 administered at baseline, week 8, and at each major assessment (post-LKM/CPT-C, 3- and 6-months).
656   *Addendum: The CAPS-5 version of the CAPS measure became available before initiation of the study*
657 *and was used instead of the CAPS-IV. The CAPS-5 was used to assess PTSD diagnostic status and PTSD*
658 *severity. The CAPS-5 is a 30-item structured interview (range 0-80).[64] It has high internal consistency (α=0.88),*
659 *high interrater reliability (ICC=0.91), and good test-retest reliability (ICC=0.78).[64] Interviews were performed by*
660 *an experienced clinician (M.S.) blinded to participant condition.*
661   The PCL-C is a 17-item self-report measure that correlates highly with scores derived from the Clinician
662 Administered PTSD Scale (CAPS).[63] The PCL has good internal consistency, item-total correlations,
663 concurrent and convergent validity, and test-retest reliability. Each item is rated by the patient on a scale of 1
664 to 5, and the total score of the PCL is calculated as the sum of the all the items. Higher scores reflect more

665 severe PTSD. [59] The PCL will be administered during the weekly monitoring phase in order to allow
666 assessment of clinical outcomes as part of mediation analyses, and will be included at weekly time points
667 (post-LKM/CPT-C, 3- and 6-months) as a secondary outcome measure.
668   Addendum: The 20-item PCL-C version that corresponds with DSM-5 PTSD criteria became available
669 before initiation of the study and was used instead of the 17-item version

670 Traumatic events. The number and type of traumatic events sustained over the course of each the Veteran's
671 life will be assessed using the **Life Events Checklist (LEC)**. The LEC assesses lifetime history of exposure to
672 a wide range of potentially traumatic events.[60] The LEC will be used to describe the study population, and to
673 establish PTSD diagnostic status as part of the inclusion criteria.

674 Depression. The depression measure at each time point will be from the NIH-sponsored **Patient-Reported
675 Outcomes Measurement Information System (PROMIS)** assessment suite. PROMIS was developed in
676 order to measure patient-reported outcomes using item response theory (IRT) and computerized adaptive
677 testing (CAT) which allows for efficient, psychometrically robust assessment of patient-reported outcomes in
678 clinical trials involving a wide range of chronic conditions, and they have been validated in over 21,000
679 persons.[10,65] CAT is a method by which the items administered are adaptive to the health status of the subject,
680 i.e., the instrument used is not "static" for each subject. Using CAT and IRT, the PROMIS measures are
681 designed to gain the maximal information content from each question by gauging the point of disease severity
682 a question is most efficient. The greater precision gained by use of these techniques has been estimated to
683 allow reduction in sample size requirements by up to half compared with "static" pen and paper instruments.[65]
684 Most PROMIS item banks utilize a 7-day recall period. These measures utilize item-response theory[66] and
685 computerized adaptive testing (CAT), in order to provide a high degree of precision. Using CAT, each domain
686 measures average 5-8 questions in length and takes only 1-2 minutes to complete. We will utilize the CAT
687 version of the PROMIS depression measure for the major assessment points, and the static version of the
688 PROMIS depression measure (SF8a) at the weekly assessments (using Survey Monkey for electronic data
689 capture).

690 Self-compassion. The **Self-Compassion Scale – Short Form (SCS-SF)**[61] is a 12-item measure of self-
691 compassion (see also broaden-and-build section of background/significance). It has been shown to be reliable
692 (Cronbach's alpha = 0.86) and to have a very high degree of correlation (r ≥ 0.97) with the longer and
693 previously validated self-compassion scale.[39]

694 Posttraumatic Cognitions Inventory (PTCI).[62] The PTCI is a 36-item measure that assesses trauma-related
695 thoughts and beliefs including negative cognitions about self, about the world, and self-blame. Items are rated
696 on a 7-point scale ranging from "totally disagree" to "totally agree." The PTCI has been found to discriminate
697 well between people who do and do not have PTSD and has been found to have good internal consistency,
698 test-retest reliability, and construct validity. The PTCI will be administered at baseline and follow-up time points
699 as a secondary outcome measure. The abbreviated 22-item version[44] will be collected weekly to assess
700 whether changes in posttraumatic cognitions mediate changes in the primary outcome measures.

701 Weekly monitoring assessment protocol. Weekly assessment of type and duration of LKM and CPT-C
702 homework practices completed along with measures of PTSD and depression and the proposed intervention
703 mediators will be assessed weekly during the twelve weeks of LKM or CPT-C treatment. The weekly
704 assessments will be administered via take home paper assessment. (See Appendix 9 for weekly items.)

705 Assessment of Usual VA Mental Health Care. In order to quantify the amount of VA mental health care that
706 study participants obtain during their involvement in the proposed study, data extraction from both the VA
707 Corporate Data Warehouse (CDW) and from the computerized patient record system (CPRS). The number of
708 individual and group psychotherapy stopcodes and mental health medication management stopcodes will be
709 recorded for all participants for the period of time they are directly involved in LKM (and equivalent time period
710 for CPT-C) from the CDW. These numbers will be cross-checked via CPRS and CPRS therapy notes will be
711 assessed to determine whether study participants were involved in treatments for PTSD during their
712 involvement in LKM or the follow-up period (and equivalent time period for CPT-C). We will also use CPRS to
713 code for psychiatric and pain medication adjustments during study involvement.

714 **Data Analysis**

715   **Overview.** Before performing the primary analyses, outliers, shape of distributions, and associations
716 between outcomes will be determined. Covariates or propensity scores will be utilized to adjust for differences
717 if imbalances between treatment groups on key variables are identified. Gender and type of trauma will also be
718 considered as covariates. All analyses will be performed using an intention-to-treat sample as well as per
719 protocol analyses. Per protocol analyses are the preferred method for non-inferiority analyses, in order to

720 avoid biasing the results toward no difference between groups, which could occur in intention-to-treat samples.
721 In addition, pattern-mixture models will be used to identify potential missing data patterns,[67] and multiple
722 imputation techniques will be used to accommodate missing data.[68]

723 **AIMS 1 and 2.** To determine if LKM is therapeutically similar to CPT-C, we will estimate the effect of
724 LKM vs. CPT-C using a multilevel mixed effects model with random effects for repeated measures. If
725 significant correlation exists between outcomes among participants in the same therapy group (i.e., ICC>0),
726 therapy group also will be included as a random effect in the model. The primary outcomes for AIM 1 are
727 participant scores on the CAPS.[60] As the models for AIM 1 and AIM 2 (PTSD and depressive symptoms,
728 respectively) will be identical, we focus on the CAPS. The analysis will include all of the primary assessment
729 time points (Baseline, post-LKM/CPT-C, 3- and 6- months). Mixed models are an appropriate choice for three
730 reasons. First, they accommodate the clustered nature of the data at multiple levels (i.e., repeated measures
731 within persons). Second, should significant correlation exist among participants in the same therapy group,
732 inclusion of group as a random factor allows for generalization of results to LKM and CPT-C groups in general
733 (not just the groups in the study). Third, they are flexible with respect to missing data.[69] Mixed effects models
734 will include treatment condition (LKM vs. CPT-C), time, and time by treatment interaction to determine if
735 differences in exist between conditions by time. Time will be modeled as a dummy variable to allow for
736 variation in effects over time. Both unadjusted and adjusted (covariates include baseline PROMIS depression
737 score for Aim 1 and baseline CAPS for Aim2, age, gender) models will be run. Subgroup effects of PTSD
738 severity on outcomes will be explored using tests of interaction.
739 A non-inferiority analysis determines if the effects of a new intervention are similar to an established
740 treatment within a pre-stated margin of or range of non-inferiority that is considered clinically acceptable (δ).[70]
741 We chose a non-inferiority margin of 10 points on the CAPS. A difference of 10 points on the CAPS
742 represents Cohen's d = 0.50 in treatment-seeking Vietnam Veterans with PTSD, for whom the SD is roughly
743 20.[71] A reduction of 10 points on the CAPS is considered the minimal effect that would be clinically
744 meaningful.[71]
745 *Addendum: The CAPS-5 measure became available before the study was initiated and was used in*
746 *place of the CAPS-IV. We defined a non-inferiority margin on the CAPS-5 using the same methodology as was*
747 *used for defining the non-inferiority margin using CAPS-IV. The primary outcome of non-inferiority of LKM*
748 *relative to CPT-C was assessed using a non-inferiority margin of 5 points on the CAPS-5, which represents 0.5*
749 *SD of baseline PTSD symptoms based on data indicating the SD of baseline CAPS-5 scores is approximately*
750 *10 in a large sample (N=198) of treatment-seeking veterans.[72] An effect size of Cohen's d = 0.5 has been*
751 *defined as the minimally important difference in prior PTSD trials.[71,73] For depression, the non-inferiority margin*
752 *was 4 points on the PROMIS depression measure, which has been defined as the minimally important*
753 *difference and corresponds to a Cohen's d effect size of approximately 0.50.[11,74]* A reduction of 4 points on the
754 PROMIS depression measure is the minimal effect considered clinically meaningful, which corresponds to an
755 effect size of approximately 0.5.[11] Hypothesis testing in a non-inferiority analysis is reversed from the standard
756 formulation. The null hypothesis (H_0) states that LKM is at least an amount δ worse than CPT-C. The
757 alternative (H_A) states that the post-treatment mean in LKM is no worse than amount δ as compared to CPT-
758 C.[75] We will assess non-inferiority at 6 month follow-up, as well as other time points (post-LKM/CPT-C, 3-
759 month follow-up) using methods outlined by Mascha and Sessler.[76] Non-inferiority of LKM to CPT-C for
760 reduction in PTSD symptoms will be claimed if the lower limit of the 95% confidence interval for difference in 6-
761 month mean CAPS scores is greater than -10. Non-inferiority of LKM to CPT-C for reduction in depressive
762 symptoms will be claimed if the lower limit of the 95% confidence interval for difference in 6-month mean t-
763 score in the PROMIS depression measure is greater than -4.[11] The test of non-inferiority is similar to the usual
764 test for differences between treatments obtained in a mixed effects model except that the non-inferiority margin
765 δ is added to the treatment effect coefficient b_3 and divided by the standard error.[76]

766
$$T_{NI} = \frac{b_3 + d}{SE}$$

767 If non-inferiority is not shown in the above analyses for AIM 1, traditional 'superiority' analyses will be
768 conducted for comparisons between the interventions. This will involve a simple comparison of means at the
769 6-month time point on the primary outcomes. We chose an effect size of d=.50[51,71] for the comparison of the
770 active treatments. Although the study is powered for the non-inferiority analyses, we also report a power
771 analysis for these preliminary analyses. Assuming an effect of d=.50 between treatment arms and a two-sided
772 α of 0.05 resulted in a power estimate of approximately 90%.

Power and Sample Size:

Sample size for the non-inferiority hypotheses specified in AIM 1 was determined using Stata statistical software.[77] Assuming a non-inferiority margin of 10 points on the CAPS (see rationale noted above) and the typical alpha for a one-sided non-inferiority test (.025),[75] a total sample of 126 participants, (63 PTSD patients per randomization arm) resulted in a power estimate of 80%. *Sample size calculations were unchanged using the CAPS-5 measure as described above.* To protect against the effects of attrition, we added 26% to this final sample size for a recruitment goal of 170 patients. This attrition estimate was based on our pilot study assessing longitudinal outcomes of LKM.

In a preliminary analysis of our LKM pilot data (see preliminary studies section), the intraclass correlation (ICC) for PTSD symptoms (using the PSS-I; n=42) was ρ= 0.00 and for depression (using the PROMIS measure) was 0.026 (p = NS for both). Additionally, pilot data based on the VAPSHCS MBSR program showing an ICC for PTSD symptoms (using the PCL; n=118) of ρ= 0.00 at post-treatment and ρ= 0.05 at follow-up (p = NS). Because our pilot data obtained at our site do not indicate significant correlation of measures within groups, we propose analyses that do not incorporate ICC results and are not powered to account for them.

Exploratory AIM: Mediators of response to LKM and CPT-C

To assess mediation, we will first assess temporality of change of the proposed mediators and outcomes (as described below). If it is established that changes in the proposed mediators precede changes in depressive and PTSD symptoms, we will assess mediation using an analytic framework developed for use in randomized controlled trials of two interventions with equivalent outcomes.[19] The framework developed by Gallagher and Resick[19] (described in more detail below) allows assessment of whether two interventions produce similar outcomes through different mediational processes. In the proposed trial comparing LKM to CPT-C, the two interventions share many common factors, but differ in the focus of the intervention (i.e., LKM emphasizes self-compassion without a focus on cognitive restructuring, whereas CPT-C places a primary emphasis on correcting maladaptive cognitions without a primary focus of developing self-compassion). We propose to examine mechanisms of change for each intervention by assessing intraindividual change in self-compassion and maladaptive cognitions, and then to examine whether intraindividual change in the proposed mediators mediates outcomes (PTSD symptoms, depressive symptoms).

Establishment of Temporal Sequence of Change in Mediators and Outcome Measures: To assess mediation, it is important to assess whether changes in the proposed mediators (self-compassion, posttraumatic maladaptive cognitions) precede change in clinical outcomes (PTSD and depressive symptoms).[78] Weekly measures will be obtained during the treatment phase, in order to provide an assessment schedule that allows measurement of the mediators before improvement occurs in clinical outcomes (PTSD and depressive symptoms). The temporal relationship between the proposed mediators and clinical outcomes will be analyzed according to methods defined by Kleim and colleagues (2012)[44] using bivariate latent growth modeling. Briefly, this first involves modeling weekly latent change processes in mediators and outcomes separately, to find the best representation of latent trajectories. A dual linear growth curve is then calculated, in which latent growth curves are simultaneously estimated for the proposed mediators and the clinical outcomes. Next, the degree to which change in the proposed mediator at week X is associated with change in PTSD at week X+1 (as well as the inverse to test whether changes in depressive/PTSD symptoms predict changes in the proposed mediators) is evaluated to examine whether the requirement of change in the mediator preceding change in the outcome is met. This process assesses whether a larger than average change on one variable is associated with a larger than average change on the other variable at a later time point. Within this framework, when, for example a greater reduction in posttraumatic maladaptive cognitions is associated with a greater reduction in PTSD symptoms in the next session, it is assumed that changes in the first variable cause changes in the second variable. These models will be utilized to determine the optimal time points (from baseline) to assess change scores in mediators and outcomes for the mediation models described below.

Mediation: Within-treatment intraindividual changes will first be analyzed for self-compassion, maladaptive cognitions, PTSD and depression using difference scores (each week's score minus baseline score for each measure) using procedures defined by Gallagher and Resick (2012).[19] The degree to which change in self-compassion mediates change in outcome in LKM relative to CPT-C will be evaluated by examining the indirect effect of treatment condition (LKM vs. CPT-C) on intraindividual change in PTSD symptoms via intraindividual change in self-compassion.

These procedures will be repeated to evaluate the degree to which change in maladaptive cognitions

828 mediates change in CPT-C relative to LKM by examining the indirect effect of treatment condition (CPT-C vs.
829 LKM) on intraindividual change in PTSD symptoms via intraindividual change in maladaptive cognitions. The
830 above analysis will be repeated for depressive symptoms.
831   Indirect effects will be calculated to yield bias-corrected and accelerated bootstrapped confidence
832 intervals of indirect effects. If the confidence interval of the indirect effect does not include zero, mediation will
833 be shown.
834
835 **Project Timeline**
836 Approximately 20-22 Veterans will be recruited for each of the 12 study cohorts. The first cohort will undergo
837 baselines assessments in month 5 (following a 4-month recruitment phase). Cohorts will be approximately
838 evenly distributed over the course of the study. We have previously been successful in obtaining timely
839 regulatory approvals for LKM and MBSR studies at VAPSHCS, including the two randomized pilot trials
840 described in the preliminary studies section.
841
842 **Limitations**
843   The study design is a fairly ambitious one with a weekly monitoring feature that could pose challenges for
844 retention and compliance with the research protocol. A modest remuneration schedule is likely to help maintain
845 compliance with the study protocol, and our previous research with PTSD and alcohol dependent individuals
846 examining frequent monitoring has shown excellent compliance. Other design considerations include the
847 inclusion of male and female participants with mixed trauma histories and inclusion of individuals with
848 Substance Abuse and/or Alcohol Dependence (AD). Briefly, most PTSD treatment trials have involved fairly
849 homogeneous samples, which while likely reducing experimental noise, also limit the generalizability of the
850 findings. We felt that the ability to obtain data that has a chance of being highly generalizable to Veterans who
851 are seeking care for PTSD, which is more often than not associated with comorbid conditions,[16] was preferable
852 to maintaining strict experimental control. In addition, we have successfully delivered LKM in mixed-gender
853 groups and our clinical impression is that both the male and the female Veterans benefited from the exposure
854 to the opposite gender in this therapeutic context.

855   Another design consideration is that each of the two interventions will be delivered in closed-group
856 format and there is some risk that people within each of the groups will influence one another to the extent that
857 there are group effects on outcomes.[79] If ICC's are significant in the proposed study, this would result in
858 decreased statistical power to detect the primary outcomes.
859
860   Despite limitations the proposed research has considerable conceptual and clinical merit and represents a
861 necessary step in examining whether LKM is associated with clinical benefit for Veterans with PTSD. Results
862 of this research can be readily applied in both VA and community settings to treat PTSD.

863
864
865 **Application Summary**
866
867   The proposed research is an extension of our previous and ongoing work. This application will address
868 a relative void in the intervention literature for PTSD by assessing the non-inferiority of a standardized
869 meditation intervention, LKM. In light of the growing interest in complementary and alternative medicine among
870 Veterans and the lack of empirical data on such approaches for common disorders, such as PTSD, this
871 research will make an important contribution to the field. We believe the proposed research is timely,
872 important, and innovative, and the track records of Drs. Kearney and Simpson and the research team indicate
873 we are capable of successfully carrying out and completing the proposed work.
874

875   1.   Kessler RC. Posttraumatic stress disorder: the burden to the individual and to society. *Journal of*
876   *Clinical Psychiatry.* 2000;61:4-12 (suppl 15).
877   2.   Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the
878   national comorbidity survey. *Archives of General Psychiatry.* 1999;56(7):617-626.
879   3.   Davidson JRT. Recognition and treatment of posttraumatic stress disorder. *Jama-Journal of the*
880   *American Medical Association.* 2001;286(5):584-588.
881   4.   Braet C, Claus L, Goossens L, Moens E, Van Vlierberghe L, Soetens B. Differences in eating style
882   between overweight and normal-weight youngsters. *Journal of Health Psychology.* 2008;13(6):733-743.
883   5.   Wachen JS, Resick P, Mintz, et al. Group Cognitive Processing Therapy for Combat-Related Post-
884   Traumatic Stress Disorder: Main Findings on PTSD and Depression. International Society for Traumatic
885   Stress Studies; November 2, 2012, 2012; Los Angeles, CA.
886   6.   Lombardo TW. Beyond Exposure for Posttraumatic Stress Disorder (PTSD) Symptoms: Broad-
887   Spectrum PTSD Treatment Strategies. *Behavior Modification.* 2005;29(1):3-9.
888   7.   Baldwin CM, Long K, Kroesen K, Brooks AJ, Bell IR. A profile of military veterans in the southwestern
889   United States who use complementary and alternative medicine - Implications for integrated care.
890   *Archives of Internal Medicine.* 2002;162(15):1697-1704.
891   8.   Kroesen K, Baldwin CM, Brooks AJ, Bell IR. US military veterans' perceptions of the conventional
892   medical care system and their use of complementary and alternative medicine. *Family Practice.*
893   2002;19(1):57-64.
894   9.   Fredrickson BL, Cohn MA, Coffey KA, Pek J, Finkel SM. Open hearts build lives: Positive emotions,
895   induced through loving-kindness meditation, build consequential personal resources. *Journal of*
896   *Personality and Social Psychology.* 2008;95(5):1045-1062.
897   10.   Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System
898   (PROMIS) Progress of an NIH roadmap cooperative group during its first two years. *Medical Care.*
899   2007;45(5):S3-S11.
900   11.   Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six Patient-
901   Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer
902   patients. *Journal of Clinical Epidemiology.* 2011;64(5):507-516.
903   12.   *American Psychiatric Association [DSM-IV-TR].* Washington, DC2000.
904   13.   Davidson JRT, Stein DJ, Shalev AY, Yehuda R. Posttraumatic stress disorder: acquisition, recognition,
905   course, and treatment. *Journal of Neuropsychiatry & Clinical Neurosciences.* 2004;16(2):135-147.
906   14.   Thomas JL, Wilk JE, Riviere LA, McGurk D, Castro CA, Hoge CW. Prevalence of Mental Health
907   Problems and Functional Impairment Among Active Component and National Guard Soldiers 3 and 12
908   Months Following Combat in Iraq. *Archives of General Psychiatry.* 2010;67(6):614-623.
909   15.   Eisen SA, Griffith KH, Xian H, et al. Lifetime and 12-month prevalence of psychiatric disorders in 8,169
910   male Vietnam War era veterans. *Military Medicine.* 2004;169(11):896-902.
911   16.   Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic-stress-disorder in the
912   national comorbidity survey. *Archives of General Psychiatry.* 1995;52(12):1048-1060.
913   17.   Cougle JR, Resnick H, Kilpatrick DG. PTSD, DEPRESSION, AND THEIR COMORBIDITY IN
914   RELATION TO SUICIDALITY: CROSS-SECTIONAL AND PROSPECTIVE ANALYSES OF A
915   NATIONAL PROBABILITY SAMPLE OF WOMEN. *Depression and Anxiety.* 2009;26(12):1151-1157.
916   18.   Schoenfeld FB, Marmar CR, Neylan TC. Current concepts in pharmacotherapy for posttraumatic stress
917   disorder. *Psychiatric Services.* 2004;55(5):519-531.
918   19.   Gallagher MW, Resick PA. Mechanisms of Change in Cognitive Processing Therapy and Prolonged
919   Exposure Therapy for PTSD: Preliminary Evidence for the Differential Effects of Hopelessness and
920   Habituation. *Cognitive Therapy and Research.* 2012;36(6):750-755.
921   20.   Schnurr PP, Friedman MJ, Engel CC, et al. Cognitive behavioral therapy for posttraumatic stress
922   disorder in women - A randomized controlled trial. *Jama-Journal of the American Medical Association.*
923   2007;297(8):820-830.
924   21.   Rosen CS, Chow HC, Finney JF, et al. VA practice patterns and practice guidelines for treating
925   posttraumatic stress disorder. *Journal of Traumatic Stress.* 2004;17(3):213-222.
926   22.   Karlin BE, Ruzek JI, Chard KM, et al. Dissemination of Evidence-Based Psychological Treatments for
927   Posttraumatic Stress Disorder in the Veterans Health Administration. *Journal of Traumatic Stress.*
928   2010;23(6):663-673.

929   23.   Saydah SH, Eberhardt MS. Use of complementary and alternative medicine among adults with chronic
930   diseases: United States 2002. *Journal of Alternative and Complementary Medicine.* 2006;12(8):805-
931   812.
932   24.   Micek MA, Bradley KA, Braddock CH, Maynard C, McDonell M, Fihn SD. Complementary and
933   alternative medicine use among veterans affairs outpatients. *Journal of Alternative and Complementary*
934   *Medicine.* 2007;13(2):190-193.
935   25.   Neff KD, Rude SS, Kirkpatrick KL. An examination of self-compassion in relation to positive
936   psychological functioning and personality traits. *J Res Pers.* 2007;41(4):908-916.
937   26.   Krupnick JL, Green BL, Stockton P, Miranda J, Krause E, Mete M. Group interpersonal psychotherapy
938   for low-income women with posttraumatic stress disorder. *Psychotherapy Research.* 2008;18(5):497-
939   507.
940   27.   Thompson BL, Waltz J. Self-Compassion and PTSD Symptom Severity. *Journal of Traumatic Stress.*
941   2008;21(6):556-558.
942   28.   Gilbert P, Procter S. Compassionate mind training for people with high shame and self-criticism:
943   overview and pilot study of a group therapy approach. *Clinical Psychology & Psychotherapy.*
944   2006;13(6):353-379.
945   29.   Carson JW, Keefe FJ, Lynch TR, et al. Loving-kindness meditation for chronic low back pain. *Journal of*
946   *Holistic Nursing.* 2005;23(3):287-304.
947   30.   Hutcherson CA, Seppala EM, Gross JJ. Loving-Kindness Meditation Increases Social Connectedness.
948   *Emotion.* 2008;8(5):720-724.
949   31.   Johnson DP, Penn DL, Fredrickson BL, Meyer PS, Kring AM, Brantley M. Loving-kindness meditation
950   to enhance recovery from negative symptoms of schizophrenia. *Journal of Clinical Psychology.*
951   2009;65(5):499-509.
952   32.   Salzberg S. *Lovingkindness: the revolutionary art of happiness.* Boston, MA: Shambhala Publications,
953   Inc.; 1995.
954   33.   Foa EB, Riggs DS. Posttraumatic stress disorder and rape. *American Psychiatric Press Review of*
955   *Psychiatry.* 1993;12:273-303.
956   34.   Herman J. *Trauma and Recovery: The Aftermath of Violence--from Domestic Abuse to Political Terror.*
957   Basic Books; 1997.
958   35.   King LA, King DW, Fairbank JA, Keane TM, Adams GA. Resilience-recovery factors in post-traumatic
959   stress disorder among female and male Vietnam veterans: Hardiness, postwar social support, and
960   additional stressful life events. *Journal of Personality and Social Psychology.* 1998;74(2):420-434.
961   36.   Fredrickson BL. The broaden-and-build theory of positive emotions. *Philosophical Transactions of the*
962   *Royal Society of London Series B-Biological Sciences.* 2004;359(1449):1367-1377.
963   37.   Johnson KJ, Fredrickson BL. "We all look the same to me" - Positive emotions eliminate the own-race
964   bias in face recognition. *Psychological Science.* 2005;16(11):875-881.
965   38.   Rounsaville BJ, Carroll KM, Onken LS. A Stage Model of Behavioral Therapies research: Getting
966   started and moving on from stage I. *Clinical Psychology-Science and Practice.* 2001;8(2):133-142.
967   39.   Neff KD. The development and validation of a scale to measure self-compassion. *Self and Identity.*
968   2003;2:223-250.
969   40.   Leary MR, Tate EB, Adams CE, Allen AB, Hancock J. Self-compassion and reactions to unpleasant
970   self-relevant events: the implications of treating oneself kindly. *Journal of Personality and Social*
971   *Psychology.* 2007;92(5):887-904.
972   41.   Kuyken W, Watkins E, Holden E, et al. How does mindfulness-based cognitive therapy work? *Behav*
973   *Res Ther.* 2010;48(11):1105-1112.
974   42.   Resick PA, Schnicke MK. Cognitive Processing Therapy for Sexual Assault Victims. *Journal of*
975   *Consulting and Clinical Psychology.* 1992;60(5):748-756.
976   43.   Resick PA, Galovski TE, Uhlmansiek MO, Scher CD, Clum GA, Young-Xu Y. A Randomized clinical
977   trial to dismantle components of cognitive processing therapy for posttraumatic stress disorder in
978   female victims of interpersonal violence. *Journal of Consulting and Clinical Psychology.*
979   2008;76(2):243-258.
980   44.   Kleim B, Grey N, Wild J, et al. Cognitive Change Predicts Symptom Reduction With Cognitive Therapy
981   for Posttraumatic Stress Disorder. *Journal of Consulting and Clinical Psychology.* 2012;Advance online
982   publication.
983   45.   Longmore RJ, Worrell M. Do we need to challenge thoughts in cognitive behavior therapy? *Clin*
984   *Psychol Rev.* 2007;27(2):173-187.

985 46. Tsuang MT, Simpson JC, Koenen KC, Kremen WS, Lyons MJ. Spiritual well-being and health. *Journal*
986   *of Nervous and Mental Disease.* 2007;195(8):673-680.
987 47. Litz BT, Gray MJ. Emotional numbing in posttraumatic stress disorder: current and future research
988   directions. *Australian and New Zealand Journal of Psychiatry.* 2002;36(2):198-204.
989 48. Resick PA, Monson CM, Chard KM. *Cognitive processing therapy: Veteran/military version.*
990   Washington, DC: Department of Veterans Affairs;2008.
991 49. Resick P. Cognitive therapy for posttraumatic stress disorder. *Journal of cognitive Psychotherapy.*
992   2001;15(4):321-329.
993 50. Resick PA, Nishith P, Weaver TL, Astin MC, Feuer CA. A comparison of cognitive-processing therapy
994   with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress
995   disorder in female rape victims. *Journal of Consulting and Clinical Psychology.* 2002;70(4):867-879.
996 51. Monson CM, Schnurr PP, Resick PA, Friedman MJ, Young-Xu Y, Stevens SP. Cognitive processing
997   therapy for veterans with military-related posttraumatic stress disorder. *Journal of Consulting and*
998   *Clinical Psychology.* 2006;74(5):898-907.
999 52. Bernardy NC, Hamblen JL, Friedman MJ, Ruzek JI, McFall ME. Implementation of a posttraumatic
000   stress disorder mentoring program to improve treatment services. *Psychological Trauma: Theory,*
001   *Research, Practice, and Policy.* 2011;3(3):292.
002 53. Seal KH, Bertenthal D, Miner CR, Sen S, Marmar C. Bringing the war back home - Mental health
003   disorders among 103 788 US veterans returning from Iraq and Afghanistan seen at Department of
004   Veterans Affairs facilities. *Archives of Internal Medicine.* 2007;167(5):476-482.
005 54. Hollon SD, Munoz RF, Barlow DH, et al. Psychosocial intervention development for the prevention and
006   treatment of depression: Promoting innovation and increasing access. *Biological Psychiatry.*
007   2002;52(6):610-630.
008 55. Imel ZE, Wampold BE, Miller SD, Fleming RR. Distinctions Without a Difference: Direct Comparisons of
009   Psychotherapies for Alcohol Use Disorders. *Psychology of Addictive Behaviors.* 2008;22(4):533-543.
010 56. MacCoon DG, Imel ZE, Rosenkranz MA, et al. The validation of an active control intervention for
011   Mindfulness Based Stress Reduction (MBSR). *Behav Res Ther.* 2012;50(1):3-12.
012 57. Weathers FW, Keane TM, Davidson JR. Clinician-administered PTSD scale: a review of the first ten
013   years of research. *Depression & Anxiety.* 2001;13(3):132-156.
014 58. Scott CK, Sonis J, Creamer M, Dennis ML. Maximizing follow-up in longitudinal studies of traumatized
015   populations. *Journal of Traumatic Stress.* 2006;19(6):757-769.
016 59. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI):
017   The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10.
018   *Journal of Clinical Psychiatry.* 1998;59:22-33.
019 60. Blake DD, Weathers FW, Nagy LM, et al. The development of a clinician-administered PTSD scale.
020   *Journal of Traumatic Stress.* 1995;8(1):75-90.
021 61. Raes F, Pommier E, Neff KD, Van Gucht D. Construction and Factorial Validation of a Short Form of
022   the Self-Compassion Scale. *Clinical Psychology & Psychotherapy.* 2011;18(3):250-255.
023 62. Foa EB, Ehlers A, Clark DM, Tolin DF, Orsillo SM. The Posttraumatic Cognitions Inventory (PTCI):
024   Development and validation. *Psychological Assessment.* 1999;11(3):303-314.
025 63. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. The PTSD Checklist (PCL): Reliability,
026   validity, and diagnostic utility. Paper presented at the 9th Annual Meeting of the International Society for
027   Traumatic Stress Studies; 1993; San Antonio, TX.
028 64. Weathers FW, Bovin MJ, Lee DJ, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5):
029   Development and initial psychometric evaluation in military veterans. *Psychol Assess.* 2018;30(3):383-
030   395.
031 65. Fries JF, Krishnan E. What constitutes progress in assessing patient outcomes? *Journal of Clinical*
032   *Epidemiology.* 2009;62(8):779-780.
033 66. Cook KF, Kallen MA, Amtmann D. Having a fit: impact of number of items and distribution of data on
034   traditional criteria for assessing IRT's unidimensionality assumption. *Quality of Life Research.*
035   2009;18(4):447-460.
036 67. Atkins DC. Using multilevel models to analyze couple and family treatment data: Basic and advanced
037   issues. *Journal of Family Psychology.* 2005;19(1):98-110.
038 68. Little R, Rubin D. *Statistical analysis with missing data.* New York: Wiley; 1987.
039 69. Raudenbush SW, Bryk AS. *Hierarchichal linear models.* Thousand Oaks, CA: Sage; 2002.

040 70. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJW, Grp C. Reporting of noninferiority and
041   equivalence randomized trials - An extension of the CONSORT Statement. *Jama-Journal of the*
042   *American Medical Association.* 2006;295(10):1152-1160.
043 71. Schnurr PP, Friedman MJ, Foy DW, et al. Randomized trial of trauma-focused group therapy for
044   posttraumatic stress disorder - Results from a Department of Veterans Affairs Cooperative Study.
045   *Archives of General Psychiatry.* 2003;60(5):481-489.
046 72. Marx BP. In:2019.
047 73. Greene CJ, Morland LA, Durkalski VL, Frueh BC. Noninferiority and Equivalence Designs: Issues and
048   Implications for Mental Health Research. *Journal of Traumatic Stress.* 2008;21(5):433-439.
049 74. Swanholm E, McDonald W, Makris U, Noe C, Gatchel R. Estimates of Minimally Important Differences
050   (MIDs) for Two Patient-Reported Outcomes Measurement Information System (PROMIS) Computer-
051   Adaptive Tests in Chronic Pain Patients. 2014;19(4):217-232.
052 75. Laster LL, Johnson MF, Kotler ML. Non-inferiority trials: the 'at least as good as' criterion with
053   dichotomous data. *Statistics in Medicine.* 2006;25(7):1115-1130.
054 76. Mascha EJ, Sessler DI. Equivalence and Noninferiority Testing in Regression Models and Repeated-
055   Measures Designs. *Anesthesia and Analgesia.* 2011;112(3):678-687.
056 77. *SSI: Stata module to estimate sample size for randomized controlled trials, Statistical Software*
057   *Components S457150* [computer program]. Boston College Department of Economics; 2010.
058 78. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. In: *Annual Review of*
059   *Clinical Psychology.* Vol 3.2007:1-27.
060 79. Baldwin SA, Murray DM, Shadish WR. Empirically supported treatments or type I errors? Problems with
061   the analysis of data from group-administered treatments. *Journal of Consulting and Clinical*
062   *Psychology.* 2005;73(5):924-935.
063