A Proof of Concept and Feasibility Trial of Compassion Meditation for PTSD

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Clinical Intervention Study Protocol

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PRÉCIS

Study Title

A Proof of Concept and Feasibility Trial of Compassion Meditation for PTSD

Objectives

1. To refine an existing compassion meditation protocol for PTSD by evaluating participants' reactions to the intervention components and refining the practices to maximize engagement and induction of cognitive/emotional states that are most likely to counteract PTSD.
2. To evaluate the acceptability of and refine a likely future control condition (i.e., relaxation).
3. To identify the best strategies by which to recruit and retain subjects (including women) in the protocol.
4. To evaluate the feasibility of conducting compassion meditation as an intervention for PTSD.
5. To establish preliminary estimates of effect size and other parameters to inform future efficacy studies of compassion meditation.
6. To identify potential mechanisms of action and predictors of response.

Design and Outcomes

This project is a feasibility and proof of concept study of compassion meditation (CM) for Veterans with posttraumatic stress disorder (PTSD; N ≈ 100). Phase 1 (N ≈ 60, nonrandomized), Protocol Refinement, will consist of up to 4 CM and 2 Relaxation groups with 6-12 participants in each group. Iterative refinement of the treatment protocols will be done based on quantitative and qualitative data from participants. Phase 2 (N ≈ 40), Pilot Evaluation is a randomized controlled study with 4 groups (2 CM and 2 relaxation groups, 6-12 in each group) to examine the feasibility of a randomized trial and to estimate response to CM.

Interventions and Duration

The interventions to be compared are CM and Relaxation Training.

- CM is a meditative practice focused on the wish that others and the self may be free of suffering. The Compassion Meditation Protocol was developed by consultant Geshe Lobsang Negi, PhD. It consists of 8 2-hour sessions and accompanying at home practice. The intervention begins with basic breathing-focused meditation and awareness of internal experience. Participants go on to cultivate compassion toward the self and others.
- The Relaxation Training Protocol utilized herein was used in Taylor et al.'s (2003) PTSD trial. It will be delivered in 8 2-hour sessions with accompanying at home practice. Participants will be taught a variety of relaxation techniques and how to apply these to enhance coping with daily stressors and symptoms.

Participant participation will be approximately 3 months. Baseline evaluation will be completed within 1 month of the beginning of the treatment groups. Groups will last 8 weeks, and post-treatment assessment will be completed at the end of the groups.

Sample Size and Population
Participants in both phases will be Veterans with PTSD who are able to consent and willing to participate (refer to Human Subjects for detailed inclusion/exclusion criteria). In Phase 1, we will run up to 4 CM groups and 2 relaxation groups; we will aim for a group size of 6-12 in each group. In Phase 2, we will conduct a pilot study with random assignment to 4 groups (2 CM and 2 relaxation groups, 6-12 in each group. We estimate that 60 people will take part in Phase 1 of the research, and approximately 40 participants in Phase 2, for a total sample size of approximately 100 people.

1. STUDY OBJECTIVES

1.1 Primary Objective
1. To refine an existing compassion meditation protocol for PTSD by evaluating participants' reactions to the intervention components and refining the practices to maximize engagement and induction of cognitive/emotional states that are most likely to counteract PTSD.
2. To evaluate the acceptability of and refine a likely future control condition (i.e., relaxation).
3. To evaluate the feasibility of conducting compassion meditation as an intervention for PTSD.
4. To establish preliminary estimates of effect size and other parameters to inform future efficacy studies of compassion meditation.

1.2 Secondary Objectives
1. To identify the best strategies by which to recruit and retain subjects (including women) in the protocol.
2. To identify potential mechanisms of action and predictors of response.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus
PTSD is a psychopathological response to exposure to a traumatic stressor and is characterized by recurrent re-experiencing of the event, avoidance of reminders of the trauma, negative alterations in mood and cognitions, and increased arousal (American Psychiatric Association, 2014). The disorder typically follows a chronic course and leads to significant work and social impairment and increased healthcare utilization (e.g., Hidalgo & Davidson, 2000; Jaycox & Foa, 1999; Stein, McQuaid, Pedrelli, Lenox & McCahill, 2000). Although there are psychotherapies that effectively reduce PTSD symptoms, additional approaches are needed because no single intervention is universally effective, acceptable and/or feasible (Bradley, Greene, Russ, Dutra, & Westen, 2005; Schottenbauer, Glass, Arnkoff, Tendick & Gray, 2008).

There is a strong demand by patients and clinicians for complementary and alternative treatments such as meditation for the amelioration of symptoms of posttraumatic stress disorder (PTSD). Mental health problems are among the most frequently cited reasons for seeking help from a complementary and alternative medicine provider (Strauss, Coeytaux, McDuffie, Nagi, & Williams, 2011) and a recent national survey shows that 40% of patients with PTSD used a

complementary and alternative medicine approach in the past year, with meditation being one of the most commonly used approaches (Libby, Pilver, & Desai,, 2012). In spite of this, there is little empirical evidence to support their use. Compassion meditation, which is a meditative practice that focuses on the wish that the self and others be free of suffering, has been associated with positive changes in nonclinical samples. In particular, compassion meditation has been shown to increase positive emotion and social connectedness, both of which are areas of deficit for individuals with PTSD. However, CM has never been evaluated in relation to PTSD.

2.2 Study Rationale

A variety of meditation techniques are currently being used to address mental and physical health issues, and several studies show that meditation is acceptable to Veterans with PTSD (Bormann et al., 2011; Kearney et al., 2012; Niles et al., 2012). It may be unwise, however, to view all meditative practices as interchangeable. For example, baseline brain activation appears to predict the type of meditation (mindfulness or compassion meditation) in which an individual will engage (Mascaro, Rilling, Negi, & Raison, 2013b).

We hypothesize that CM will relieve PTSD symptoms and improve quality of life by fostering positive emotion and social connectedness, processes that are negatively impacted by PTSD. Evidence for this hypothesis comes from observed responses to CM and loving kindness meditation (LKM), a closely related approach. Hutcherson, Seppala and Gross (2008) compared a 7-minute LKM exercise to an imagery exercise and found that even this very brief intervention, as compared to imagery, led to increased positive mood and decreased negative mood. Beneficial effects are also observed when LKM is delivered over multiple sessions as an intervention. LKM delivered in six 60-minute sessions over 7 weeks to workers (n = 102), led to increased positive emotion as compared to WL control (n = 100) (Fredrickson, Cohn, Coffey, Pek, & Finkel, 2008). Results from a small pilot study (n = 18) of LKM for negative symptoms of schizophrenia showed that the practice increased positive emotion and decreased negative emotion (Garland et al. 2010) and indicates that this technique can induce positive emotion in clinical samples. Evidence from functional MRI shows activation in areas typically associated with positive affect (left medial prefrontal cortex and anterior cingulate gyrus) in an expert meditator engaged in CM (Engstrom & Söderfeldt, 2010). Positive emotions are thought to enhance coping (Fredrickson, 2001) and have been associated with resilience, i.e., the ability to recover from negative experiences and to change based on situational demands (Tugade & Fredrickson, 2004). In particular, positive emotions have been tied to the process of coping with highly stressful events. For example, Fredrickson and colleagues (2003) found that positive emotions were a critical component in resilience among college students after the September 11 terrorist attacks. Similarly, bereaved caregivers who experienced positive emotion during their grief found more positive meaning in their loss and demonstrated more long-term goal-setting and planning, which corresponded to greater well being 12 months later (Moskowitz, 2001). CM is also thought to enhance social connectedness. LKM has been associated with more positive explicit and implicit reactions to others (Hutcherson et al., 2008), and CM is linked to increased empathic accuracy and activation or associated brain circuitry (Mascaro, Rilling, Negi, & Raison, 2013a). A sense of connection, or belongingness, is associated with better psychological and social functioning (Hagerty, Williams, Coyne, & Early, 1996), including reduced anxiety and greater self-esteem (Lee & Robbins, 1998), and may have a protective effect against stress, depression and PTSD (see, for example Cacioppo, Hughes, Waite, Hawkley, & Thisted, 2006; Cacioppo & Patrick, 2008). Conversely, social isolation may be the strongest and most reliable predictor of suicidal

thoughts and behavior (Van Orden et al., 2010) and deficits in empathy have been associated with verbal aggression in v eterans with PTSD (Teten, Miller, Bailey, Dunn, & Kent, 2008).

CM has not been specifically evaluated for PTSD but has been applied for stress reduction and in one clinical sample. Pace et al. (2009) recruited 61 college students into a study comparing CM and health education discussion. Participants were assessed using a standardized stress test (public speaking followed by mental arithmetic) and physiological measures. The more students practiced meditation at home, the less distress they reported after the stress test. In the single study with a psychiatric population, Johnson et al. (2011) conducted a pilot study of LKM with individuals diagnosed with schizophrenia-spectrum disorders (n = 18). Eighty-eight percent completed the treatment, and the practice was perceived to be easy, enjoyable and useful. Participants actively engaged in the meditation, practicing an average of 3.7 days per week. LKM was associated with a large effect size increase in positive emotion and life satisfaction, a large effect size reduction in negative symptoms and anhedonia, and a medium effect size reduction in asociality. These gains generally were maintained over a 3 month follow-up period (Johnson et al., 2011). Finally, Carson et al. (2005) applied LKM for low back pain. They found that, as compared to standard care, LKM led to reduced general psychological distress, anxiety and hostility after the intervention and 3 months later.

Interventions. The initial CM group for Phase I of this study will follow the existing Emory Compassion Meditation Protocol. The protocol will be iteratively refined until we have a version (and accompanying manual) that has been optimized for veterans. This final version will be used in Phase 2.

Relaxation Training was selected as the control condition. It was selected because it is a good match for nonspecific aspects of the meditative practice (e.g., attention, support, contact with a mental health provider) and it is structurally similar to meditation (e.g., restful, in session and at home exercises).

Both groups will be delivered in 8 two-hour sessions by a trained therapist.

3. STUDY DESIGN

Design. The proposed project is a feasibility and proof of concept study of compassion meditation (CM) for posttraumatic stress disorder (PTSD). Phase 1 ($N \approx 60$, nonrandomized), Protocol Refinement, will consist of up to 4 CM and 2 Relaxation groups with 6-12 participants in each group. Iterative refinement of the treatment protocols will be done based on quantitative and qualitative data from participants. Phase 2 ($N \approx 40$), Pilot Evaluation is a randomized controlled study with 4 groups (2 CM and 2 relaxation groups, 6-12 in each group) to examine the feasibility of a randomized trial and to estimate response to CM.

Outcomes. In Phase 1, outcomes will include treatment credibility, qualitative reactions to groups, time spent practicing, satisfaction, emotional responding, social connectedness, self-compassion and heart rate variability (HRV).

Study population and groups. Participants in both phases will be Veterans with PTSD who are able to consent and willing to participate. Co-occurring disorders such as depression, anxiety, or treated substance abuse or dependence problems are permitted provided that PTSD is the primary presenting complaint. We estimate that 60 people will take part in Phase 1 of the research and approximately 40 participants in the second phase, for a total sample size of approximately 100 people.

Study location. The study will take place at the VA San Diego Healthcare System, with groups conducted at the Oceanside Mental Health Clinic.

Duration. Phase 1 will last approximately 18 months, with 6 months of therapist training and 12 months of recruitment and delivery of the interventions. Phase 2 will last approximately 12 months. For a given participant, involvement in the study will last approximately 3 months, including assessments before and after the group and the 8-week intervention.

Interventions. The first CM group in Phase 1 will follow the existing Emory Compassion Meditation Protocol. This well-developed protocol has been used extensively with non-clinical populations but some initial refinement will be done to assure that the material is accessible to veterans. The subsequent groups will be delivered using the protocol version developed with the prior group until a well-received protocol has been established. The initial relaxation group will follow Dr. Taylor's protocol with minor modification to match the timeline of the CM protocol (i.e., extending sessions from 90 minutes to 2 hours and providing similar amounts of homework) and modality of administration (group rather than individual). If necessary, this protocol will be refined based on participant feedback as well. The final versions of the protocols will be employed in Phase 2. Both types of groups will be conducted in person by a trained licensed clinical psychologist in eight 2-hour sessions.

Randomization. There is no randomization in Phase 1. In Phase 2, groups will be randomized in a 1:1 allocation ratio to CM or Relaxation Training; no stratification will be used. The assessor will be kept blind to treatment condition. Random assignment of groups to study conditions will be conducted by study statistician, Dr. Golshan, after the groups have been formed. Prior to enrollment, the study statistician will write a program in SPSS (IBM Software Group. SPSS User' Guide, Version 21. Chicago, Il, 2013) to create a list of subject identification numbers with randomized treatment assignments (2 CM and 2 relaxation groups), which will be held by the unblended project coordinator during the trial. Variable blocked randomization will be used with random block size (4 or 6). Separate lists (up to 4) of replacement subject identification numbers will also be created so that replacement subjects are assigned the same treatment as subjects they are replacing. Subjects will be randomized to study treatment group in a 1:1 ratio.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

To be included in this study, an individual must be a (1) veteran of (2) at least 18 years of age with (3) PTSD as defined by DSM-5 and the (4) capacity to consent and (5) capacity/willingness to comply with study procedures. We expect the demographic make-up to approximate that of the VASDHS, which has a majority men and Caucasians. Co-occurring disorders such as depression, anxiety, or treated substance abuse or dependence problems are permitted provided that PTSD is the primary presenting complaint. There will not be a restriction on concomitant medication use, but the individual's provider must not anticipate changes during the study period. There is no restriction on prior therapy experience but an individual may not be simultaneously receiving another psychosocial treatment to address PTSD. Pregnant women will not be excluded and contraception is not necessary as there is no known risk to the woman or fetus associated with meditation or relaxation. No additional protections are needed.

4.2 Exclusion Criteria

The following are criteria for exclusion: (1) serious suicidality or homicidality that has required urgent or emergent evaluation or treatment within the past three months, (2) a known, untreated substance use disorder (inclusion is possible if there is evidence that the individual has been afforded and is complying with treatment for the substance problem), (3) serious Axis I mental disorders, such as psychotic disorders or bipolar type I, or serious dissociative symptoms (4) cognitive impairment that would interfere with consent or treatment, (5) circumstances that lead to recurrent traumatization (e.g., engaged in a violent relationship) and (6) concurrent enrollment in any other treatment specifically targeting PTSD symptoms or social functioning (e.g., couples therapy). Participants can continue current pharmacological treatment (provided they have stabilized on medication, i.e., no additional treatment response is expected, and that no changes are anticipated during the study period) or any supportive or nonspecific therapy. If a participant is institutionalized or imprisoned during the course of the study, he/she will be withdrawn. Pregnant women will not be excluded from the study.

4.3 Study Enrollment Procedures

Potential participants will be recruited from VA mental health clinics and the community. We will interface with staff at the VA Medical Center, VA Oceanside Community Based Outpatient Clinic, and Vet Center clinics to encourage referral of interested patients to the study. Clinicians will introduce the study to their patient and if the veteran is interested will give his/her permission to pass their name and phone number to the study coordinator. We will use a tool adapted from other approved VA studies that provides a summary of the study objectives, lists patient's name and phone number and that the patient initials. This tool will be given to the study coordinator. We will also recruit from the community through posting flyers in local mental health clinics, by use of advertisements in periodicals (especially those that focus on complementary and alternative healing practices) and via Web-based resources. The coordinator will maintain a study log to document the source of all potential participants; we will match this information with data about whether or not they participated and, if not, reasons for ineligibility to subsequently analyze the effectiveness of various recruitment practices.

This study will be conducted at the VA Medical Center in compliance with Title 45 Part 46 of the CFR pertaining to protection of human subjects. Signed consent documents for VA subjects use VA form 10-1086. Consenting will take place at the Oceanside VA clinic with a trained assessor/study coordinator in a private room and the participant will be given ample time to read the consent form and ask questions. At the first visit, prior to initiation of any study-related procedures, subjects will give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, risks, and potential benefits. Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continuing throughout the individual’s study participation. Upon reviewing the document, the assessor will explain the research study to the participant and answer any questions that may arise. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants as needed. The investigator will explain study procedures. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if

they decline to participate in this study. VA subjects will consent to the audio-video recording using VA form 10-3203.
Decisional capacity will be assessed based on the interviewer's judgment during the dialog that takes place during recruitment and screening. In addition, the participant participates in a comprehensive psychological assessment as part of the screening including questions about traumatic brain injury. We also anticipate that the clinician referral will screen out anyone with severe cognitive problems. Participants with questionable decisional capacity will be excluded from the study.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The interventions used for this study will include CM and Relaxation Training. The interventions will be of equal length – 8 two-hour sessions – with approximately equal at home practice of the skills. Both types of groups will be conducted in person by a trained licensed clinical psychologist in an outpatient mental health clinic.

The first CM group in Phase 1 will follow the existing Emory Compassion Meditation Protocol. This well-developed protocol has been used extensively with non-clinical populations but some initial refinement will be done to assure that the material is accessible to veterans. The subsequent groups will be delivered using the protocol version developed with the prior group until a well-received protocol has been established. The initial relaxation group will follow Dr. Taylor's protocol with minor modification to match the timeline of the CM protocol (i.e., extending sessions from 90 minutes to 2 hours and providing similar amounts of homework) and modality of administration (group rather than individual). If necessary, this protocol will be refined based on participant feedback as well. The final versions of the protocols will be employed in Phase 2.

Week	Emory Compassion Meditation Protocol	Taylor Relaxation Training Protocol
1	Developing Attention and Stability of Mind: Provide rationale for the practice and introduce breath meditation for cultivation of a basic degree of refined attention and mental stability as the foundation for the practice. Homework: 5 minute daily meditation with journal, log of mindfulness exercises	Treatment Rationale and Initial Relaxation Exercise: Provide initial rationale for treatment protocol and establish goals as they relate to the relaxation training. Initial in-session relaxation exercise. Homework: 5 minute daily relaxation with self-monitoring
2	Cultivating Insight into the Nature of Mental Experience: The stabilized mind is employed to gain insight into the nature of the inner world of thoughts, feelings, emotions and reactions. Homework: 10 minute daily meditation with journal, log of mindfulness exercises	Checking Patient's Understanding of Rationale, Correction and Further Relaxation Training: Similar format to Week #1, with review of week's activities and clarification of rationale. Homework: 10 minute daily relaxation with self-monitoring
3	Cultivating Self-Compassion: The participant observes the innate aspirations	Reviewing At Home Practice, Problem-Solving Difficulties, Progressive

	for happiness and well being as well as those for freedom from unhappiness and dissatisfactions, i.e., which mental states contribute to fulfillment and which ones prevent it. The participant then makes a determination to emerge from the toxic mental and emotional states that promote unhappiness. Homework: 20 minute daily meditation with journal	Relaxation: Similar format to Week #2, with review of week's activities and problem-solving. Homework: 20 minute daily relaxation with self-monitoring
4	Developing Equanimity: Normally one tends to hold fast to categories of friends, enemies, and strangers and to react unevenly to people, based on those categories. By examining these categories closely, the participant comes to understand their superficiality and learns to relate to people from a deeper perspective: everyone is alike in wanting to be happy and to avoid unhappiness. Homework: 20 minute daily meditation with journal	Reviewing Homework and introduce Relaxation with script: Review of at home practice, engage in progressive relaxation with script and record this week. Introduce directed relaxation for "red flag" situations in which participants know they will face difficulty with anxiety and other symptoms. Homework: 20 minute daily relaxation with self-monitoring
5	Developing Appreciation and Gratitude for Others: When the participant realizes interdependence with others and the many benefits that others offer every day, the participant develops appreciation and gratitude for them. Homework: 30 minute daily meditation with journal	Reviewing Homework and next Relaxation with script: Review of at home practice, engage in progressive relaxation with script and record this week. Discussion of "red flag" situations this week. Homework: 30 minute daily relaxation with self-monitoring
6	Developing Affection and Empathy: Deeper contemplation and insight into the ways in which myriad benefits are derived from countless others, along with awareness that this kindness should be repaid, enables the participant to relate to others with a deeper sense of connectedness and affection. Homework: 30 minute daily meditation with journal	Reviewing at-home practice and next Relaxation with script: Review of at home practice, engage in progressive relaxation with script and record this week. Homework: 30 minute daily relaxation with self-monitoring
7	Realizing Wishing and Aspirational Compassion: Enhanced empathy for others, coupled with intimate awareness of their suffering and its causes, naturally gives rise to compassion: the wish for others to be free from suffering and its conditions.	Reviewing Homework and next Relaxation with script: Review of at home practice, engage in progressive relaxation with script and record this week. Homework: 30 minute daily relaxation with self-monitoring

	Homework: 30 minute daily meditation with journal	
8	Realizing Active Compassion for Others: In the final step, the participant is guided through a meditation designed to move from simply wishing others to be free of unhappiness to actively committing to assistance in their pursuit of happiness and freedom from suffering.	Reviewing at-home practice, next Relaxation and Relapse Prevention: Review of at home practice, engage in progressive relaxation and record at home this week. Introduce relapse prevention concept.

Refinement strategies. The interventions will be refined based on participant feedback, which will be solicited on a weekly basis through a variety of measures (refer to the Measures section for more detail) as well as through direct inquiry about reactions to the group. Participants will understand the goal of refining the intervention, so will be encouraged to provide honest feedback about their experience.

Dr. Negi or a designated supervisor from Emory will review the recording of every group meeting and meet with the VASDHS team on a weekly basis. In that meeting, they will discuss their observations of the group as well as feedback from participants. In particular, they will be looking for any difficulty in understanding the concepts being presented (different approach? more or less time for discussion?), the perceived appropriateness of examples/metaphors (did Veterans relate personally? do they fit with military/veteran culture?), challenges in engaging in the practice (to what extent did Veterans engage in practice outside the session? any observable discomfort or lack of engagement in the class setting?). Based on that material, they modify that session in the protocol and plan for the next class session (e.g., choosing to explain again material that was not well understood, to give an alternative metaphor to assist in understanding a concept, or to modify a practice). Adjustments made to the original protocol will be incorporated into the manual by Drs. Lang, Casmar and the team and reviewed by the Emory group for use in the next iteration of the intervention. In addition, the therapist and Emory team will meet at the end of the set of classes to discuss the class as a whole and to incorporate additional information that was gathered after treatment (refer to Measures). The month before the next group begins will be used to make additional refinements for the next set of classes and to review the entire revised protocol. Decisions about protocol changes will be made by consensus. Some examples of observations about the procedures or intervention and potential refinements are presented below. Published trials will be used as benchmarks to determine low or poor performance.

Observation	Potential Refinements
Low proportions of patients enrolling in the study or beginning group sessions	Better informational material for patients and providers, alternate mechanisms for reaching potentially interested individuals
Low treatment credibility	Modification of manner in which the rationale is discussed
Poorly received material or overall satisfaction; high drop-out	Modification of explanations, metaphors or exercises based on the nature of the feedback (logic, understandability, applicability and efficacy in applying it)

Poor homework compliance	Modify explanations of rationale for homework, incorporate strategies to increase motivation or reduce barriers to practice, modify exercises, institute between-session reminders
Increase in negative emotion, little change in positive emotion, social connectedness or self-compassion	Modify nature, length or order of topics

In addition, Dr. Hurst will conduct qualitative interviews with study participants during and after treatment to gather information about the perceived acceptability and utility of the approach. With female participants she will also emphasize the role their gender has played in their reactions to the intervention.

Potential adverse effects. At the eligibility assessment and other assessments for enrolled subjects, the interview questions and/or questionnaires may produce discomfort or anxiety from the discussion of personal, emotional, or anxiety-provoking topics. Meditation and relaxation have been evaluated in prior studies with patients with PTSD, and have been shown to be safe and well-tolerated.

5.2 Handling of Study Interventions

The interventions will be delivered following treatment manuals, which will be developed in Phase 1. It will not be possible for the patient or therapist to be blind to treatment condition.

The prerequisite for training in the CM protocol is at least one year of contemplative practice and having attended at least one 7-day, teacher-led retreat. The training itself involves a 9 day training/retreat followed by an 8-week practicum. The practicum includes attendance at an 8-week (1.5 hours/week) CM course delivered by staff from Dr. Negi's group, a 2.5 hour seminar and discussion week's material, daily practice and journaling about the practice, readings and development of class plans. The practicum concludes with a 17-hour weekend workshop.

Training in the relaxation protocol will involve careful review of the treatment manual and hour:hour audio/video-based supervision of its execution.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Participants can continue current pharmacological treatment (provided that they have stabilized on medication, i.e., no additional treatment response is expected, and that no changes are anticipated during the study period) or any supportive or nonspecific therapy. Detailed information on these treatments will be collected to be used to explore differential effect of the compassion meditation.

5.3.2 Required Interventions

None

5.3.3 Prohibited Interventions

Participants based on concurrent enrollment in any other treatment specifically targeting

PTSD symptoms or social functioning (e.g., couples therapy). If a participant is institutionalized or imprisoned during the course of the study, he/she will be withdrawn.

5.4 Adherence Assessment

We will follow accepted standards (Perepletchikova & Kazdin, 2005) in establishing and assessing the CM integrity and fidelity. This includes: a) treatment manuals with weekly objectives, outcomes, and agendas, b) clinician training, and c) ongoing evaluation of treatment integrity through audio-rating of therapy sessions and supervision. A fidelity measure will be developed for each intervention at the end of the refinement phase and will be utilized in the pilot phase. In addition, ongoing supervision based on review of sessions will be used, with corrective feedback as needed in weekly supervision. The participant evaluation method of quality assurance, which involves asking each participant to complete a brief checklist that queries the content of their session, will be employed as well.

Participant adherence will be gauged by records of between-session practice.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Phase 1.

	Baseline	Session 1	Session 2	Session 3	Session 4	Session 5	Session 6	Session 7	Session 8	Post-treatment
Demographics	X									
MoCA	X									
MINI	X									
DES	X									
Emory Treatment Resistance Interview for PTSD (ETRIP)	X									X
Credibility		X								
SCS-R	X									X
SCS-SF	X									X
Reactions to group		X	X	X	X	X	X	X	X	
CSQ-8										X
Practice Diary		X	X	X	X	X	X	X	X	
mDES		X	X	X	X	X	X	X	X	
LEC-5/PCL-5		X	X	X	X	X	X	X	X	
PHQ-9		X	X	X	X	X	X	X	X	
AUDIT-C		X	X	X	X	X	X	X	X	
HRV	X 72 hr	X	X	X	X	X	X	X	X	X 72 hr

Phase 2

	Screening /Baseline	Session 1	Session 2	Session 3	Session 4	Session 5	Session 6	Session 7	Session 8	Post-treatment
Demographics	X									
MoCA	X									
MINI	X									
DES	X									
Emory Treatment Resistance Interview for PTSD (ETRIP)	X									X
CAPS-5	X									X
BSI	X									X
SDS	X									X
SWLS	X									X
PHLMS	X									X
SCS-R	X									X
SCS-SF	X									X
PROMIS pain	X									X
PROMIS sleep	X									X
Credibility		X								
Reactions to group		X	X	X	X	X	X	X	X	
Practice Diary		X	X	X	X	X	X	X	X	
CSQ-8										X
mDES		X	X	X	X	X	X	X	X	
PCL-5		X	X	X	X	X	X	X	X	
PHQ-9		X	X	X	X	X	X	X	X	
AUDIT-C		X	X	X	X	X	X	X	X	
HRV	X 72 hr	X	X	X	X	X	X	X	X	X 72 hr

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Following consent, participants will complete the following set of measures to establish their fit with inclusion/exclusion criteria. For participants meeting study entry criteria, baseline evaluation will immediately follow.

•Demographics: age, gender, race/ethnicity, relationship status, years of education, SES/income/living situation, occupation/work status, branch of service/highest rank

Eligibility:

•Dissociative Experiences Scale (DES; Bernstein & Putnam, 1986): score of 30 or greater will trigger clinical evaluation of dissociative symptoms.

•Mini International Neuropsychiatric Interview (MINI 6.0; Sheehan et al 1998): 15-30 minute interview used to establish PTSD and absence of serious mental illness, untreated substance dependence, serious suicidality, supplemented with questions to assess homicidality and current trauma exposure

•Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005): brief (~10 minutes) clinician-administered cognitive screening test. If the score is < 26, patients will be referred for additional evaluation and excluded, unless a qualified clinician provides clearance to participate.

• Emory Treatment Resistance Interview for PTSD (ETRIP; phenxtoolkit.org) is a tool that combines self-report and interview-based review of treatments received for PTSD.

Consenting Procedure

This study will be conducted at the VA Medical Center in compliance with Title 45 Part 46 of the CFR pertaining to protection of human subjects. Signed consent documents for VA subjects use VA form 10-1086. Consenting will take place at the Oceanside VA clinic with a trained (per VA standards) assessor/study coordinator in a private room and the participant will be given ample time to read the consent form and ask questions. At the screening/baseline visit, prior to initiation of any study-related procedures, subjects will give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, risks, and potential benefits. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Upon reviewing the document, the assessor will explain the research study to the participant and answer any questions that may arise. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants as needed. The investigator will explain study procedures. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. VA subjects will consent to the audio-video recording using VA form 10-3203. Decisional capacity will be assessed based on the interviewer's judgment during the dialog that takes place during recruitment and screening. In addition, the participant participates in a comprehensive psychological assessment as part of the screening including questions about traumatic brain injury. We also anticipate that the clinician referral will screen out anyone with severe cognitive problems. Participants with questionable decisional capacity will be excluded from the study.

Consent documents will be stored securely (locked cabinet in a locked room and separate from subject data). The PI and coordinator will be responsible for assuring that the current consent documents are use at all times. In addition, the VA performs an annual consent audit to review compliance and to correct sources of any identified errors.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment is defined as the date all of the screening criteria are met and the individual agrees to participate (typically the screening/baseline visit.

Baseline Assessments

Phase 1:

•Short form of the Self Compassion Scale (SCS-SF; Raes, Pommier, Neff, & Gucht, 2011), 12 items
•Social Connectedness Scale – Revised (SCS-R; Lee, Draper & Lee, 2001), 20 items
•Heart rate monitoring

Phase 2:

•Brief Symptom Inventory (BSI; Derogatis, 1983), 53 items
•Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013), 45-60 minute clinician-rated measure referencing the Life Events Checklist (LEC) for lifetime trauma
•Philadelphia Mindfulness Scale (PHLMS; Cardaciotto, Herbert, Forman, Moitra, & Farrow, 2008), 20 items
•PROMIS measures of pain intensity, pain interference, sleep disturbance and sleep-related impairment
•Short form of the Self Compassion Scale (SCS-SF; Raes, Pommier, Neff, & Gucht, 2011), 12 items
•Social Connectedness Scale – Revised (SCS-R; Lee, Draper & Lee, 2001), 20 items
•Sheehan Disability Scale (SDS; Sheehan, Harnett-Sheehan, & Raj, 1996), 3 items
•Satisfaction with Life Scale (SWLS; Diener, Emmons, Larsen, & Griffin, 1985), 5 items
•Heart rate monitoring

Randomization

Phase 2 randomization will occur within 1 month of baseline assessment and within 1 week of the beginning of treatment groups.

6.2.3 Blinding

In Phase 2, all study personnel will remain blind to treatment condition until data is locked with the exception of (a) Ms. Robinson, who will execute randomizations and (b) the study therapists, who will execute the interventions. The supervisors will be aware of some identifying features of individuals (e.g., first name, appearance) in the groups under their review. There is no need for unblinding procedures as the treating clinician will not be blind to condition.

6.2.4 Followup Visits (sessions 1-8)

In both Phases, the following measures will be completed between or before sessions and collected by therapists at group meetings.

•Credibility, 3-item measure adapted from Borkovec & Nau, 1972 (end of session 1 only).

•Modified Differential Emotions Scale (mDES; Fredrickson et al., 2003), daily ratings of the strongest experience of 19 specific emotions in the preceding 24 hours
•Practice diary of time spent in and reactions to daily practice
•Reactions to group, survey and interview-based methods to gather reactions to group sessions and practices.
•Within-session heart rate monitoring (pending IRB approval)

6.2.5 Completion/Final Evaluation (after session 8)

The final evaluation will be completed within 1 week after completion of session 8.

Phase 1:
•Short form of the Self Compassion Scale (SCS-SF; Raes, Pommier, Neff, & Gucht, 2011), 12 items
•Social Connectedness Scale – Revised (SCS-R; Lee, Draper & Lee, 2001), 20 items
•Client Satisfaction Questionnaire (CSQ-8; Attkisson & Greenfield, 1994), 8-items
•Emory Treatment Resistance Interview for PTSD (ETRIP; phenxtoolkit.org)
•Heart rate monitoring

Phase 2:
•Brief Symptom Inventory (BSI; Derogatis, 1983), 53 items
•Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013), 45-60 minute clinician-rated measure referencing the baseline LEC and post-treatment LEC for trauma during participation
•Philadelphia Mindfulness Scale (PMS; Cardaciotto, Herbert, Forman, Moitra, & Farrow, 2008), 20 items
•PROMIS measures of pain intensity, pain interference, sleep disturbance and sleep-related impairment
•Short form of the Self Compassion Scale (SCS-SF; Raes, Pommier, Neff, & Gucht, 2011), 12 items
•Social Connectedness Scale – Revised (SCS-R; Lee, Draper & Lee, 2001), 20 items
•Sheehan Disability Scale (SDS; Sheehan, Harnett-Sheehan, & Raj, 1996), 3 items
•Satisfaction with Life Scale (SWLS; Diener, Emmons, Larsen, & Griffin, 1985), 5 items
•Emory Treatment Resistance Interview for PTSD (ETRIP; phenxtoolkit.org)
•Client Satisfaction Questionnaire (CSQ-8; Attkisson & Greenfield, 1994), 8-items
•Heart rate monitoring

For participants who terminate treatment early, we will make every effort to get them to complete the post-treatment measures. Early termination would most commonly occur because a participant stops attending groups but could also based on clinical judgment that termination would be in the participant's best interest. This information is important part of the feasibility of this study.

7. SAFETY ASSESSMENTS

At the eligibility assessment and other assessments for enrolled subjects, the interview questions and/or questionnaires may produce distress or discomfort from the discussion of personal, emotional, or anxiety-provoking topics. Assessors will be trained to identify signs of such distress and to engage a licensed clinician if it should occur.

Meditation and relaxation have been evaluated in prior studies with patients with PTSD, and have been shown to be safe and well-tolerated. It is unlikely but possible that some distress will arise during the intervention. In particular, it is possible that sitting quietly with one's internal experience during meditation practice, having compassion for oneself (in cases where guilt and shame predominate), or trying to wish a perpetrator to be free of suffering will be emotionally challenging for people with PTSD. The likelihood of such distress is equal to or less than that associated with current empirically supported treatments for PTSD, which typically involve disclosure of the traumatic event or challenge difficult beliefs about the event(s).

The course of PTSD is often characterized by fluctuations in symptoms, particularly based on reminders of traumatic experiences. Thus, it is possible that significant exacerbations of PTSD symptoms will occur during the course of treatment. Exacerbations of co-occurring conditions, including depression or suicidality, alcohol or substance use or dissociation, are also possible. As has been demonstrated previously, significant exacerbation of symptoms during psychotherapeutic treatment of PTSD is relatively rare and has no impact on rates of attrition or improvement (Foa et al., 2002). In order to monitor such changes, the following measures will be administered on a weekly basis.

•Alcohol Use Disorders Identification Test (Saunders, Aasland, Babor, de la Fuente, & Grant, 1988) consumption questions (AUDIT-C), 3 items
•Patient Health Questionnaire, depression items (PHQ-9; Spitzer, Kroenke, & Williams, 1999), 9-item self-report depression scale, anchored to the past week
•PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013), 20 items, anchored to the past week

Rates of suicidality and homicidality are elevated in individuals with depression and PTSD. Suicidality will be evaluated weekly through the PHQ-9. Both suicidality and homicidality will be monitored by therapists, who will receive additional training in management of these issues, including introduction to site-specific procedures and resources. Dr. Lang will be notified immediately about high risk patients (e.g., cannot establish a plan with their therapist to assure their safety, hospitalization required).

Thus the possible adverse events (AEs) during both of these interventions include:

- Alcohol use
- Anxiety
- Depression
- Discomfort
- Dissociation
- Homicidality
- Substance use
- Suicidality

If an AE occurs, the therapist, in consultation with Dr. Lang, will decide what measures are needed to manage the problem. Referrals for additional services will be provided as necessary.

7.1 Specification of Safety Parameters

Distress will be identified by a clinically significant increase in total score on the AUDIT, PHQ-9 or PCL or by increases on specific items, such as PHQ item 9 which queries suicidality.

At each contact with the participant, the assessor or therapist will seek information on AEs by specific questioning. Information on all AEs will be recorded immediately in the study records and VA CPRS. All AEs occurring during the study period will be recorded on AE forms.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Weekly symptom monitoring is standard practice for monitoring safety during treatment of PTSD. Dr. Lang will review AEs on an ongoing basis as they occur and in aggregate, along with Dr. Golshan, at the end of each group.

7.3 Adverse Events and Serious Adverse Events

An **adverse event (AE)** will be defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recordedRepor regardless of their relationship to the study intervention.
A **serious adverse event (SAE)** will be defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

Expected psychiatric AEs will be solicited through weekly assessments and therapist inquiries. Other types of medical AEs, which are very unlikely to be related to the study interventions, will be unsolicited but could be noted by therapists during weekly inquiries about how each participant is doing.

Information on all adverse events will be recorded immediately in AE forms. All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events (SAEs) that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately. Minimum information required for each AE includes type of event, duration (start and end dates), severity, seriousness, causality to study intervention, action taken, and outcome.

Evaluating Adverse Events. Assessment will include the intensity (severity) of the event and the relationship to study intervention. Severity of AEs will be graded using the following criteria as guidelines: 1. Mild: Nuisance, barely noticeable. 2. Moderate: Uncomfortable, troublesome symptoms not significantly interfering with daily activities or sleep. 3. Severe: Symptoms significantly interfere with daily activities or sleep. The relationship of the AE to the study will be specified using the following definitions: 1. Not Related: Concomitant illness, accident or event with no reasonable association with treatment. 2. Unlikely: The reaction has little or no temporal sequence from participation and/or a more likely alternative etiology exists. 3. Possibly Related: The reaction follows a reasonable temporal sequence from participation and follows a known response pattern to the intervention; the reaction could have been produced by the study intervention or could have been produced by the subject's clinical state or by other modes of treatment administered to the subject. 4. Probably Related: The reaction follows a reasonable temporal sequence from participation and cannot be reasonably explained by the known characteristics of the subject's clinical state. 5. Definitely Related: The reaction follows a reasonable temporal sequence from participation and cannot be explained by the known characteristics of the subject's clinical state.

7.4 Reporting Procedures

Reporting of AEs. Negative events that occur during study involvement do not constitute adverse events unless they lead to physical harm (in which case the injury is the AE) or deterioration of mental health functioning (in which case the symptoms are the AE). Negative events that may potentially affect response to the intervention or study involvement should be reported as AEs. Examples might include legal problems or traumatic events.

An AE form will be placed in the participant folder. This form is cumulative and captures adverse events of a single participant throughout the study. The study therapist will document each AE reported on the form. The study coordinator will periodically review and compile the information into summary or table form for reporting to both the Independent Monitoring Committee (IMC) and the VASDHS IRB at the time of continuing review.

Reporting of Serious Adverse Events and Unanticipated Problems. An AE occurring in a participant enrolled in a research study is serious if it results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Examples of possible UPRs for psychotherapeutic interventions:

1. Psychosis or mania
2. New onset or clinically significant exacerbation of an Axis I disorder
3. Suicide and suicide attempts.

Any study-related unanticipated problem posing risk of harm to subjects or others and any serious adverse event regardless of relatedness will be reported immediately to the PI, the VASDHS IRB within 10 days using the VASDHS Human Research Protections Program form REPORT OF UNANTICIPATED PROBLEM INVOLVING RISK TO SUBJECT OR OTHERS (dated 7/9/12), and NCCAM according to requirements.

7.5 Follow-up for Adverse Events

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

7.6 Safety Monitoring

This project will be monitored by an Independent Monitoring Committee. Refer to Data and Safety Monitoring Plan.

8. INTERVENTION DISCONTINUATION

An intervention can be discontinued if the participant chooses to do so or if the therapist or Dr. Lang believes it is in the participant's best interest. If the therapist or Dr. Lang judges that a subject requires a different approach or higher intensity care, the subject will be provided with referrals for outpatient or inpatient care, as appropriate. Participants will be asked to complete the all remaining assessments if they discontinue early.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This project is a feasibility and proof of concept study of compassion meditation (CM) for Veterans with posttraumatic stress disorder (PTSD; N ≈ 100). Phase 1 (N ≈ 60, nonrandomized), Protocol Refinement, will consist of up to 4 CM and 2 Relaxation groups with 6-12 participants in each group. Iterative refinement of the treatment protocols will be done based on quantitative and qualitative data from participants. Phase 2 (N ≈ 40), Pilot Evaluation is a randomized controlled study with 4 groups (2 CM and 2 relaxation groups, 6-12 in each group) to examine the feasibility of a randomized trial and to estimate response to CM. The study is not hypothesis driven, but rather developmental in nature.

The primary outcome measures in Phase 1 (see section 6.2) are related to refinement of the intervention, i.e., participants' behavior and reactions to the material and change in processes that are believed to be modified by CM (i.e., positive emotion, social connectedness, self-compassion). The primary outcome measures in Phase 2 (refer to section 6.2) are related to estimating the amount of change in symptomatology, functioning and psychological processes thought to be associated with CM.

9.2 Sample Size and Randomization

For Phase 1, we estimated sample size based on past experience in intervention development; we believe that we will need to run 4 CM groups to achieve Phase 1 refinements (e.g., Lang, Norman, & Casmar, 2006). For the relaxation protocol, which was used in a prior PTSD study, we will begin with our modified version and expect 2 groups will be sufficient given the very minor modification. We will aim for a group size of 6-12, which can be recruited within the 1-month period we have allocated to recruitment before each group. Thus, we estimate that 60 people will take part in Phase 1 of the research.

In Phase 2, we will conduct a pilot study with 4 groups (2 CM and 2 relaxation groups, 6-12 in each group) to examine the feasibility of a randomized trial and response to CM. Thus, we anticipate approximately 40 participants in the second phase

Treatment Assignment Procedures

In phase 2, groups will be randomly assigned a treatment condition in a 1:1 ratio. The assessor will remain blind to these assignments; the study team will be careful not to disclose which group or therapist is seeing a given participant and participants will be asked to refrain from discussing the nature of their intervention during assessments. There is no need for breaking blind as treating clinicians will be aware of the treatment assignment.

9.3 Definition of Populations

Participants in both phases will be Veterans with PTSD who are able to consent and willing to participate. Co-occurring disorders such as depression, anxiety, or treated substance abuse or dependence problems are permitted provided that PTSD is the primary presenting complaint. Sixty people will take part in Phase 1 of the research and approximately 40 participants in the second phase, for a total sample size of approximately 100 people. This is intent to treat protocol and all subjects will be included in the study data analysis.

9.4 Interim Analyses and Stopping Rules

Not applicable

9.5 Outcomes

9.5.1 Primary Outcome

The primary outcomes of Phase 1 are participant reactions to the group (credibility, satisfaction, attendance, practice compliance, and weekly qualitative and quantitative feedback) as well as variables that reflect changes that are expected with practice of CM (positive emotion, social connectedness, self compassion). These includes: Client Satisfaction Questionnaire, credibility score, modified Differential Emotions Scale, time spent in and reactions to daily practice, reactions to group, short form of the Self Compassion Scale and Social Connectedness Scale. Refer to section 6.2 for the schedule of administration and descriptions of measures.

The primary outcome of Phase 2 is the CAPS-5, which quantifies PTSD symptomatology.

9.5.2 Secondary Outcomes

The secondary outcomes of Phase 1 are the rate of study enrollment based on various types of recruitment strategies as well as gender.

The secondary outcomes of Phase 2 include symptoms that frequently co-occur with PTSD (Brief Symptom Inventory, PROMIS measures of pain intensity, pain interference, sleep disturbance and sleep-related impairment), functioning/quality of life (Sheehan Disability Scale and Satisfaction with Life) as well as variables that capture the mechanisms by which CM may create change, including positive emotion (modified Differential Emotions Scale), social connectedness (Social Connectedness Scale), self-compassion (Short form of the Self Compassion Scale) and mindfulness (Philadelphia Mindfulness Scale).

9.6 Data Analyses

Although majority of data will be quantitative, some qualitative data also will be collected. Dr. Golshan has experience with qualitative coding and analyses. Dr. Hurst also has been added to the study team for her experience with qualitative interviewing, coding and analyses. We will analyze qualitative data using atlas.ti, a qualitative data analysis software package. Qualitative data analysis starts with coding, a process in which quotes are marked and labeled. The labeled quotes are then sorted and grouped, so that categories, then concepts, then themes can be developed. As is often standard practice for qualitative data analysis, analysis will be concurrent with data acquisition.

Quantitative data will be analyzed using SPSS version 18. These data will be examined initially for missing values. The primary aims of our data analytic strategy in phase 1 will be directed toward the development of CM and collection of data that will inform modification of the interventions. In phase 2 it will be directed toward examining the feasibility of CM. We would like to emphasize that, although we aim to estimate an effect sizes to assist in future power calculations, this is not our major focus. Recent work by Kraemer (2006) has highlighted important limitations of this aim due to the large standard error surrounding the pilot study effect size. As a result, we will focus our analyses on a feasibility of conducting a larger CM study and report our findings with this limitation in mind. Our goal is to collect important data regarding the development of CM protocols, our ability to implement recruitment strategies, and the feasibility of the treatment and measurements. Information derived from our research will leads

to better-designed full-scale studies and informs decisions regarding whether it is worthwhile to commit additional resources to future CM treatment development. Due to our small sample size our statistical analytical findings should be interpreted with caution.

For quantitative data, descriptive statistics will be used to summarize the variables as well as to detect outliers and data entry errors. When applicable, normality of the distribution will be examined for outcome variables with a normal probability plot. HRV measures will be generated from heart rate data per the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force, 1996). Chi- squares and Analysis of Variance will be used to assess the effectiveness of the randomization procedures by comparing participants in each treatment condition on baseline variables. Although there are important limitations associated with the analysis of our phase 2 data, we do propose to conduct limited statistical analyses. First, keeping in mind the theoretical and practical issues reviewed above, all analyses will be considered preliminary. We will calculate an estimated effect size for our primary outcome, though it will be interpreted with caution, and in the context of the 95% confidence interval that surrounds it. It will also be interpreted within the context of other important information such as the clinical significance of study findings, and existing data from prior relevant research studies.

Primary analyses will assess whether CM is superior to Relaxation. The two groups will be compared on CAPS, BSI, SDS and Philadelphia Mindfulness Scale using analysis of variance. We are also particularly interested in evaluation of patterns of missing data, dropout rates, distributional properties of variables, and correlations among measures. Missing data will be examined to assess randomness. The pattern of missing data will be examined according to the procedure recommended by Little and Rubin (1987), which includes comparing group differences in the primary outcomes of subjects with versus without missing data. We will test whether the drop-outs are random or systematic by comparing the drop-outs with the study completers on the baseline data. An absence of significant differences would support the random nature of drop- outs. Dropout rate will be compared between the groups using chi-square analysis. Given the limited sample size, multiple linear regression may be used carefully to examine whether group assignment predicts PTSD symptom severity at the follow-up assessment while controlling for initial values. Other potential covariates will include baseline demographic or clinical variables (e.g., concomitant medication use) that are not equivalent between the two treatment groups. Effect size for the difference between groups will be calculated according to procedures described by Cohen (1988). We will also explore the effect of patterns of missing data using Mixed Effects models (random regression models). We will perform sensitivity analyses for the impact that potentially informative missing data and dropout may have on the analyses. The mixed effects framework is robust with respect to drop-out and missing data, unless the drop-out mechanism or cause of missing is informative. We will use pattern-mixture models to assess if there is bias due to drop out or missing data.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Indicate how information will be collected for each participant and by whom. For example if a blinded observer will perform outcome assessments, state who this person will be. Describe methods for maintaining confidentiality of participant records. Identify any data that will be

recorded directly on the CRFs (i.e. no prior written or electronic record of data) as this will be considered source data. (ICH Guidelines, E6.4.9)

Trained assessors will administer the measures for this study. Data collected in this project includes a structured interview and self-report measures about mental health symptoms, including alcohol use, quality of life, functioning and response to meditation practice. Designated staff members will have access to individually identifiable private information about human subjects. All such staff will receive training in proper handling of research data, and systems will be put in place to maintain subject confidentiality to the greatest extent possible. For example, paper data will be stored in locked file cabinets in locked rooms. Subject names (including consent forms and the key associating names with subject numbers) and contact information will be stored separately from other study data, which will be identified using a subject ID number. Electronic data will be stored on a password-protected secure server.

10.2 Data Management

Data management will be supervised by the study statistician, Dr. Golshan. He has more than 28 years experience in data management and analysis. The computer systems to be used (VA and Veterans Medical Research Foundation) are HIPAA compliant and housed in locked rooms, accessible only to authorized personnel and employees. All subjects are assigned a unique ID number. The patient names are never used in conjunction with the unique clinic ID number. The single name-to-ID relational file is kept in an encrypted form electronically and in a locked filing cabinet physically. Data will be collected on paper forms and entered into an already existing data management system. Prior to inferential analyses, data will be examined for missing values and statistical outliers. All statistical transfer routines are inherently secure via their operating platform and they contain no patient names or personal data.

10.3 Quality Assurance

10.3.1 Training

Assessment. The assessor in Phase 2 will be a doctoral-level psychologist with familiarity with diagnostic interviewing. Dr. Gray will provide study-specific training prior to conducting interviews. Training for the MINI will include a didactics on the interview, including the suicidality/homicidality assessment, and administration of practice interviews with a mock patient. Training in the CAPS will include review of training materials, observation of CAPS administration, and diagnostic matching on three CAPS interviews. To establish matching, Dr. Gray will co-rate the training interviews conducted by the assessor. A match occurs when the assessor and Dr. Gray agree on the diagnosis and are within 2 points of severity (frequency + intensity) on all of the symptom clusters (PTSD criteria B, C, and D). Each assessor will be considered trained on CAPS when he or she matches Dr. Gray on three interviews (this requirement may be reduced with documentation of prior rigorous CAPS training). If the assessor does not match on three interviews after five attempts, Dr. Gray will provide additional training or the assessor will be replaced. Dr. Gray will supervise the assessor's interviews throughout the study, and all interviews will be audio-recorded in case detailed review of an interview is needed. We will follow standard procedure for ensuring inter-rater reliability over time. Each assessor's score will be compared to the Dr. Gray "gold standard" rating. Intra-class correlation coefficients (ICCs) of each assessor must be .90 or higher. If the ICC falls below .90, retraining will be done. Reliability will be re-established annually or more frequently if requested by the project PI or the study statistician.

Interventions.

We will follow accepted standards (Perepletchikova & Kazdin, 2005) in establishing and assessing the integrity and fidelity of the interventions. This includes: a) treatment manuals with weekly objectives, outcomes, and agendas, b) clinician training, and c) ongoing evaluation of treatment integrity through audio-rating of therapy sessions and supervision.

The CM protocol will be taught using the Emory Intensive Teacher Training Program. The program is designed to help potential teachers explore effective contemplative pedagogy, understand and adapt to the needs of various populations, and deepen their personal meditation practice. The prerequisites for this training are having a regular meditation practice of at least one year and having attended at least one teacher-led residential retreat. The first portion of the training (taught as a week-long or two-weekend intensive) involves an introduction to the key concepts, skills, and practices, including understanding the theory and practice of CM, learning how CM differs from other meditation-based programs and recognizing the rationale and significance of teaching secularized meditation programs. The second portion of the training, which is a retreat, affords participants an opportunity to deepen their practice and experience with CM. Participants are expected to continue deepening their personal meditation practice on their own after the intensive training. The third training component involved supervised administration of the protocol. A supervisor from Emory will watch a video- recording of every class and provide feedback to the therapist prior to the next class.

The relaxation protocol will be conducted following the Taylor manual. Dr. Lang will review recordings of every session to assure adherence to the protocol. A fidelity measure will be developed for each intervention at the end of the refinement phase and will be evaluated in the pilot phase. To identify problems early, the Emory group will listen to audiotapes of each session. Corrective feedback will be provided as needed in weekly supervision. The participant evaluation method of quality assurance, which involves asking each participant to complete a brief checklist that queries the content of their session, will be employed as well.

10.3.2 Quality Control Committee

Data monitoring will be the responsibility of Drs. Lang and Golshan.

10.3.3 Metrics

Outcome measures will be checked for missing and impossible values as well as for internal inconsistencies.

10.3.4 Protocol Deviations

A protocol deviation or violation is any change, divergence, or departure from the study design or procedures of a research protocol. Investigators are required to conduct their research according to the plans reviewed and approved by the IRB. Staff will be trained to avoid protocol deviations to the extent possible. Instances where this does not occur, either inadvertently due to circumstances beyond the investigator's control or due to errors of omission or commission by research project staff, will be reported.

Protocol deviations will be recorded and maintained by the study coordinator on the Protocol Deviation Log and reviewed by Drs. Lang and Golshan.

Protocol deviations that do not affect participant safety or data integrity will be reported to the VASHS IRB at continuing review. Any protocol deviation resulting in harm or risk to the participant must be reported within ten business days to the VASDHS IRB using the VASDHS Human Research Protections Program form REPORT OF UNANTICIPATED PROBLEM INVOLVING RISK TO SUBJECT OR OTHERS (dated 7/9/12).

10.3.5 Monitoring

The VA San Diego conducts annual reviews of consent forms to assure compliance. Research assistants and therapists will be trained to review all instruments for completeness before the participant leaves the appointment. Drs. Lang and Golshan will review the data set for completeness at the end of each group cycle.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the VA San Diego IRB and R&D Committee.

11.2 Informed Consent Forms

Consenting will take place at the Oceanside VA clinic with a trained assessor/study coordinator in a private room and the participant will be given ample time to read the consent form and ask questions. At the first visit, prior to initiation of any study- related procedures, subjects will give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, risks, and potential benefits. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Upon reviewing the document, the assessor will explain the research study to the participant and answer any questions that may arise. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants as needed. The investigator will explain study procedures, including the variable length of follow-up in this study, and let the participant know how many follow-up assessments he/she will be asked to complete. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. VA subjects will consent to the audio-video recording using VA form 10-3203. Decisional capacity will be assessed based on the interviewer's judgment during the dialog that takes place during recruitment and screening. In addition, the participant participates in a comprehensive psychological assessment as part of the screening including questions about traumatic brain injury. We also anticipate that the clinician referral will screen out anyone with severe cognitive problems. Participants with questionable decisional capacity will be excluded from the study.

11.3 Participant Confidentiality

Patient confidentiality will be protected to the extent permitted by law. Participant names will be held separate from data. Subjects will be assigned a unique ID number, and the single

name-to-ID relational file will be kept in an encrypted form electronically and in a locked filing cabinet physically.

Designated staff members will have access to individually identifiable private information about human subjects. All such staff will receive training in proper handling of research data, and systems will be put in place to maintain subject confidentiality to the greatest extent possible. For example, all data will be stored in locked file cabinets in locked rooms. Subject names (including consent forms and the key associating names with subject numbers) and contact information will be stored separately from other study data, which will be identified using a subject ID number. Electronic data will be stored on a password-protected secure server. All statistical transfer routines are inherently secure via their operating platform and they contain no patient names or personal data.

All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NCCAM, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCAM, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

Not applicable.

13. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the VA San Diego and the NCCAM prior to submission. All analyses and reports will be done or supervised by Drs. Lang and Golshan. All abstracts and manuscripts will be reviewed by the research team and must be approved prior to be reviewed by any other individual.

14. REFERENCES

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15. SUPPLEMENTS/APPENDICES