Study Title: Feasibility Study of Compassion Meditation Intervention for Older Veterans in Primary Care with Anxiety or Mood Disorders

NCT #: NCT03964246

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VASDHS IRB
Human Subjects Protocol

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Section 1 - Preliminaries

Principal Investigator:

Barton W. Palmer, PhD

Protocol Title:

Feasibility Study of Compassion Meditation Intervention for Older Veterans in Primary Care with Anxiety or Mood Disorders

IRB Protocol Number:

H180199

Protocol Nickname:

Compassion Meditation

Form Template Version:

v20150115

Date Prepared:

09/21/2020

Please be advised that this protocol application form has changed as a result of the 2018 Common Rule. There are new questions and sections, and you may be required to provide additional information to previous sections.

1a) Is this study considered human research?

- (•) Yes
- ( ) No
- ( ) I don't know

4) What is the estimated duration of the entire study? (From IRB approval to IRB closure)

36 months

Section 5 - Lay Language Summary

5) Provide a summary or synopsis of the proposed study using non-technical language (not more than 1 paragraph)

Many older Veterans in VA primary care clinics experience anxiety and depressive symptoms, but only a minority of these Veterans seek care through VA mental health services. Research suggests that some older Veterans with psychological distress under-utilize mental health services due to perceived stigma of treatments focused on mental health symptoms. However, prior research with civilians, including one study of Veterans with PTSD, suggests a strengths-focused intervention that provides group training in compassion meditation may be effective in reducing negative emotions and increasing positive emotions and well-being. The proposed project is designed to examine the feasibility of this approach with Veterans ages > 55 years with anxiety or depression. Twenty to 30 participants will be enrolled in a 10-week CM training group (with 8-10 participants in each group). The groups will be conducted with a manualized CM intervention, although part of the goal of the feasibility study is to identify and adapt the intervention to the needs of this specific population. As part of establishing feasibility for a subsequent large-scale study, 10 additional participants will be enrolled in a 10-session manualized psychoeducational group focused on topics in healthy aging. The latter group will be conducted to examine the feasibility and appropriateness of employing this as a control condition in a larger follow-up study. The information from the study will guide and support development of a larger-size, more definitive study, planned as the follow-up after this project. If successful, this line of research could open the door to a novel and effective treatment that widens acceptance by older Veterans with psychological distress.

Section 6 - Specific Aims

6) Provide a statement of specific aims and hypotheses that serve as the basis for this protocol. Emphasize those aspects that justify the use of human subjects.

Aims: To collect pilot data to establish the feasibility of a randomized controlled trial (RCT) of a manualized Compassion Meditation (CM) group treatment to restore functioning in older Veterans with psychological distress. Key questions include:
(1) Will older Veterans with anxiety and/or depression enroll in and complete the proposed CM intervention?
(2) What is the completion rate?
(3) Do participants adhere to the treatment (complete practice at home)?
(4) Are modifications required for the intervention to make it more acceptable and appropriate for older Veterans with emotional distress (e.g., length of session, pace of material, mechanism for supporting home
practice)?
(5) Does CM show promise for improving well-being, symptom severity, and/or positive psychological factors relevant to successful aging?
We also seek to optimize the assessment strategy for a future Merit Award application, including to explore feasibility of inflammatory biomarkers as a CM intervention outcome.

Section 7 - Background and Significance

7) Provide a succinct discussion of relevant background information to justify performing the proposed study.

Critical unmet need: Over the past decade, there has been unprecedented growth in the number of older Veterans who are at elevated risk for clinically significant emotional distress, but are less likely than younger Veterans to utilize specialty mental health VA clinics. These mental health concerns can result in considerable disability, medical comorbidity, higher health care utilization and costs, reduced physical and mental well-being, and higher mortality). The VA's Primary Care – Mental Health Integration (PCMHI) services are an important component in addressing such concerns, but older age remains associated with low mental health service utilization among psychologically distressed Veterans (Blais et al., 2015). If compassion-based interventions can be effectively tailored such that the benefits generalize to older

Veterans, then there is a unique opportunity for an evidence-based, novel treatment that not only reduces psychological distress, morbidity and mortality, but also promotes "healthy aging" and increases well-being (Jeste et al., 2015).

The proposed feasibility study of a compassion meditation (CM) intervention represents an essential foundation for subsequent larger (VA Merit supported) research to investigate CM as a means to address a critical unmet need among older Veterans with psychological distress. The feasibility, acceptability, and effectiveness of the approach in this population are not yet known, but if successful, then there is high potential benefit as an innovative wellness/recovery-focused intervention that has shown benefit for other populations. If properly adapted and validated for older Veterans with psychological distress, CM may not only reduce mental health symptom severity, but promote positive mental and physical well-being.

Fostering recovery through positive/strengths-focused interventions: The goal of VA Rehabilitation Research and Development (RR&D) is to maximize functional recovery. In the broader field of mental health recovery and rehabilitation, as well as positive psychology and psychiatry, there has been increased recognition of the clinical importance of not only treating the primary psychiatric symptoms, but of simultaneously building and promoting positive psychological factors, such as compassion, resilience, and optimism (Jeste et al, 2015; Seligman, Rashid, & Parks, 2006) A "strengths-based" approach is core to most recovery models, i.e. recovery is not limited to symptom management, but focused on fostering a return (or enhancement) of functioning and well-being, even in the presence of physical or mental health challenges. CM has been shown to be beneficial among (primarily) younger, non-VA, non-clinical samples not only in terms of reducing emotional distress, but also in promoting recovery-relevant constructs including well-being and positive psychological factors (Kirby, Tellegen, & Steindl, 2017). However, the experiences, concerns, and preferences of older Veterans tend to differ in significant ways from their civilian counterparts, as well as from younger Veterans; therefore, interventions developed and validated in other populations cannot be assumed efficacious for older adults. Thus, the line of research catalyzed by the presently proposed feasibility study represents a novel and critical contribution to rehabilitation /recovery research and Veteran well-being.

Compassion meditation (CM): CM is a meditative practice focused on cultivating compassion based on an awareness of common humanity out of which is derived a heartfelt wish that the self and others may be free of suffering. Prior research in civilian samples has found this type of practice to be associated with increases in positive emotion and reductions in perceived stress and negative mood. In Kirby et al.'s (2017) recent meta-analysis of compassion interventions, there were moderate effect size improvements in negative emotions (anxiety, depression, general psychological distress) and positive emotions and outcomes (including self-compassion, compassion for others, and well-being). CM may also improve social connection and its associated effects on psychosocial functioning and may improve self-esteem and health. Although there have been few Veteran-focused studies of CM interventions, two recent small trials by Dr. Lang (Co-Investigator for the proposed project) and colleagues found decreased negative emotions and increased social connectedness among Veterans with PTSD receiving CM (Lang et al., 2017).

Most reported studies of compassion-based interventions have been conducted in non-Veteran, non-older adult, and non-clinical samples. Also, the older Veteran population is predominantly male, but with the exception of Dr. Lang's work, samples in the published research have been predominantly female (e.g., only 26% of the participants in the studies in Kirby et al.'s (2017) meta-analysis were male). Thus, the adaptations required to maximize effectiveness of CM for older Veterans with clinically significant anxiety and/or depression, particularly outside the context of PTSD, is presently unknown.

Improving acceptance/utilization of positive psychological interventions: Prior research has shown that the perceived stigma of mental health concerns is a barrier to mental health treatment seeking and acceptance, particularly among older adult (Conner et al., 2010). As CM and other positive psychological interventions are more saliently focused on promoting strengths, they may be perceived as carrying lower stigma than interventions directly focused on reducing mental health symptoms, such as depression or anxiety, and thus may result in higher acceptability and utilization. Previous work suggests the acceptability of mindfulness-based intervention for older adults (Geiger et al., 2016; Oken et al., 2017); this project will evaluate whether this acceptability generalizes to CM as applied to older psychologically distressed Veterans.

Biological mechanisms: One of the key national mental health research priorities has been identification of biological mechanisms underlying mental health concerns and/or their health consequences and treatment effectiveness. Depression, anxiety, and general psychological distress are associated with accelerated biological aging, which may in turn be mediated by chronic inflammation or changes in stress-induced inflammatory response that are associated with elevated blood-based inflammatory biomarkers (Van der Kooy et al., 2007; Vogelzangs et al., 2013, 2016; Wolkowitz et al., 2011). Results from two studies, albeit in adolescents or college students, suggest possible reductions in C-reactive protein levels and/or interluekin-6 response following a CM intervention. There is also evidence that related component practices, such as mindfulness, reduce inflammatory responses (Rosenkranz et al., 2013). In a recent comprehensive review, Black & Slavich (2016) found possible effects of mindfulness meditation on inflammation, immune function, and biological aging, but also noted the limitations of the existing work warrant further research before definitive conclusions can be drawn. This study will provide essential

information to guide and support a larger VA Merit Award application for more definitive investigation of the potential efficacy of CM for improving health of older adults, and the biological mechanisms through which this may occur.

Section 9 - Design and Methods

9) Describe the research design and the procedures to be used to accomplish the specific aims of the project. Provide a precise description of the planned data collection (include what systems or databases will be used/accessed to gather data), analysis and interpretation. For chart review studies, include the timeframe of collection. Address sample size, inclusion of women and minorities. Define in clear terms exactly what will be done to the human subjects.

Participants: Participants will be up to 40 men and women Veterans in VASDHS ages 55 years or older who are self- and/or clinically identified through the Primary Care/PCMHI services with mild-to-moderate anxiety and/or depressive symptoms and meet the inclusion/exclusion criteria below.
Inclusion criteria: (1) VASDHS patient, (2) current age > 55 years, (3) current mild-to-moderate anxiety or depressive symptoms (as defined below), (4) stated intention to attend the 10 group sessions at the scheduled times at the VASDHS in addition to the baseline and follow-up study assessment visits, as well as to complete the outside homework assignments, and (5) provides written informed consent for participation.
Because this is a feasibility study and because all participants who enroll in the study will demonstrate capacity to consent to the research study, there will be no age limit.
Exclusion criteria: (1) No active suicidality/homicidality in the preceding six months, (2) untreated alcohol or substance use disorders (those co-enrolled in the VASDHS Alcohol and Drug Treatment Program will be eligible), (3) changes to psychiatric medications within six months of baseline evaluation (changes to medications during the course of the study will be permitted as determined appropriate by Veteran's treating clinicians, but changes will be recorded to further describe the sample), (4) medical and/or psychiatric instability interfering with current ability to engage in the group sessions and outside homework assignments.
As part of their clinical connection to PCMHI all participants will have completed the PHQ-9, which includes a question about thoughts of death during the past 2 weeks, but we will also directly ask potential participants if they have had suicidal ideation, or thoughts of harming others, with a plan or intention within the past year. If enrolled, participants also sign a HIPAA permitting us to examine CPRS records. The CPRS has mandatory annual suicide risk screening, flags for patients deemed high risk suicide, and mandatory Suicide Behavior Reports suicidal behavior not previously documented in the CPRS, as well as disruptive behavior flags and reports.
Suicidality/homicidality in the preceding six months: As part of their clinical connection to PCMHI all participants will have completed the PHQ-9, which includes a question about thoughts of death during the past 2 weeks, but we will also directly ask potential participants if they have had suicidal ideation, or thoughts of harming others, with a plan or intention within the past year. If enrolled, participants also sign a HIPAA permitting us to examine CPRS records. The CPRS has mandatory annual suicide risk screening, flags for patients deemed high risk suicide, and mandatory Suicide Behavior Reports suicidal behavior not previously documented in the CPRS, as well as disruptive behavior flags and reports.
Cognitive impairment and decisional capacity: Capacity to consent to research is an important issue in ensuring that voluntary consent is authentic and valid. This is an issue Dr. Palmer has studied extensively (e.g. see MCIDs: PMC5279898, PMC6085078, and PMC3382031). Given the minimal risk nature of this study, we will not explicitly assess cognitive or decisional capacity. However, Dr. Palmer will train the staff obtaining informed consent in procedures (such as pausing after describing the study purpose and asking the potential participant to explain the purpose of the study in their own words – see Palmer et al. "effective use of consent forms and interactive questions in the consent process" PMID: 18512654). Staff will be trained to be alert to participants who do not appear to understand the overall purpose of the study and the nature of the compassion meditation or psychoeducational groups, that this is a research project, or that participation is completely voluntary. Participants, who do not appear able to understand these basics, even after re-explanations, will not be enrolled.
As we are not conducting a formal cognitive assessment, such as with the MOCA, we will not be making explicit determinations of the individuals level cognitive functioning. If, however, obvious cognitive impairment is demonstrated that appears to be undocumented, then with the participants' consent, we will alert the Primary Care Provider about this concern. As the participants are drawn from PCMHI, however, obvious levels of cognitive impairment would presumably be noticed by the PCP or PCMHI clinicians.
Definition of psychological distress: For this feasibility study, psychological distress will be defined as mild-to-moderate depressive or anxiety symptoms. As older adults are more likely to exhibit clinically relevant symptoms that may not meet specific DSM syndrome criteria (Grenier et al., 2011) our enrollment will be symptom rather than syndrome focused. All Veterans referred to the PCMHI service are screened for depressive symptoms with the nine-item Patient Health Questionnaire (PHQ-9) , and for anxiety symptoms with the seven-item Generalized Anxiety Disorder scale (GAD-7). We will enroll Veterans who score in the mild-to-moderate range on either scale (i.e. PHQ-9 total = 5-14 or GAD-7 total 5-14 points).

Methods and measures:

Sociodemographic and clinical characteristics: To characterize the sample, baseline measures will include age, education, gender, relationship status, medical comorbidity, and active medications, as determined through participant interview and/or review of available records in the VA Computerized Patient Record System (CPRS).

CM intervention: Through the experience and feedback from the three successful CM groups we will adapt the CBCT-Vet(Lang et al., 2017) intervention for use in older adults with anxiety or depressive symptoms. This adaptation will be conducted with input from Dr. Negi and Mr. Harrison (developers of CBCT® and consultants for the proposed project), and the experience and expertise of the study team. Expected adaptations include changing the focus of examples from PTSD to anxiety and depression, as well as adjustments for appropriate use with older Veterans. The CBCT-Vet includes 10 90-minute sessions that will be led by Dr. Casmar, a VA Staff Psychologist and Co-Investigator on the proposed project, who is certified in CBCT® with significant experience in administering CBCT-Vet. Sessions 1 - 4 assist participants in basic mindfulness breathing practices; sessions 4 - 8 focus on personal analysis of factors underlying difficulties with compassion for self or others; the final two sessions (9 and 10) review content and assist with relapse prevention. Session by session topics are: (1) Introduction and learning breathing meditation, (2) Focused attention, (3) Creating space, (4) Mindful awareness, (5) Re-engaging with heroic spirit, (6) Seeing ourselves in others, (7) Appreciation and gratitude, (8) Empathy and engaged compassion, (9) "Putting it all together," and (10) "Putting it all together 2."

Our target is to have 5-8 participants completing each 10-week intervention, thus we will enroll up to 10 per group to account for possible attrition. Two or three of the CBCT-Vet groups (depending on the degree of modification needed based on the initial group) will be conducted sequentially, such that information in the first group can be used to adapt the manualized intervention for the next group.

Psychoeducational healthy aging group: As part of this project, we will develop and test a 10-week psychoeducational group focused on topics in healthy aging to examine its feasibility as a control condition for a subsequent VA Merit-supported randomized controlled trial. Dr. Palmer, in addition to his VA position and roles, is an active member of the Center for Healthy Aging at UC San Diego. The Center for Healthy Aging has multiple resources for community education regarding healthy aging, including a library of videotaped community-focused talks, such as increasing happiness, mental resilience and health, nutrition, and physical activity. We will incorporate these videos as part of 90-minute sessions wherein the key information from talks is shown to participants, with a follow-up discussion and review period led by the group facilitator. In the context of the present feasibility study, we anticipate modifying and refining the content and format of the group in response to participant feedback.

Process and outcome measures: As a feasibility study, we will not be testing hypotheses regarding the efficacy of CBCT-Vet in reducing psychological distress with inferential statistics. However, in order to support our planned subsequent VA Merit application, we will be examining descriptive statistics of observed patterns and estimated effect sizes of change on key measures described below.

Baseline and post-intervention: Each participant will meet individually with a trained Research Assistant (RA; To Be Named (TBN)) for two 90-minute assessment sessions (baseline and post-intervention). The final assessment will be scheduled within 2-weeks of the participant's final intervention group session. Measures will include:

Psychological distress: Brief Symptom Inventory-18 (BSI; depression, anxiety, and somatization) (Boulet & Boss, 1991).

Compassion, empathy, mindfulness, and social connectedness: As a feasibility study, we will use a larger array of measures than we anticipate employing in a subsequent VA Merit-supported RCT. Although we have prior experience with each of these measures in other contexts, their use in this feasibility study will enable us to more comprehensively identify those with most potential and which are most appropriate for this population. Measures will include: Self-Compassion Scale – Short Form, Toronto Empathy Questionnaire, Cognitive and Affective Mindfulness Scale – Revised, Social Connectedness Scale - Revised and the UCLA Loneliness Scale - Third Edition.

Well-being/Quality of Life: Physical and mental composite scores from the 12-item Short Form Health Survey (SF-12) and Satisfaction with Life Scale.

General positive psychological factors: 10-item version of the Connor-Davidson Resilience Scale , Life Orientation Test – Revised (a measure of optimism) , San Diego Wisdom Scale (SD-WISE)) and Center for Epidemiological Studies – Depression Scale (CES-D; happiness factor).

Biomarkers: At the baseline and final visits, approximately 15 mL (2-3 teaspoons) of blood will be drawn from each participant by the VA Clinical Laboratory via standard blood draw. Three inflammatory markers will be assayed: high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-). Assays will be conducted using standardized methods through the VASDHS 6th floor research laboratory of Co-I Richard Hauger, MD.

Additional final visit measures: Participants will complete the modified Differential Emotions Scale (mDES) (Fredrickson et al., 2003) at each weekly session to assess changes in positive emotion during the course

of treatment. Credibility of the interventions will be assessed at the final visit with a 3-item measure adapted from Borkovec & Nau (1972) and the Client Satisfaction Questionnaire (Attkisson & Greenfield, 1994) as well as via post-intervention interviews.

Analytic plan:

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 and residuals of regression model with a normal probability plot. The present project is intended as a feasibility study that will inform, support, and guide development of a subsequent larger-scale VA Merit Award project. Therefore, the primary analysis will be descriptive rather than hypothesis testing. Since the interventions are delivered by group (8-10 participants per group), it is possible that measured or unmeasured characteristics of the participants in a given group or their interactions may affect psychological response to the intervention, attendance, and study outcomes. The analysis plan described below is based on no cluster effect of class. But we will assess the impact of clustering effects by fitting a random effects model for each outcome, and, if necessary, a random class effect will be included in the model to account for the correlations between the individuals in the same class. The intraclass correlation coefficient (ICC) will also be estimated to understand the correlation within class and provide advice for sample size adjustment in future studies.

Will older Veterans with psychological distress [anxiety and/or depression] enroll in and complete the proposed CM intervention? What is the completion rate? Do participants adhere to the treatment (complete practice at home)? We will assess the following outcome measures for enrollment, completion, and adherence to treatment:

1) *Enrollment rate* defined as the proportion of consented subjects among all screened and eligible patients;

2) *Initiation rate* defined as the proportion of subjects who initiate the intervention among all consented subjects;

3) *Completion rate* defined as the proportion of subjects who complete 6 or more sessions (out of a total of 10 sessions) of intervention among those who start the intervention;

4) *Practice time at home* defined as average minutes that subjects practice at home each week. The mean (and SD) or percentage will be calculated and the 95% confidence intervals will be estimated for all outcomes.

The associations between patient characteristics and other clinically important baseline variables with the enrollment, completion and adherence will be assessed using univariate tests (Wilcoxon rank sum test, Kruskal-Wallis test, Fisher's exact test, or Spearman correlation coefficient).

Does CM show promise for improving well-being, symptom severity, and/or positive psychological factors relevant to successful aging? We will evaluate the improvement in depression and anxiety (BSI), social connection (SCS-R), satisfaction with life (SWLS) and positive emotions (mDES) from baseline to post-intervention using a linear random effect model and time will be included as a main effect in the model. The random effects model is suitable for examining changes in outcomes in longitudinal studies. It will include all available data, minimizing the effects of missing data on the analyses.

We will also examine the mean (and SD) change scores for each inflammatory biomarker (hs-CRP, IL-6, and TNF-), as well as the association of these changes with practice time.

Sample size assessment:

The sample size was determined based on practical consideration. Since this is a feasibility study, the goal is to examine the effect size such that it can guide future studies. We plan to enroll a total of approximately 24 to 30 participants for the CM groups (3 groups, 8-10 per group) as well as 10 participants for the healthy aging group. Sample size analyses were focused on the CM group, and performed using statistical package R.
A two-sided type I error of 0.05 was assumed.

The sample size justification was conducted for assessing the enrollment and completion rates (primary outcomes). We assessed the precision of estimates based on projected sample size. From previous investigations, the estimated enrollment and completion rates are between 0.57 and 0.82. Therefore, we considered a range of rate from 0.60 to 0.90 and estimated the margin of error (half of the width) for the 95% confidence interval of enrollment and completion rates The margin of error of a 95% confidence interval for a proportion is 1.96*p*(1-p)/(Square-root of *n*) where *n* is the estimated sample and p is the estimated rate. If an estimated intervention initiation rate is 0.80, a sample size of 30, 27 and 24 will produce a two-sided 95% confidence interval with a margin of error of 0.058, 0.071 and 0.064, respectively. For an estimated completion rate of 0.60, a sample size of 30, 27 and 24 will produce a two-sided 95% confidence interval with a margin of error of 0.086, 0.091 and 0.096, respectively.

We assessed the power for detecting a significant change in psychological outcomes. With a sample size of 24, 27 and 30, we will have 80% power to detect an effect size of 0.53, 0.56 and 0.60 for the change in outcomes from baseline to post-intervention. These effect sizes are achievable based on previous studies, where we observed an effect size of 0.5 for PHQ-9 (mean = 2.3, SD = 4.6), 0.65 for SCS-R (mean = 6.4, SD = 9.9), 1.4 for SWLS (mean = 9.0, SD = 6.6), 0.53 for mDES positive emotion (mean = 4.8, SD = 9.1), and 5.35 for mDES negative emotions (mean = 7.5, SD = 1.4).

Women and ethnic minorities*:* Women and ethnic minorities will be included in proportion to their representation of Veterans in the VASDHS and PCMHI program. This proportional sampling plan fosters both feasibility of the study and overall generalizability of findings. We recognize that the issues of anxiety and depression among women Veterans is exceptionally important, but warrants separate studies designed and focused specifically to address the issues of most salience to women Veterans.

Children*:* No children will be included as the scientific focus of this project is on older Veterans

Temporary COVID-19 Updates*

***Virtual Research Sessions and Cisco WebEx:** During the COVID-19 administrative hold, ORD-funded grants are not permitted to have in-person study visits (including blood draw) for non-clinically critical research assessments. Therefore, we will conduct Compassion Meditation (CM) group therapy sessions and individual pre- and post-intervention sessions using the VA-approved telehealth technology, "Cisco WebEx." We will use Cisco WebEx to conduct the remaining CM group therapy sessions and post-intervention sessions with the first participant cohort as well as to conduct virtual research sessions with future cohorts that are enrolled during the COVID-19 administrative hold. We will use Cisco WebEx to create digital recordings of the group therapy sessions for training and supervision of the study therapist. The recordings will be stored as digital files on the secure VASDHS R-drive network in the PI's R Drive folder (R: Palmer B) and will only be accessible to VA IRB-approved study staff. The use of Cisco WebEx to conduct virtual research visits is explained to participants in the new Verbal ICF/Script (see attached "Uploaded Documents").

Cisco WebEx is a subscription-based managed service that connects VA to a fully featured FedRAMP Cloud solution. It offers resources for conferencing, webinars, training, collaboration and more. VA staff can schedule and host conferences with both internal VA users and external participants. It is a PIV-enabled and integrates Single Sign-On (SSO). Only staff that need to host or scheduled a meeting need an account.

All scheduled WebEx meeting links will be emailed to each participant securely via Azure encrypted email one day prior to the scheduled meeting day.

Additional information about Cisco WebEx privacy and security features is included in Sections 9.11 and 27.5.

Prior to the first virtual group session, a member of the study team will assist each participant in using Cisco WebEx to ensure participants are comfortable using the program during the virtual research visits. The study therapist, Dr. Malaktaris, will also review proper participant etiquette and expectations for the new virtual format. Dr. Malaktaris will review the previous 3 therapy sessions materials and ensure the participants are comfortable moving forward in the remaining virtual therapy sessions. During the virtual group sessions, a member of the study team will be available to assist participants with any difficulties they may have.

We will also mail a packet to each participant, which will include information and instructions for virtual research visits, instructions for using Cisco WebEx, and printouts of the weekly study questionnaires. Participants will be instructed NOT write their name, date, initials, or any other personally identifiable information on any of these documents. Prior to each of the group training sessions, a member of our study team will meet one-on-one with each participant via Cisco WebEx to review and collect participants' responses to the questionnaires.

***Blood-Based Inflammatory Biomarkers:** The collection of blood-based inflammatory biomarkers, which were included for exploratory purposes, will not be collected during the COVID-19 administrative hold.

***New "Uploaded Documents" for use during COVID-19 Administrative Hold:**

1. Verbal ICF/Script for virtual study sessions with the current participant group
2. General instruction letter for virtual research visits
3. "Joining a WebEx Meeting" instruction letter
4. "Participating in a WebEx Meeting" instruction letter
5. CAIR Pandemic Questionnaire**
6. 4-item Duke Social Support Index**
7. 6-item De Jong Gierveld Loneliness Scale**

**The CAIR Pandemic Questionnaire was developed by the VA Center of Excellence for Stress and Mental Health (CESAMH). The nature of our study population (ages 55 years and above, identified in VA primary care) includes risk factors for worse reactions to infection from this virus. In addition to the profound medical challenges inherent to the COVID-19 pandemic, the necessary safety and prevention social distancing requirements are likely to affect social interactions, relationships, and loneliness. Some aspects of these changes may be positive for some persons,

and negative for others. The focus of the study on anxiety and depressive symptoms in terms of compassion, self-compassion, and connectedness, also has direct relevance to these secondary effects of the pandemic. Thus, in order to collect systematic data on the effects of the pandemic on our participants in these aspects, we will administer the CAIR Pandemic Questionnaire, 4-item Duke Social Support Index, and 6-item De Jong Gierveld Loneliness Scale.

Post-Intervention and Participant Withdrawal Data**

**As a result of the COVID-19 administrative hold, 3 participants withdrew from the study because of lack of technology (devices and/or WIFI) necessary for virtual training sessions and data collection. With their permission, we will mail the post-intervention study questionnaires (except MOCA and PHQ-9) to the participants who withdrew from the study in order to obtain important post-intervention and withdrawal data. Participants will be compensated $75 for their time. Participants will be given a pre-paid and addressed envelope to return their completed questionnaires to the study team at VASDHS. They will be instructed NOT to write any PII or VASI on their questionnaires or return envelope.

[redacted]

Section 9.8 Questionnaires & Surveys

9.8) Provide the name and a reference for questionnaires/surveys that are standard or identify them here and attach a copy of the questionnaire/survey. ***Questionnaires or surveys that are not clinical standard references must be uploaded. Reference the help link for additional information related to surveys administered to VA personnel and approved platforms for web-based surveys.***

10-item version of the Connor-Davidson Resilience Scale (Campbell-Sills & Stein, 2007)

12-item Short Form Health Survey (Ware, Kosinski, & Keller, 1996)

6-item short-form De Jong Gierveld Loneliness Scale (De Jong Gierveld & Van Tilburg, 2006)

4-item Duke Social Interaction Subscale (Landerman et al. 1989)

3-item intervention credibility measure (Borkovec & Nau, 1972)

CAIR Pandemic Impact Questionnaire (CESAMH, 2020)

Center for Epidemiological Studies – Depression Scale (Fowler & Christakis, 2008)

Client Satisfaction Questionnaire (Attkisson & Greenfield, 1994)

Cognitive and Affective Mindfulness Scale – Revised (Feldman et al., 2007)

Generalized Anxiety Disorder scale (Spitzer et al., 2006)

Life Orientation Test – Revised (LOT-R; optimism)(Scheier, Carver, & Bridges, 1994)

Modified Differential Emotions Scale (mDES) (Fredrickson et al., 2003)

Patient Health Questionnaire – 9 item (Kroenke, Spitzer, & Williams, 2001)

San Diego Wisdom Scale (Thomas et al., 2019)

Satisfaction with Life Scale (Diener et al., 1985)

Self-Compassion Scale – Short Form (Raes et al., 2011)

Social Connectedness Scale - Revised (Lee, Draper, & Lee, 2001)

Toronto Empathy Questionnaire (Spreng et al., 2009)

UCLA Loneliness Scale - Third Edition (Russell, 1996)

References for above scales:

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Fowler, J. H., & Christakis, N. A. (2008). Dynamic spread of happiness in a large social network: longitudinal analysis over 20 years in the Framingham Heart Study. Bmj, 337, a2338.

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[redacted]

Section 10 - Human Subjects

10) Describe the characteristics of the proposed subject population. Include age, gender, ethnicity, and health status as appropriate. ***Note: Data about people are still considered "human subjects" by the IRB, so even if you do not intend to contact the patients whose charts you will review, you still describe the characteristics related to the subjects whose charts you will review.***

- **Provide inclusion and exclusion criteria as appropriate. Provide a statement how non pregnancy is confirmed if pregnancy is an exclusion criteria.**
- **For multisite studies, provide the total number of subjects from all sites and include description of the local site's role as a coordinating center if applicable.**
- **Indicate the number of VA participants to be studied.**
- **Indicate the estimated number of consented subjects that will fail the screening process, if any.**

The sample for the proposed study will include up to 40 Veterans identified through the Veterans Affairs San Diego Healthcare System (VASDHS) Primary Care Mental Health Integrated (PCMHI) program. Participants will be men and women, ages 55 years and older, with mild-to-moderate symptoms of anxiety or depression as defined by a score of 5 to 14 on the 7-item Generalized Anxiety Disorder Scale (GAD-7) or 5 to14 on the 9-item Patient Health Questionnaire (PHQ-9).

Inclusion criteria: (1) VASDHS patient, (2) current age > 55 years, (3) mild-to-moderate anxiety or depressive symptoms (as defined above) at the time of enrollment, (4) stated intention to attend the 10 group sessions at the scheduled times at the VASDHS in addition to the baseline and follow-up study assessment visits, as well as to complete the outside homework assignments, and (5) provides written informed consent for participation.

Exclusion criteria: (1) No active suicidality/homicidality in the preceding six months, (2) untreated alcohol or substance use disorders (those co-enrolled in the VASDHS Alcohol and Drug Treatment Program will be eligible), (3) changes to psychiatric medications within six months of baseline evaluation (changes to medications during the course of the study will be permitted as determined appropriate by Veteran's treating clinicians, but changes will be recorded to further describe the sample), (4) medical and/or psychiatric instability interfering with current ability to engage in the group sessions and outside homework assignments.

As part of the routine clinical service/care, all Veterans referred to the PCMHI service are screened for depressive symptoms with the PHQ-9, and for anxiety symptoms with the GAD-7. Thus we do not expect screen failures among participants who consent the consent process.

Section 10.6 Avoiding coercion of students or employees

10.6) Indicate how coercion of students and/or employees will be avoided:

Students will not be included.
Employees of the investigators will not be recruited, but other VASDHS employees can be recruited /enrolled.

Section 11 - Recruitment

11) Describe, step-by-step, the plans for recruitment of subjects (or selection of subjects as in record review). This description must include how, when, and where potential subjects are approached as well as procedures for identifying potential participants (through medical records, physician referral, third-party sources, etc.). Include how selection is equitable. Indicate if vulnerability to coercion may be present and if so plans to ensure voluntary participation.

Recruitment:

Potential participants will be recruited through the VASDHS PCMHI program. The investigators will inform the clinical providers of the PCMHI clinics about the study and will provide VASDHS IRB-approved Provider Referral Information sheets, which will assist referring providers in identifying and referring potential participants to the study. Referring PCMHI clinicians who are meeting individually with potential Veteran participants may indicate Veteran interest in participation through a VA-encrypted email or a separate (or addendum to clinical visit) CPRS note using the text template below:

CPRS note: "Veteran is willing to be contacted by phone regarding CBCT study (PI Palmer) by the PI or study staff." Provider will add Carolyn Eidt to CPRS note to alert us to its presence.

In addition, PCMHI providers will be given our IRB-approved participant brochure summarizing the project that can be given to appropriate patients to call our study staff for further information about the study.

Screening:

We request a partial HIPAA waiver to conduct pre-screening CPRS chart review for all interested participants to ensure there are no immediate exclusion criteria noted prior to initiating contact with interested participants via phone (see Protocol Section 12).

Individuals who agree to be contacted by phone by the PI or study staff, as well as those who call our study phone number, will be asked to provide verbal consent to participate in a brief telephone screen (see attached Oral Consent/Phone Screen form). If no immediate exclusions are identified via the telephone screen, participants will be scheduled to come in for an in-person study visit (i.e., "Baseline Visit"), to review and discuss the information in the IRB-approved informed consent and HIPAA documents, and to be screened to determine eligibility to participate in the Compassion Meditation sessions.

During the Baseline Visit, Dr. Palmer, Lang, or Maglione, or an appropriately trained RA under our supervision will meet with the participant to review and discuss the information in the IRB-approved informed consent and HIPAA documents. Participants will be provided with an opportunity to read the consent document and/or to have it read to them. After thorough discussion, including answering any questions from the potential participant, willing participants will be asked to sign the informed consent and HIPAA documents to indicate their consent to participate.

Equity will be fostered by adherence to the inclusion/exclusion criteria listed above as the basis for enrollment. As part of the informed consent process, potential participants will be informed that participation is entirely voluntary so as to minimize any potential feelings of coercion or undue influence.

Section 11.1 Recruitment Materials

11.1) Identify all recruitment materials (flyers, advertisements, letters, etc.) that will be used; include the web address for any web-based advertisements. The text of all communications with prospective participants must be reviewed and approved by the IRB before it can be used. You will be reminded to attach copies of recruitment materials to the initial submission packet.
Note: Posting of flyers with pull tabs is not permitted within VASDHS (including the VMRF building).

The recruitment materials will include a VASDHS IRB-approved Provider Referral Information sheet, which will be given to PCMHI referring providers only, as well as an IRB-approved participant brochure that may be given to potential Veterans participants. Any additional recruitment materials will be submitted as protocol amendments for IRB review and approval; no recruitment materials will be used unless and until approved by the VASDHS IRB.

Section 12 - Informed Consent

12) Indicate whether or not each category of consent is involved in this study:

12a) Will the study team obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without (or prior to) obtaining informed consent of the prospective subject or the prospective subject's LAR?

(•) Yes ( ) No

Check one or both of the below boxes if they apply to this study:

Overall, risks of harm from this protocol itself appear unlikely and/or are unlikely to result in enduring harm or disability.

Section 15 - Risk Management

15) Describe the procedures for protecting against or minimizing any potential risks/discomforts, and the adequacy of resources for conducting the study and resources participants may need as a consequence of the research. When applicable, include detail of the following safety measures: (a) The type of safety information to be collected, including AEs; (b) Frequency of safety data collection; (c) Frequency or periodicity of review of cumulative safety data; (d) Statistical tests for analyzing the safety data to determine if harm is occurring; and (e) Conditions that trigger an immediate suspension of the research. See ? for further requirements.

Interviewers are trained to be sensitive and respectful of any concerns that subjects may have, including their right to refuse to answer any questions that make them uncomfortable, and their right to stop the interview, leave a group session, or terminate participation at any time. Study staff are also trained to be alert and offer breaks as appropriate to the participant's needs.

Confidentiality of study materials is protected by using coded ID numbers, rather than names or other personally identifiable information (PII), on hardcopy and electronic study documents and in any analyses. Hard copy data will be maintained in locked file cabinets at the VASDHS and electronic data will be stored in password-protected files in the PI's R Drive folder behind the secure VA firewall. All hardcopy and electronic data will be accessible only to IRB-approved study personnel. The code-book that links ID numbers to participants will be maintained in a locked cabinet accessible on a "need to know" basis to IRB-approved study personnel.

As per standard VA group therapy protocols, during group sessions all participants will be reminded of the importance of keeping information about others in the group confidential, and participants will also be informed of this risk and their right to not reveal private information during the group sessions.

The compassion meditation training as well as the psychoeducational healthy aging groups will be led by experienced clinical psychologists, with VA privileging for provision of psychotherapy and mental health clinical assessments. The group leader will be sensitive and alert for participants whose conditions appear to worsen and referral for appropriate standard clinical care will be made. In addition, no changes to psychotropic treatment will be initiated as part of participation in this study.

Risks involved in phlebotomy are minimized by using only highly experienced, licensed phlebotomists at the VA Clinical Laboratory who will have a fully self-contained phlebotomy kit for each subject. After data extraction, any residual blood from each sample will be destroyed and the extracted data will be subsequently stored in password-protected files in the PI's R Drive folder behind the secure VA firewall.

In addition, Drs. Palmer, Lang, Maglione, and Casmar are VA-approved mental health clinicians, and one or more will be available at all times in person or by phone during study visits to assess and address any emergent clinical concerns that may arise.

Section 17 - Potential Benefits

17) Discuss benefits that may be gained by the subject as well as potential benefits to society in general (see ? for guidance)

Through this project, we will learn more about the feasibility of employing compassion meditation training in future larger scale studies to examine its potential as an effective intervention for psychological distress among older Veterans in primary care. This is important given the under-utilization of mental health services among psychologically distressed, older VA patients. In addition, as a strengths-focused intervention, we may find CM more acceptable to this population than are symptom-focused treatments. We will also learn whether the psychoeducational group focused on healthy aging is a feasible control condition for subsequent use in a randomized clinical trial. Veterans may or may not benefit from participation in either group. Participants in the psychoeducational group may learn useful information relevant to promoting successful aging, such as information about exercise, diet and nutrition, as well as positive mental health factors such as resilience. It is possible that participants in the compassion meditation training group may experience improvement in positive emotions, reduced negative emotions, and better social connectedness.

The feasibility information from this study is of critical importance to guide and inform a subsequent larger-scale VA Merit Award application that will be focused on a hypothesis driven RCT to determine the

effectiveness of compassion meditation training as an intervention for psychological distress among older Veterans. It will provide information about adaptations needed to the specific manualized compassion meditation protocol/manual, CBCT-Vet, and for the psychoeducational healthy aging group, so that both are feasible and appropriate for the future RCT and for use with this study population. This line of research, moreover, can fill an essential unmet need for novel strengths-focused interventions to address anxiety and depressive symptoms among older Veterans in primary care.

Section 18 - Risk/Benefit Analysis

18) Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

Given the potential value for research that may benefit future patients, as well as the possible but uncertain benefit to participants, and the relatively minor associated risks, with adequate provisions for protection against risks, the risks associated with this protocol are reasonable and outweighed by potential benefits.

Section 20 - Compensation for Participation

20) Provide all details and justifications of the compensation plan. See ? for detailed requirements.

Participants will receive payment for participation at 2 time points: $100 for the first visit and $150 for the final visit, for a total of $250 per person. This level of compensation is concordant with that provided in similar psychosocial intervention research and is intended to compensate participants for the time and burden associated with the research procedures and assessments.

Post-Intervention and Participant Withdrawal Data:
Participants who withdrew from the study due to lack of technology (devices and/or WIFI) necessary for virtual training sessions and data collection during the COVID-19 administrative hold will be compensated $75 for completing the post-intervention questionnaires.

[redacted]

Section 22 - Bibliography

22) List relevant articles that the IRB can use to provide necessary background for the protocol. Do not include an extensive NIH-grant-style bibliography. (Up to 5 recommended, but use more if needed to support the protocol or citations above.)

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Vogelzangs, N., Beekman, A. T., de Jonge, P., & Penninx, B. W. (2013). Anxiety disorders and inflammation in a large adult cohort. Transl Psychiatry, 3, e249.

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