Department of Veterans Affairs Internal Review Board

Research Protocol

Content Requirements for Full Committee Review

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Department: Mental Health and Behavioral Sciences Service (MHBSS)

Study Title: Mindful Self-Compassion for combat deployed Veterans with Moral Injury and co-occurring PTSD-SUD.

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Location of Study:
All assessment and intervention sessions will be conducted at the Veterans Affairs Medical Center in Providence, Rhode Island.

Time Required to Complete the Research:
The project start date is 10/01/2018 and the study will continue until 09/30/2021 (with NCE).

NCT Number: NCT03681288

Contents

1. Synopsis

PTSD-SUD is particularly common following combat exposure, and Veterans with PTSD-SUD experience more severe symptomatology, increased risk of suicidality, poorer quality of life, and poorer response to existing treatments than Veterans with either disorder alone. Combat Veterans often report experiencing moral injury defined as perpetrating, failing to prevent, or witnessing acts that violate the values they live by in their civilian lives. Veterans who negatively appraise their actions or inaction during combat may experience guilt, a common posttraumatic reaction. Posttraumatic guilt has been implicated as a risk factor for the development and maintenance of several forms of psychopathology including PTSD, SUD, depression, and suicidality.

Mindful Self Compassion (MSC) combines the skills of mindfulness and self-compassion, providing self-soothing skills to respond to difficult thoughts and feelings. Self-compassion (SC) emphasizes kindness towards one's self, a feeling of connectedness with others, and mindful awareness of distressing experiences. Furthermore, because SC is negatively associated with self-criticism, rumination, thought suppression, anxiety, and depression, and positively associated with healthy psychological functioning, it is well suited to addressing posttraumatic psychopathology, shame, and guilt.

This proposal will begin to address a gap in the field's knowledge about MSC, and its role in the treatment of co-occurring disorders in Veterans with moral injury. The study will recruit 48 Veterans with PTSD-SUD and moral injury to participate in pilot groups of MSC. We will evaluate changes in self-compassion, post-traumatic guilt, shame, and PTSD and SUD symptom severity. In addition to symptom reduction, we will focus on functional outcomes (e.g., quality of life, suicidality).

The specific aims of the proposed study are as follows: 1) to test acceptability and feasibility of MSC with Veterans with PTSD-SUD and moral injury, 2) to provide preliminary evidence of the effects of MSC, and 3) refine study procedures and make adaptations to MSC as applied to Veterans based upon experience gained in the pilot in preparation for a fully powered RCT to test the effectiveness of MSC.

2. Abbreviations and Acronyms

PTSD = Posttraumatic Stress Disorder
SUD = Substance Use Disorder
OEF/OIF/OND = Veterans of Operation Iraqi Freedom, Operation Enduring Freedom, and Operation New Dawn
PE = Prolonged Exposure
MSC = Mindful Self-Compassion
SC = Self-Compassion
SCFT = Self-Compassion Focused Treatment
RCT = randomized control trial

SEM = Standard Error of Measurement
NCCIH = National Center for Complementary and Integrative Health
DSM = Diagnostic and Statistical Manual
CPT = Cognitive Processing Therapy
CBT = Cognitive Behavioral Therapy
IRB = Institutional Review Board

3. Introduction

3.1 Background, significance, rationale

PTSD-SUD is common following combat exposure, affecting a rapidly increasing number of U.S. military Veterans (Petrakis, Rosenheck, & Desai, 2011). The co-occurrence of these disorders presents added challenges to the VA treatment delivery system, presently in need of effective integrated treatments. Veterans with PTSD-SUD experience more severe symptomatology, increased risk of suicidality, reduced quality of life, and poorer response to existing treatments than Veterans with either disorder alone (Maguen et al., 2010; Nash, 2007; Possemato, Wade, Andersen, & Ouimette, 2010). Furthermore, research examining Veterans of Operation Iraqi Freedom, Operation Enduring Freedom, and Operation New Dawn (OIF/OEF/OND) suggests that a significant number are at risk of poor community reintegration upon return home from deployment (Resnik & Allen, 2007). These findings underscore the need to effectively and efficiently address comorbidity in Veterans who present to treatment.

One approach is to develop interventions that target mechanisms thought to underlie multiple highly prevalent disorders, such as guilt and shame related to traumatic experiences. The experience of a moral injury suggests the inability to contextualize or justify actions (or inaction), and the unsuccessful accommodation of those morally challenging events into pre-existing moral schemas, resulting in guilt and shame (Litz et al., 2009). Posttraumatic guilt has been implicated as a risk factor for the development and maintenance of several forms of psychopathology including PTSD, SUD, depression, and suicidality (Bryan, Morrow, Etienne, & Ray-Sannerud, 2013; Hendin & Haas, 1991; Hyer, McCranie, Woods, & Boudewyns, 1990; Litz et al., 2009; Sher, Braquehais, & Casas, 2012). However, to date, treatments for posttraumatic psychological health have been primarily disorder specific, with a focus largely on symptom reduction. Therefore, greater understanding of modifiable factors that influence PTSD-SUD and functional impairment is needed to enhance treatment efforts and aid the readjustment of war Veterans.

Moral Injury is a Promising Target for Intervention. Combat soldiers face many moral and ethical challenges (Drescher et al., 2011; Litz et al., 2009). They may violate their own deeply held moral beliefs, witness the unethical behaviors of others, or question the justness of their country's involvement in war. As a result, they may experience internal conflict between morally questionable actions and their beliefs. In addition, soldiers often witness intense human suffering and cruelty, thereby shaking many core beliefs about humanity (Worthington & Langberg, 2012).

Litz and colleagues present a model of moral injury (Litz et al., 2009) highlighting the distress and difficulties commonly faced by combat Veterans. Initial empirical work exploring the potential causes of and consequences associated with moral injury suggest that the construct is distinct from the classic fear-based conception of trauma. In a qualitative study, findings indicated that the most commonly identified stressors that might precipitate a moral injury included betrayals (e.g., leadership failures, failure to act in accordance with one's personal values), incidents involving injury or harm to civilians (e.g., killing, unnecessary destruction of property), within-rank violence (e.g., friendly fire incidents), inability to prevent death/suffering, and ethical dilemmas/moral conflicts (Drescher et al., 2011). Likewise, just as potential causes of moral injury extend beyond threat to life, the potential indicators of moral injury also extend beyond anxiety and fear-based emotional responding (Flipse Vargas, Hanson, Kraus, Drescher, & Foy, 2013). In addition to PTSD and mental health disorders routinely assessed in military populations, possible indicators of moral injury include disproportionate guilt and shame, social or relational issues (e.g., avoiding intimacy, anger, reduced trust in other people), spiritual/existential problems (e.g., loss of spirituality or weakened religious faith, lack of forgiveness), substance use, and suicide and other self-harm behaviors (Drescher et al., 2011; Flipse Vargas, Hanson, Kraus, Drescher, & Foy, 2013; Litz et al., 2009).

Trauma-related guilt is highly prevalent and well-documented among military Veterans. In a Veteran sample with PTSD, 54% endorsed experiencing posttraumatic guilt in their lifetime, 35% reported being moderately to extremely bothered by these symptoms (Miller et al., 2013). Guilt has been shown to partially mediate the relationship between combat exposure and symptoms of PTSD and depression in Veterans (Browne, Evangeli, & Greenberg, 2012; Marx et al., 2010) and has been implicated as a risk factor for the development of multiple forms of posttraumatic psychopathology, including SUD (Dearing, Stuewig, & Tangney, 2005; Ianni, Hart, Hibbard, & Carroll, 2010; Kim, Thibodeau, & Jorgensen, 2011; Leskela, Dieperink, & Thuras, 2002; Marlatt & Donovan, 2005). Guilt related to trauma is also associated with suicidal ideation, particularly among combat Veterans (Bryan, Morrow, et al., 2013; Hendin & Haas, 1991; Hyer et al., 1990). Furthermore, shame has been robustly associated with substance use, anger, and aggression (Farnsworth, Drescher, Nieuwsma, Walser, & Currier, 2014). Several studies have found that shame is associated with higher risk for suicide in service members (Bryan, Ray-Sannerud, Morrow, & Etienne, 2013), even when controlling for concurrent depression and PTSD symptoms (Bryan, Morrow, et al., 2013). Numerous clinical descriptions of combat-related symptomatology specify shame and self-condemnation as a central source of dysfunction and an obstacle to recovery (Clewell, 1987; Haley, 1974; Singer, 2004).

Treatment Targeting Guilt and Moral Injury is Needed. The VA-DoD Clinical Practice Guidelines for comorbid PTSD-SUD (Defense, 2010), and an Institute of Medicine report on treating PTSD in Veterans (Institute of Medicine, 2012) concluded that more research is needed to develop and evaluate treatments that address PTSD-SUD comorbidity. Currently, Seeking Safety (Najavits, 2002) is the most widely implemented and available approach for co-occurring PTSD-SUD. Outcome findings, however, have been mixed and it has not outperformed treatment as usual in clinical trials (Hien, Cohen, Miele, Litt, & Capstick, 2004), including with Veteran samples (Bowen et al., 2014; Hien et al., 2009). If, as suggested by the self-medication hypothesis, avoidance and

distress related to guilt and shame cognitions are contributing to substance use, resolution or amelioration of moral injury and associated guilt and shame may be necessary for substance use treatment to be fully effective. Current front-line interventions for trauma have shown efficacy in reducing PTSD in military samples (Eftekhari et al., 2013; Monson et al., 2006), but concerns about client drop-out, nonresponse rates, and the fit between the proposed therapeutic mechanisms and moral injury raise questions about the effectiveness of these interventions for all forms of trauma (Nash & Litz, 2013; Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008). Further, posttraumatic guilt appears to be less amenable to change by exposure based treatments such as prolonged exposure (PE; Foa, Chrestman, & Gilboa-Schechtman, 2008) than other forms of posttraumatic distress and has been found to impede the processing of fear and other emotions related to traumatic events (Arntz, Tiesema, & Kindt, 2007; Brewin, Dalgleish, & Joseph, 1996; Foa & Meadows, 1997; Henning & Frueh, 1997; Mills et al., 2012; Nishith, Nixon, & Resick, 2005; Pitman et al., 1991; Riggs, Dancu, Gershuny, Greenberg, & Foa, 1992). Consequently, trauma-related guilt and shame may continue to burden Veterans who struggle with PTSD and potentially prevent them from being able to recover (Kubany & Watson, 2003).

Therefore, there is a need for additional and complementary therapeutic options targeting trauma-related moral emotions such as guilt and shame. These emotions are highly distressing, challenging to treat, and associated with poorer psychosocial function and maintenance of multiple disorders including PTSD-SUD. A recent review (Farnsworth et al., 2014) of the moral injury literature suggests that as a complement to evidenced-based treatment approaches, interventions that promote mindfulness and target the elicitation of positive moral emotions (e.g., self-compassion) may work to improve spiritual, social, and psychological functioning by promoting tolerance and adaptive responses to negative emotional states (Gilbert, 2009; Hayes, Strosahl, & Wilson, 2011; Neff & Germer, 2013).

3.2 Mindful Self-Compassion

Mindful Self-Compassion (MSC; Neff & Germer, 2013) is an 8-session group program that combines the skills of mindfulness and self-compassion (SC), utilizing self-soothing skills to respond to difficult thoughts and feelings with kindness, sympathy, and understanding through meditation. A growing body of research has documented the beneficial effects of directing compassion toward oneself, a process that Neff describes as "being touched by and open to one's own suffering, not avoiding or disconnecting from it, generating the desire to alleviate one's suffering and to heal oneself with kindness" (p. 87; Neff, 2003). MSC is negatively associated with aversive emotions, including guilt and shame (Gilbert & Procter, 2006), self-criticism, rumination, thought suppression, anxiety, and depression in the general population. In addition, SC is positively associated with healthy psychological functioning (e.g., overall life satisfaction; MacBeth & Gumley, 2012; Neff, 2012; Neff, Rude, & Kirkpatrick, 2007). MSC is therefore well suited to address moral injury, negative moral emotional states (e.g., guilt and shame) and poor psychosocial functioning among Veterans (Section 7.6 and Appendix D describe the components of the intervention).

Role of MSC in PTSD-SUD Treatment. Mindfulness and SC are overlapping but distinct constructs that characterize how people relate to emotional distress. MSC combines the awareness of mindfulness and the self-soothing qualities of SC to bring attention to and tolerate difficult

emotions. The overarching philosophy is that individuals need mindfulness to be self-compassionate; one has to be aware that one is suffering while one is suffering, otherwise there cannot be a compassionate response. In other words, mindfulness can be viewed as the first step in learning to be more self-compassionate. Self-compassion comes next and is the emotional attitude of mindfulness in the face of suffering. Whereas mindfulness training orients the practitioner to moment-to-moment experience, compassion training focuses on the experiencer. Both mindfulness and SC allow one to live with less resistance to oneself and one's life (C. Germer, personal communication, July 2016).

Recent literature links both mindfulness and SC with improvement in multiple life domains (Neff, 2012), reduced emotional stress (Gilbert & Procter, 2006; Neff, 2012), and lower levels of psychopathology (MacBeth & Gumley, 2012), including reduced levels of shame and self-criticism among clinical and general cohorts (Albertson, Neff, & Dill-Shackleford, 2015; Gilbert & Procter, 2006; Leaviss & Uttley, 2015; Shahar et al., 2015). SC has also been shown to be a modifiable trait for civilians and Veterans that can increase via SC focused programs (Gilbert & Procter, 2006; Kearney et al., 2013; Neff & Germer, 2013); as well as mindfulness-based programs (Kuyken et al., 2010; Shapiro, Astin, Bishop, & Cordova, 2005; Shapiro, Brown, Thoresen, & Plante, 2011). MSC is a promising treatment for guilt, shame, and experiential avoidance, mechanisms that can impede PTSD and SUD treatment and successful reintegration of Veterans, and thereby has the potential to bolster treatment outcomes. Further, research suggests that self-compassion serves as a buffer to negative emotion while simultaneously encouraging taking responsibility for personal failures (Leary, Tate, Adams, Batts Allen, & Hancock, 2007). Thus, MSC may be ideally suited for work with moral injury in that it does not require acquittal from personal culpability in order to provide benefits. Given the complexity of Veterans presenting with PTSD-SUD, treatment often involves a multi-pronged approach. MSC is promising as an addition to treatment programs or for non-responders to trauma-focused treatments.

Mindfulness and SC have been associated with reduced experiential avoidance among civilian (Keng, Smoski, Robins, Ekblad, & Brantley, 2012) and Veteran (Vujanovic, Niles, Pietrefesa, Schmertz, & Potter, 2013) samples, a mechanism associated with the maintenance of PTSD-SUD symptoms (Foa, Steketee, & Rothbaum, 1989; Held, Owens, Schumm, Chard, & Hansel, 2011; Tangney, Stuewig, & Mashek, 2007), and shame (Kubany & Watson, 2003). SC has been associated with a greater willingness to engage painful emotions and a lower need to avoid painful experiences (Leary et al., 2007; Neff et al., 2007). Individuals high in SC may be less likely to feel threatened by and, therefore, avoid painful thoughts, memories, and emotions. Instead, they may be more likely to experience a natural process of exposure to trauma-related stimuli (Vujanovic et al., 2013). Additionally, SC practice may activate the innate soothing and self-regulating functions (Gilbert, 2014), which, in turn, helps balance the overactive threat system commonly observed with posttraumatic stress (Lee & James, 2013).

Regarding substance use, there is evidence to suggest lower levels of mindfulness, and SC among those with alcohol use disorders than the general population (Brooks, Kay-Lambkin, Bowman, & Childs, 2012), indicating that increasing mindfulness and SC may aid in reducing the reliance on substances to avoid negative affect and psychiatric symptoms. Indeed, research indicates that

civilian participants with substance use disorder who received mindfulness-based relapse prevention exhibited significantly lower risk of relapse to substance use and heavy drinking and, among those who continued to use substances, significantly fewer days of substance use and heavy drinking at the 6-month follow-up (Bowen et al., 2014).

Mindfulness & Self-Compassion Treatment with Veterans. Few studies have directly examined SC treatment among Veterans; however, preliminary findings suggest that SC is a modifiable and teachable trait in this population (Held & Owens, 2015; Kearney et al., 2013). In an uncontrolled treatment study, a sample of 42 Veterans with PTSD completed a 12-week loving-kindness meditation course designed to facilitate feelings of compassion for self and others. SC was negatively associated with total symptom severity, and participants reported increases in SC and decreases in PTSD symptoms at posttreatment and 3-month follow-up. Moreover, changes in SC mediated the reduction in PTSD symptoms, suggesting that compassion may serve as a mechanism for moral repair (Kearney et al., 2013).

Similarly, significant associations were found among mindfulness and SC with PTSD symptom severity and functional disability in 115 trauma-exposed Iraq and Afghanistan Veterans (Dahm et al., 2015). Results indicated that mindfulness and SC were each uniquely, negatively associated with PTSD symptom severity and functional disability.

Another study examined the concurrent and prospective relationship between SC and PTSD symptom severity after accounting for level of combat exposure and baseline PTSD severity (Hiraoka et al., 2015). SC was negatively associated with baseline PTSD symptoms and predicted 12-month PTSD symptom severity after accounting for combat exposure and baseline PTSD severity. Findings suggest that SC is a potentially modifiable factor implicated in the development and maintenance of PTSD and that interventions that increase SC may be beneficial for treating chronic PTSD symptoms in Veterans.

Finally, one study examined the effects of a 4-week self-administered SC training on trauma-related guilt in comparison to a stress-inoculation control group in 47 homeless male Veterans (Held & Owens, 2015). Participants in both interventions reported increased levels of SC and equal reductions in trauma-related guilt, providing preliminary evidence for the use of SC and stress-inoculation as effective interventions for guilt.

In sum, a small but growing body of research indicates that mindfulness and SC have theoretical relevance for understanding moral injury and associated guilt and shame, as well as the development and maintenance of PTSD and substance use in war Veterans.

3.3 Summary and Significance

Use of alternative therapies in the treatment of Veterans is an area of increased interest within the VA (US Dept of Veteran Affairs, 2011), and a 2016 objective of the National Center for Complementary and Integrative Health (NCCIH) is to conduct studies in “real world” clinical settings to test the safety and efficacy of complementary health approaches (NCCIH, 2016). Veterans with co-occurring PTSD-SUD are more likely to have increased psychiatric symptoms, medical problems, social and family problems, unemployment, suicidality and poorer treatment

compliance (Brown, Recupero, & Stout, 1995; McGovern, June 2005; Najavits et al., 2007; P. Ouimette, Moos, & Finney, 2003; P. C. Ouimette, Finney, & Moos, 1999; Read, Brown, & Kahler, 2004). Services researchers have also tracked higher residential, inpatient, and other treatment utilization (Calabrese et al., 2011; Edens, Kasprow, Tsai, & Rosenheck, 2011). Posttraumatic guilt and shame have been linked to several forms of psychopathology and distress, including PTSD and SUD. MSC has been shown to reduce key symptoms of posttraumatic symptomology, including avoidance, rumination, depression, anxiety, and overall distress. However, MSC has not been examined in Veterans thus far. There have been a handful of VAs nationally that have initiated the implementation of MSC among Veterans (G. Serpa, personal communication, February 2018), however the program has not been systematically evaluated and there has been no data published to date. This intervention has the potential to improve outcomes for Veterans with moral injury and add to existing options for practitioners to more effectively help their patients with this challenging comorbidity. If, as hypothesized, MSC leads to increased SC, and reductions in posttraumatic guilt, shame, this would reduce burden and stress on Veterans, caregivers, and healthcare systems. Given the chronicity of symptoms for Veterans with PTSD-SUD and the need for alternative and integrated treatment approaches for co-occurring disorders, this study represents an innovative and significant contribution to the field.

4. Objectives *

Our objective is to conduct a Stage I study of MSC with Veterans with co-occurring PTSD-SUD. The primary goals of this project are to conduct a pilot study of MSC with Veterans with PTSD-SUD within a group modality and evaluate changes in self-compassion, post-traumatic guilt, shame, and PTSD and SUD symptom severity. In addition to symptom reduction, we will focus on functional outcomes (e.g., quality of life, suicidality). The specific aims of the proposed study are as follows:

1. To test acceptability and feasibility of MSC with Veterans with PTSD-SUD and moral injury as indicated by recruitment, retention rates, and participant feedback.
2. To provide preliminary evidence of the effects of MSC. We hypothesize that:
    2a. Participants will endorse increased self-compassion, and reduced posttraumatic guilt and shame following MSC.
    2b. Participants will report improved quality of life, lower PTSD and depressive symptoms, and greater percent days abstinent (PDA) post-treatment and at follow-up after completing MSC.
3. EXPLORATORY AIM: Suicidality. We hypothesize that MSC will decrease suicidal ideation. This aim will be evaluated descriptively by examining clinically meaningful change pre- to post-treatment.
4. To refine study procedures and make adaptations to MSC as applied to Veterans based upon the experience gained in the pilot in preparation for a fully powered RCT to test the effectiveness of MSC.

5. Study Methodology *

5.1 Overview of Design

This project will use a non-randomized, longitudinal design to conduct a pilot trial of MSC with Veterans who endorse moral injury and are presenting for PTSD-SUD treatment. We will recruit 48 eligible Veterans who will be consented in person. They will then complete their baseline assessment with a trained clinician by their choice of in person, via VA Video Chat, Zoom for Healthcare or by telephone and attend 8 sessions of MSC group format with trained clinicians. In general, groups will be held in person in the PVAMC. During the time of the COVID-19 pandemic, groups will be held virtually via VA Video Chat (VVC) or Zoom for Healthcare. Participants will complete follow-up assessments at post-treatment, and 1-month follow-up virtually via VA Video Chat (VVC), Zoom for Healthcare, or by telephone (see Table 1). Participants will also have the option to complete the self-report measures during baseline, follow-up (post-treatment and one-month), and process assessments (during group) through Qualtrics. Qualtrics will be used for self-report measures only and will include the following measures: PCL, SCS, CSQ, ISS, TRGI, IES, TRSI, Qual-LIFE, WHODAS, and PHQ. The same procedures will be used for Qualtrics across all time points including baseline, process measures during group, post-treatment and one-month follow up. We will gather feedback from participants in order to guide potential refinement of the MSC protocol for further study.

5.2 Setting and Feasibility of Recruitment

The PVAMC is the site for the proposed research and includes specialized outpatient programs in PTSD and substance use. During fiscal year 2013, approximately 3,600 Veterans with a primary or secondary diagnosis of PTSD received outpatient mental health services at PVAMC. It is estimated that the prevalence of co-occurring PTSD-SUD among treatment-seeking Veterans with PTSD is approximately 40% (Milliken, Auchterlonie, & Hoge, 2007; Thomas et al., 2010). We further estimate that between 27%-36% of Veterans with PTSD-SUD will endorse significant moral injury based on current research examining posttraumatic guilt in Veterans with PTSD and alcohol use disorder (S. Norman, personal communication, May 29, 2015). These numbers are more than sufficient to meet our recruitment goals (N=48). We estimate that we will need to assess approximately 48 Veterans (20% more than our target sample) in order to allow for those who may be ineligible or will discontinue participation after the initial evaluation. At the expected rate of 2-3 participants per month, the timeline for recruitment is approximately 12 months. We are aware of the difficulties in recruitment for this population and acknowledge that long waitlists can lead to dropout. As such we have elected to have smaller groups (4 groups of 6 members) in order to minimize wait time.

5.3 Experimental condition - MSC Program

MSC (Neff & Germer, 2013) is an 8-session group program designed to teach SC and mindfulness skills. For the purposes of this study, we elected to include the original MSC protocol unchanged as a first step to investigate its feasibility among Veterans with PTSD-SUD. The MSC program includes 2 core meditations, 9 additional meditations, and 18 informal SC practices. The ultimate goal is to be in the presence of personal suffering with a sense of safety, so that the pain is felt and the process of healing can begin. Participants are encouraged to be experimental in how

they adapt the practices to their own lives. MSC sessions will highlight the three interacting components of SC: 1) self-kindness versus self-judgment, 2) a sense of common humanity versus isolation, and 3) mindfulness versus over-identification when confronting painful thoughts and emotions. Each session of the program focuses on a specific topic as well as formal and informal SC exercises (See Appendix D). In order to be considered as receiving a sufficient dose of treatment, participants must attend at least 5 of the 8 sessions.

6. Study population

6.1 Participants

We will recruit 48 Veterans who endorse moral injury and co-occurring PTSD-SUD (4 groups of 6 - 12 each) enrolled at the Providence VA Medical Center. Potential subjects will be receiving PTSD or substance use treatment services at the PVAMC, and will be referred by clinicians in these respective clinics (or self-refer) for participation in the study.

Eligibility criteria were designed to recruit a representative sample of Veterans with co-occurring PTSD-SUD. Eligible participants will be enrolled at the Providence VA Medical Center:

Inclusion criteria:

1) moral injury as captured by at least one "strongly agree" response on the Moral Injury Events Scale;
2) diagnosis of PTSD (within the last 30 days) confirmed by the Clinician Administered PTSD Scale (CAPS) with a total symptom score of 25 or more;
3) diagnosis of a substance use disorder confirmed by the Structured Clinical Interview for DSM-5 Section E (SCID-E);
4) willing and able to provide informed consent. and
5) not currently receiving trauma-focused treatment.

Exclusion criteria:

1) individuals with an acute psychotic disorder or acute psychotic symptoms are not eligible if their symptoms are unstable and if they are not well connected with appropriate mental health services;
2) patients with a psychiatric hospitalization or suicide attempt within the past month will be excluded; and
3) Currently receiving trauma-focused treatment (e.g., PE, CPT, CBT for PTSD). Patients currently enrolled in trauma-focused treatment may be enrolled when they have completed the treatment if they remain interested and continue to have PTSD.
4) individuals with life-threatening or unstable medical illness. Diagnoses of mild cognitive impairment (e.g. mTBI) and other anxiety and depressive disorders will not be excluded because of their high comorbidity with PTSD and SUD.[80]

7. Study procedure *

7.1 Recruitment, Screening, and Informed Consent Procedures

Recruitment Procedures. Participants will be recruited from a range of sources. The primary recruitment source will be the Providence VA Medical Center, including the OEF/OIF/OND specialty primary care clinic, the Returning Veterans Outreach Program, Collaborative Addiction and Recovery Service (CARS), and the Trauma Recovery Service (TRS). Drs. Shea, Capone and Eaton are members of the TRS clinic staff and will coordinate efforts with the appropriate mental health staff to refer patients to the study. The current TRS clinic caseload includes close to 1800 Veteran with PTSD, average of 7-8 referrals per week. Thus, the PVAMC has a very large pool of potential participants for recruitment. Study participants will also be recruited through outreach efforts to local Vet Centers and CBOC's, military family organizations, community-based troop support organizations, and Veteran organizations.

A recruitment flyer and brochure will be designed to reach eligible veterans. Included on this flyer and brochure is contact information for the project coordinator. Flyers and brochures will be distributed in the PVAMC mental health clinics and available to view on clinic television monitors. Additionally, flyers will be posted on the Providence VA Medical Center's Facebook page, sent out electronically via MyHealthEVet and to those people who follow the PVAMC's Twitter account. All postings will be sent electronically by the PVAMC's Public Relations Officer who has approved all newly proposed recruitment methods pending the PVAMC's Institutional Review Board (IRB)'s approval. Language to be used on Twitter by the PVAMC's Public Relations Officer will be approved by the PVAMC's IRB as well.

Screening Procedures. Potential subjects will be receiving or presenting to care for PTSD, substance use or other mental health services and will be referred for participation by clinicians providing those services. Additionally, Veterans may self-refer via posted flyers.

If interested, potential participants will have the option of signing a form giving permission to the investigators to contact them, or they can contact the investigators directly. In addition, should the referral come directly from the potential participant's provider (without the form providing permission to contact), potential participants will be sent a recruitment letter (see Appendix A) notifying them that the study coordinator will be contacting them by phone to invite them to participate in a phone screening for the study. Approximately one week after the recruitment letter is sent, the project coordinator will contact potential participants by telephone (see phone script, Appendix B) to provide information that will enable potential participants to decide whether they want to be considered for the study (i.e., purpose of the study, description of the intervention condition, audio recording of sessions, time commitment required for both treatment and assessment, and schedule of payments).

The project coordinator will review the patient's electronic medical record to screen for broad eligibility criteria (e.g., absence of psychotic disorder diagnosis or suicide attempt in the last month) and chart diagnoses (we will obtain a waiver of written informed consent in order to screen referred Veterans' medical charts to determine preliminary eligibility, i.e., PTSD symptoms, substance use).

Interested and eligible individuals will obtain an appointment with the project coordinator. During this next stage of screening, interviewers will review the Informed Consent forms to explain the study in greater detail.

Informed Consent Procedures. The participant will be fully informed of the nature and extent of study participation, the objectives of the study, and the MSC intervention. Participants will also be informed about the follow-up assessments they will complete. Participants will be given as much time as they need to review the consent form, to ask questions as needed, and to make a decision as to whether or not to participate. Participants will be told that they may refuse participation without any negative consequences, and that if they decide to participate, they will be free to withdraw from the study at any time. Informed consent is considered an ongoing process and members of the research team will regularly answer questions about the study and inquire about the subject's experience as a participant throughout the duration of the study. The project coordinator and evaluators will be trained to ensure that participants comprehend the study and the consent form and willingness to adhere to study conditions. Potential participants will sign the consent and receive a copy to take home.

Consent visits will be held face-to-face following the COVID-19 precaution guidelines including social distancing and proper PPE equipment (e.g., face masks). All consent procedures will take place in Building 32 at the Providence VA Medical Center. After reviewing the consent form, the interviewer will ask the participant if they are interested in proceeding with the next phase of screening to determine if s/he meets all study inclusion/exclusion criteria. If s/he is willing to proceed s/he will also be asked to sign a HIPAA authorization form.

Once the consent procedures are complete, participants may elect to continue with the initial assessment in-person or remotely via video (VVC or Zoom) or via telephone. The screening assessment takes about 2-3 hours and is done by a trained interviewer.

Initial Screening Assessment

- The interviewer will ask you questions about your stressful life experiences and related problems, your use of alcohol and drugs, and your mood.
- The interviewer will also ask you about current and past mental health treatments you may have received, including medications.
- You will receive compensation in either a $50 gift card or electronic funds transfer (EFT) for your time after the interview is done.
- If you are eligible for the study based on these questions, you will go on to the next step in the study. If you are not eligible, you will be finished with the study. We will refer you back to your treatment providers at the VA for continued treatment.

In the final stage of screening, assessors will complete interviews to establish inclusion and exclusion criteria, as described below (see Measures). Participants that do not meet the inclusion criteria will be referred back to their current treatment providers at PVAMC. Participants

providing informed consent and meeting inclusion/exclusion criteria as confirmed by the baseline will be scheduled for an initial MI session (see Appendix E) with a study therapist and then will be assigned to receive 8 sessions of MSC. If participants are determined to be ineligible, they will not complete the MI session, nor be assigned to MSC.

For this study, participants will not be randomly assigned to treatment condition; all eligible subjects will receive MSC in a group format facilitated by MSC certified teachers (TBD).

With the exception of participating in trauma-focused treatments, participants may continue to receive their existing mental health services (e.g., medication management, skills-based groups) and we will carefully track these throughout their involvement in the study.

All participants will be assessed immediately post-treatment and at 1-month follow up. Participants will be compensated for time spent completing the three assessments and will receive $50 for each assessment in the form of gift cards to local stores (e.g., CVS) or Electronic Funds Transfer (EFT) per assessment. We anticipate that the baseline assessment will take approximately 2.5-3 hours and follow-ups will take approximately 2 hours to complete. We will attempt to obtain follow-up data on all participants, regardless of whether or not they complete the intervention portion of the study.

7.2 Measures

If informed consent is granted, the participant will be interviewed by an on-site member of the research team for the baseline assessment. If the subject continues to meet eligibility criteria (i.e., PTSD and SUD diagnoses are confirmed), he or she is invited to continue participation in the study. In either case, the subject receives a $50 gift card for completing the baseline interview.

All assessment measures are described below and summarized in Table 1.

Table 1. Measures by assessment point

	Baseline	During TX (wkly)	Post-TX FU	1M FU
Feasibility Assessments				
Client Satisfaction Questionnaire			X	
Home SC Practice		X	X	X
Self-Compassion				
Self-Compassion Scale	X	X	X	X
Impact of Event: Avoidance Subscale	X		X	X
Guilt/Shame and Moral Injury				
Trauma-Related Guilt Inventory	X		X	X
Internalized Shame Scale	X		X	X
Trauma Related Shame Inventory	X		X	X
Moral Injury Questionnaire	X			
Moral Injury Events Scale	X			
Quality of Life & Functioning				

Quality of Life Enjoyment and Satisfaction Questionnaire	X		X	X
The WHO Disability Assessment Schedule	X		X	X
PTSD & SUD Assessments				
Clinician Administered PTSD Scale	X		X	X
PTSD Checklist	X	X	X	X
SCID Substance use disorders section	X			
Timeline Follow-Back	X		X	X
Full Combat Exposure Scale	X			
Exploratory Aim				
Beck Scale for Suicidal Ideation	X		X	X
Screening & Control Measures				
Demographics	X			
Treatment Services Received	X		X	X
Patient Health Questionnaire	X		X	X
COVID-19 Measure	X		X	X

Feasibility Assessments:

Client Satisfaction Questionnaire (Larsen, Attkisson, Hargreaves, & Nguyen, 1979): an 8-item questionnaire assessing treatment satisfaction.

Rates of recruitment, retention, and attendance will also be used as measures of feasibility.

Home SC Practice: will be assessed by self-report of type, frequency, and duration.

Self-Compassion Outcomes:

Self-Compassion Scale(Neff, 2003): is a 26-item self-report questionnaire in which respondents describe how they relate to themselves during times of distress. Higher scores reflect higher levels of SC.

Impact of the Event (Avoidance)-Revised(Weiss & Marmar, 1997): Used to measure avoidance of difficult thoughts and feelings.

Guilt, Shame and Moral Injury Outcomes:

Trauma-Related Guilt Inventory (Kubany et al., 1996): is a 32-item self-report measure assessing traumatic guilt. The TRGI has three scales—Global Guilt, Distress, and Guilt Cognitions.

Internalized Shame Scale (Cook & Coccimiglio, 2001): is a 30-item self-report measure assessing shame proneness scored on a 5-point Likert scale. The ISS yields sum scores for two subscales, self-esteem and internalized shame.

Trauma Related Shame Inventory (Øktedalen, Hagtvet, Hoffart, Langkaas, & Smucker, 2014): is a 24-item measurement instrument that assesses for shame within the context of trauma.

Moral Injury Questionnaire-Military Version (Currier, Holland, Drescher, & Foy, 2015): assesses a comprehensive range of moral injury events that might occur in warzone deployments. The measure covers several different types of betrayals (i.e., by peers, leadership, trusted civilians, or self), acts of disproportionate violence in the warzone (e.g., acts of revenge and/or retribution,

unnecessary destruction of civilian property), incidents involving death/harm to civilians, acts of violence committed within military ranks (i.e., friendly fire incidents), inability to prevent death/suffering, and ethical dilemmas or moral conflicts from deployment-related decisions/actions (e.g., violating rules of engagement to save the life of a comrade or civilian.
Moral Injury Events Scale (Nash et al., 2013): The MIES is a 9-item scale measuring exposure to events in a military context with the potential to contradict deeply held moral beliefs and yields two subscales: 1) perceived transgressions and 2) perceived betrayals. Participants rate their agreement/ disagreement to each situation on a scale of 1 = strongly disagree to 6 = strongly agree.

Quality of Life and Psychosocial Functioning Outcomes:
Quality Of Life Enjoyment & Satisfaction Questionnaire (Endicott, Nee, Harrison, & Blumenthal, 1993): is a validated self-report measure that includes 8 subscales examining a variety of domains. The 16-item General Activities sub-scale will be used to measure perceptions of satisfaction with daily life.
The World Health Organization Disability Assessment Schedule (Üstün, 2010): is a 26-item self-report measure of functional disability in the past 30 days. It provides a total score based on six domains: mobility, self-care, cognition, getting along with others, participation in society, and life activities.

PTSD and SUD Assessments:
Clinician Administered PTSD Scale for DSM-5(CAPS-5; Weathers et al., 2013) will be administered to assess diagnostic criteria for PTSD. Participants must meet criteria on this measure, considered the "gold standard" for PTSD diagnosis, to be eligible for the study. Participants must also have a total score of 23 or greater, which constitutes at least a moderate (or clinically significant) level of symptom severity. The follow-up version will be used at post-treatment and at 1-month follow-up as a primary measure of outcome.
Structured Clinical Interview Patient Edition, Section E (SCID; First et al., 1996): For the present study, DSM-5 version of the SCID, Section E, will be administered at baseline to assess for the presence of current (past three months), severe substance use disorder (SUD) and alcohol use disorder (AUD). Diagnostic information from the SCID-I/P will be used to assess eligibility criteria as well as for descriptive purposes.
PTSD Checklist (PCL-5; Weathers et al., 2013) is a 20-item self-report measure that assesses DSM-5 symptoms of PTSD and PTSD symptom severity on a 5-point scale. The self-report rating scale is 0-4 for each symptom, from "Not at all" to "Extremely." We will use this measure to track PTSD symptoms throughout treatment.
Timeline Follow-back (Sobell & Sobell, 1992): gathers self-report information about alcohol and other substance use for the past 90 days.
Full Combat Exposure Scale (Hoge et al., 2004): is an18-item measure designed to assess a range of combat elements (e.g., receiving small arms fire, provided aid to wounded). Participants rate their frequency of exposure to each situation on a scale of 0 = never to 4 = 10 or more.

Exploratory Aim Assessment:

Beck Scale for Suicidal Ideation (Beck & Steer, 1991): is a 21-item self-report of current (past week) intensity of attitudes, behaviors, and plans to commit suicide.

Screening and Control Measures:

Demographics: Basic demographics (e.g., age, gender, race/ethnicity) will be collected at the baseline assessment as well as military service information (e.g., branch of service, rank, number of deployments).

Treatment Utilization (Keller et al., 1987): The Longitudinal Interval Follow-Up Assessment (LIFE) treatment section provides information about mental health and medical treatments, including number of hospitalizations, days spent in hospital, and number of outpatient visits for non-mental health medical treatments, mental health contacts, including inpatient and outpatient treatment, and psychiatric medications, including dosages. A baseline version (LIFE-Base) assesses mental health treatment received prior to entering the study. We will adapt the LIFE-Base to assess whether prior treatment focused specifically on PTSD or substance use. The LIFE treatment section will be administered at post-treatment and at the 1-month follow-up assessments to track any non-study treatment received.

Patient Health Questionnaire (PHQ; Spitzer et al., 1999) self-administered 9-item survey assessing severity of depressive symptoms. This self-report measure will be used to track symptoms that are commonly comorbid with PTSD and expected to change along with PTSD.

Coronavirus Stressor Survey (COVID-19; McLean & Cloitre, 2020) self-administered 10-item survey assessing different levels of stressful experiences related to the ongoing coronavirus pandemic. is a survey will be used to determine stressors patients face during the coronavirus pandemic? This assessment will be given at all assessment timepoints

Process Assessments. During treatment, MSC teachers will administer the Home SC Practice and the PTSD Checklist (PCL), and the Self-Compassion Scale (SCS) to each participant every week in order to regularly assess severity of PTSD symptoms, level of self-compassion and home practice. Regular assessment of symptoms will help inform treatment directions and track symptoms over the course of treatment. During the COVID-19 pandemic, these weekly assessments will be completed either over the telephone or via a Qualtrics survey. Qualtrics surveys will be preferable as they reduce burden on staff and participants. All participants will be asked if they are comfortable receiving a Qualtrics survey to complete self-reported assessments, and if not, will continue to complete assessments over the telephone. Qualtrics is accessed through Brown University credentials and is a HIPAA compliant platform. The surveys within Qualtrics for process assessments will include the PCL and SCS. Participants will be sent their own participant-specific link to the survey. The links will be sent to the participant's email by study staff using their secure VA email accounts only. Furthermore, participants will be informed that: "This link cannot be forwarded to others, it is unique to your study ID number" in the email containing the link to the survey. They will be reminded to keep all study communications confidential and to complete the survey in privacy. When participants fill out the surveys, the data comes back to the website, only linked to their unique study ID. See section 8.1 for details about Qualtrics data security.

Follow-up Assessments. Upon completion of the treatment sessions, the participants will again be interviewed by a member of the research team (i.e., post-treatment follow-up and one-month follow-up). The post-therapy assessment will consist of the Client Satisfaction Survey, Home SC Practice, SCS, Impact of the Event, Avoidance Subscale, TRGI, ISS, QoL, WHO, CAPS, PCL, TLFB, BSSI, Treatment Services Received, PHQ-9. The subject is compensated in the form of a $50 gift card for completing the assessment. All research activities, including all assessments and therapy sessions will be conducted on-site at the Providence VA Medical Center. During the COVID-19 pandemic, follow-up assessments will be completed remotely via telephone or Zoom. Participants will also have the option to complete the self-report assessments during follow-ups through Qualtrics. For follow-ups, assessments within Qualtrics would include PCL, SCS, CSQ, ISS, TRGI, IES, TRSI, Qual-LIFE, WHODAS, and PHQ. The same process used for Qualtrics during the group assessments would be used for the follow-up assessments.

Intervention Feedback and Post-Intervention Exit Interviews

During week 4 and at the end of the MSC intervention, participants will complete questionnaires assessing the perceived usefulness and comprehension of MSC modules and the appropriateness of the daily home practice assignment. At the conclusion of the 8-week MSC intervention, participants will also complete a brief satisfaction measure, as well as a semi-structured qualitative exit interview conducted by either Drs. Capone or Eaton. The interview will be used to collect further information regarding the perceived usefulness and applicability of MSC. Further, to determine the safety, feasibility and acceptability of the intervention, we will examine adherence to intervention sessions, percent of completed home practice logs, dropout rates, and adverse events. Dr. Eaton, along with co-investigators will consult regularly to review and discuss participant feedback and exit interview responses and consider potential modifications to the MSC intervention.

7.3 Assessor Training and Evaluation

The project assessor will complete standardized training to criterion for the CAPS, SCID and TLFB assessments. Training will be conducted by Dr. Capone. The assessor will observe a minimum of two assessments for each measure and then be observed for a minimum of two assessments. The assessor will not complete assessments until achieving at least .80 interrater reliability on practice assessments. During the study, a random sample (20%) of audio recordings will be independently evaluated by Dr. Capone on a monthly basis to provide feedback and evaluate interrater reliability. The assessor's ratings will be compared with Dr. Capone's ratings and any discrepancies in ratings will be discussed.

7.4 Procedures to Enhance Completion of Assessment Protocols

A number of procedures will be used to minimize the likelihood that participants will fail to complete the schedule of assessments. Self-report measures will be completed at the time of the assessment and reviewed for completeness before the participant leaves. We will monitor carefully for fatigue and encourage breaks if needed. We will obtain the name and phone number of a close relative, friend, or other person who is likely to maintain contact with the participant, and to contact that person if attempts to contact the participant are unsuccessful. Post-treatment and the 1-month follow-up assessment will be conducted in person. The

participant will receive a letter or telephone call one week prior to the interview and a similar reminder a few days prior.

Five contact attempts will be made before a participant is considered to be unreachable at that time point. Participants who fail to appear for a scheduled assessment will be contacted by phone, or mail or email when necessary, for rescheduling. If participants move away during their participation in the study or are otherwise unavailable for an in-person interview, we will perform follow-up assessments over the telephone to avoid missing data. Participants will be compensated $50 for the pre-treatment, post-treatment, and follow-up interviews.

7.5 Compensation

Participants will be compensated for the time required to complete all assessments. They will be paid $50 for the baseline, post-treatment, and 1-month follow-up assessments.

7.6 Description of Mindful Self-Compassion Intervention

Mindful Self Compassion will be conducted either in person or virtually via video visits using VA Video Chat or Zoom for Healthcare in a group setting over 8 sessions, 2-2.5 hours per session dependent on level of COVID-19 limitations placed upon research. The program is designed to teach SC and mindfulness skills. The MSC program includes 2 core meditations, 9 additional meditations, and 18 informal SC practices. The ultimate goal is to be in the presence of personal suffering with a sense of safety, so that the pain is felt and the process of healing can begin. Participants are encouraged to be experimental in how they adapt the practices to their own lives. MSC sessions will highlight the three interacting components of SC: 1) self-kindness versus self-judgment, 2) a sense of common humanity versus isolation, and 3) mindfulness versus over-identification when confronting painful thoughts and emotions. Each session of the program focuses on a specific topic as well as formal and informal SC exercises (See Appendix D). In order to be considered as receiving a sufficient dose of treatment, participants must attend at least 5 of the 8 sessions.

The treatment groups will be conducted by trained MSC teachers (TBD). Each session of the program focuses on a specific topic, and the content is outlined in Table 2.

Table 2. MSC Sessions

Session Number	Topic
1	Discovering Mindful Self-Compassion
2	Practicing Mindfulness
3	Practicing Loving Kindness
4	Discovering your Compassionate Voice
5	Living Deeply
6	Meeting Difficult Emotions
7	Exploring Challenging Relationships
8	Embracing Your Life

7.7 Therapist Selection, Supervision and Adherence Monitoring

Therapists will be certified MSC Teachers, having completed the MSC Teacher Training Program. Since the therapists will have already been trained and certified in MSC, no additional training will be conducted with regard to the conduct of MSC. Two MSC teachers will lead the treatment groups over the course of 8 weeks. Therapists will be carefully supervised by Dr. Greg Serpa (a MSC teacher and National Mindfulness Consultant for the Department of Veteran Affairs) using audio recordings of group therapy sessions. These recordings will be reviewed only by study research staff including Dr. Serpa (a licensed clinical psychologist at the VA Greater Los Angeles Healthcare System) to see how well those conducting the sessions and the interviews are doing. Recordings will be kept confidential and will be stored in a restricted file on a secure VA server, and only our research team including Dr. Serpa will be able to hear them.

Dr. Serpa will have access to our secure research server (\\vhaproappres01.v01.med.va.gov\RESEARCH_PROTOCOLS\Eaton\MSC) and recorded sessions to provide supervision to our study staff. Bi-weekly clinical supervision sessions will examine clinical issues and adherence to the study protocol. Every caution will be taken to protect disclosure of information protected under HIPAA during supervision with Dr. Serpa. Audio recordings will be identified via study ID number and not include any personal identification of participants. Supervision will focus on broad clinical issues, flow of group material, and adherence to study protocol.

Study investigators will listen to audio-recordings of each therapist and complete fidelity rating sheets for each session. Further, Dr. Serpa will provide bi-weekly supervision of therapists to evaluate their implementation of and adherence to the therapy manuals. In addition, therapists will keep a session by session "MSC Session Tracking Form," which includes self-ratings about the "% of time" spent "using the manual" and covering the relevant module content.

All sessions will be conducted locally and audio recorded using Cyber Acoustics cvl-1084 USB Desktop Microphones and the VA computers' Windows audio recording program. The USB microphones will plug directly into the computer using the sound recorder program. These audio recordings will be saved and stored on the VA secure server behind the VA firewall (\\vhaproappres01.v01.med.gov\research_protocols\Eaton\MSC-R). For supervision purposes, Dr. Serpa will have access to a VA approved encrypted thumb drive (FIPS 140-2 Validated Removable Storage Device: Aegis Secure Key - USB 3.0) to download audio and listen off-site. These data will be used only for the purpose of training, supervision, and adherence ratings.

7.8 Timetable

Table 3. Timeline of the proposed project

	Year 1				Year 2			
Activities	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Research team recruitment and training	X	X						
Obtain IRB approvals	X	X						
Recruitment of participants		X	X	X	X			
Treatment phase			X	X	X	X		
Follow-up phase				X	X	X	X	
Data collection, entry, and management			X	X	X	X	X	
Statistical analyses						X	X	X
Report writing, preparation & submission							X	X

8 Data Management *

8.1 Data Management

All data collected for this study will be used for research purposes only. Study data (all de-identified), including digital recordings of assessments and therapy sessions, will be managed using the secure VA server. Only research staff will have access to the original data. The project coordinator will oversee data management procedures. He/she will be responsible for initial editing and correction of forms before data is entered. As forms are entered into the database, they will be checked against the participant-tracking file to ensure that all data that are gathered have been entered. Furthermore, (1) data sheets will be stored in locked offices of research study staff, building 32 of the PVAMC, (2) data will be entered in coded form, (3) data will be stored on a secure server behind the VA firewall (\\vhaproappres01.v01.med.va.gov\research_protocols\Eaton\MSC-R, (4) data will be protected from unauthorized access by passwords, (5) information that might potentially allow an individual participant to be identified will not be allowed in any publications or reports sent to individuals outside the study, (6) all employees who are to handle data will be trained in confidentiality policies and procedures, and (7) all data-related incidents will be reported to the local ISO and PO per VA policy.

Study files will be maintained in accordance with the Department of Veterans Affairs Record Control Schedule 10-1. Only personnel involved in the study will have access to the data base.

The Brown University-licensed Qualtrics provides a web-based, secure, Health Insurance Portability and Accountability Act (HIPAA) compliant platform which meets all VA security/encryption/storage requirements; their data handling procedures meet strict privacy standards (https://www.qualtrics.com/privacy-statement/). The Brown University Qualtrics surveys will not contain any PHI; patient study ID will be imbedded in the link to the survey itself. Anyone with access to the survey links will be able to access the surveys; however, they will not be able to view participant responses that were submitted as part of the survey. The Brown University Qualtrics data centers utilize many security measures. Brown University Qualtrics' database access is restricted and requires authorization. The PI and co-investigators will be able to access the study Brown University Qualtrics account. Only those staff who need access to

Brown University Qualtrics to perform their job duties will be given user access. Web traffic does not directly access the database and database requests are reversed proxy via an application server to the database. All information is secured via industry standard firewalls and stringent IT security policies and procedures. Brown University Qualtrics utilizes industry standard web application firewalls and DDOS protection. Brown University Qualtrics also leverages panel partners who are meticulous in their multiple levels of security, which include redundant data centers, secure servers, encryption which includes one-way encryption, numeric IDs, secure .NET platforms, security clearance, industry standard firewalls, 24/7 monitoring of data centers, confidentiality agreements, and physical, electronic, and managerial procedures. Brown University Qualtrics uses Transport Layer Security (TLS) encryption (also known as HTTPS) for all transmitted data and protect surveys with passwords and HTTP referrer checking. Data are processed by application servers and sent to database servers for storage. Web data are delivered to the respondent in the form of survey questions, graphics, and other content created in the survey design. While Brown University Qualtrics typically tracks IP addresses as part of its protocol, our research project will opt out of IP address tracking to ensure that survey responses remain confidential. Once a participant completes a survey on Brown University Qualtrics, the data will be downloaded from the Brown University Qualtrics secure server and securely stored on the VA's network server and combined with the study's REDCap dataset at the PVAMC. It will then be permanently deleted/destroyed on the Brown University Qualtrics server by the study team. The Brown University Qualtrics study account can be accessed from the VA network system/VA workstation; thus, the downloaded data can be directly saved on the VA server and entered into the REDCap database, eliminating any need for data transfer. No personally identifiable data outlined in the list of 18 HIPAA identifiers are collected as part of the Brown University Qualtrics survey.

8.2 Privacy and Confidentiality

Every effort will be taken to protect the confidentiality of the participants in this study. First, all study personnel who are to handle data will be trained in conducting responsible research and confidentiality policies and procedures. In addition, all research data will be kept in locked files under a study ID number. The name-number code will be kept in a separate locked file. Computerized data will be de-identified and stored on a secure server at PVAMC.

Participants will be informed that some information regarding participation in this study will be included in their VA electronic medical record. Specifically, a brief note indicating that the patient has consented to participate in the study and a note documenting the completion of their participation will be included. Weekly research appointments will also be documented but no detailed information regarding participants' progress will be provided unless there are acute safety concerns. Records will be maintained per Veterans Affairs Record Control Schedule 10-1.

The study therapists may have access to information the participant shares in sessions, not immediately available to their other clinical mental health team members. Therefore, a clear understanding of precisely what information will be freely shared among site personnel is very important. Only necessary information will be shared with the participant's treatment team and these are explained in detail in the consent form. The study therapists will share information

about attendance and status in the therapy, and may share information about the participant's use of substances, PTSD symptom severity, or deterioration in psychiatric symptom or functioning. Specific details about the participant's traumatic experiences and the specifics of the actual study therapy will not be shared unless there is a safety issue (e.g., acute suicidality, marked deterioration in clinical status). In case of a safety issue, only that information critical to maintaining patient safety will be revealed.

Participants will also be informed that due to the nature of groups being held virtually via VVC or Zoom for Healthcare during the COVID-19 pandemic that there are additional precautions that need to be adhered to including finding a private space for phone/video sessions to help keep their sessions private. Participants will be informed that it might be possible that others may overhear or walk into the cameras view allowing identification of other group members during the session.

Participants will also be informed that issues with confidentiality may include study therapists/staff having to work with participants during group sessions on well-being or safety checks if the participant's behavior warrants clinical intervention. Procedures to be used will mirror interventions used in clinical practice. First, in an effort to maintain confidentiality during such an episode, study staff will immediately remove the participant from view to other participants and mute the audio while other study staff work directly with the participant in need. Study staff will then attempt to contact participant directly via telephone. If unable to contact participant, study staff will contact participant's emergency contact for a wellness check. If study staff are unable to contact the participant's emergency contact, study staff will contact the police in order to have them conduct a wellness check. At all times study staff will inform the PI of the status of the participant and the status of the wellness check until the issue is resolved.

As part of standard clinical safety protocol practice, each participant is informed of these limits of confidentiality and the procedures utilized should we become concerned about their safety or the safety of others at the time of the baseline session.

Adverse Event Reporting

8.2 Adverse Events

Under the direction of the PI, all members of the research team (co-investigators, coordinator, therapists) will participate in monitoring adverse events. At each contact, participants will be queried about any physical, emotional, mental, or behavioral problems since the last contact and a determination will be made whether the participant's report of a condition, symptom or event is "serious" and/or "unexpected." A serious AE would include death or disability, life-threatening events, hospitalization or prolonging of existing hospitalization, and atypical and rapid deterioration in functioning. An "unexpected" AE is an event that was not anticipated by or the specificity or severity is inconsistent with the study protocol.

In the case of an Adverse Effect (AE) or unanticipated problem, these incidences will be reported to the IRB per IRB requirements.

9.2 Procedure for the Withdrawal/Termination of Subjects

It will be made clear that participation in this research study is completely voluntary, and the participant may decide to stop his/her participation at any point in the study. A participant will be withdrawn from the entire study if, at any time during the study:

1. The PI feels that continuation in the study would be detrimental, as evidenced by the participant reporting discomfort during study procedures or not meeting study inclusion requirements, including safety aspects, or based on psychiatric health assessment.
2. The participant so desires.

If the participant is terminated from the study by the PI, he/she will be thanked for his/her participation, and the appropriate referrals will be made to ensure follow-up treatment/services are received, if and as needed.

9 Statistical Analysis

9.1 Overall Approach

Our analytical approach is commensurate with Phase I research and will focus primarily on evaluating feasibility of the MSC protocol and examining clinically meaningful change. Statistical analyses will be conducted using intent-to-treat analytic strategies.

9.2 Basic Statistical Analysis

Initial statistical analyses will provide descriptive statistics on the demographic and clinical characteristics of the study participants using means, standard deviations, median, and range for continuous variables and frequencies and percentages for categorical variables.

10.3 Determining Acceptability and Feasibility of Study Procedures and MSC

We will examine whether recruitment met proposed targets within the time frame (N=48 participants). To determine the feasibility and acceptability of MSC, we will examine rates of session attendance, drop outs, completion of assessments, number of adverse events, degree of adherence to the intervention protocol, qualitative exit interviews, and satisfaction ratings. We anticipate that retention in MSC will be comparable to other contemplative and alternative treatments for PTSD with an expected retention rate of at least 75%, and mean satisfaction with MSC in the highest ranked category (>28 of possible 32 points, extremely satisfied). We would consider completion of a minimum of 75% of post-treatment and follow-up assessments to indicate feasibility. We also expect fewer than 5% experiencing adverse events. Home practice will also be examined and the number of minutes spent engaged in MSC formal and informal exercises will be assessed. Finally, therapist input will be collected regarding ease of delivery of the protocol, content, flow, and experience with engaging Veterans in the treatment.

10.4 Clinically Meaningful Change

We hypothesize that participants will endorse increased self-compassion, and reduced posttraumatic guilt and shame following MSC therapy. As a stage 1 study with a small sample,

statistical analyses will focus on direction of effects from pre- to post-treatment and whether there is suggestive evidence of clinically meaningful change. We will examine effect sizes, recognizing the inherent difficulties in relying on effect sizes generated from pilot studies to power larger trials (Kraemer, Mintz, Noda, Tinklenberg, & Yesavage, 2006), and that confidence intervals could potentially be large. Preliminary analyses will include examining patterns of missing data, non-normality of outcome variables, and univariate statistics on all key variables. Consistent with previous behavioral therapy research, we will examine clinically meaningful change using the standard error of measurement (SEM), operationally defined as a reduction in scores by at least one SEM (Eisen, Ranganathan, Seal, & Spiro, 2007).

10.5 Bivariate Correlations

We hypothesize that participants will report improved quality of life, lower PTSD and depressive symptoms, and greater percent days abstinent (PDA) post-treatment and at follow-up after receiving MSC therapy. In this pilot study, we will not have adequate power to investigate whether these mechanisms mediate treatment effects. However, we will be able to examine bivariate correlations among baseline posttraumatic guilt, shame, and SC scores and measures of baseline PTSD, depression, and substance use. We will also examine whether changes in quality of life, posttraumatic guilt, shame, and SC over the course of treatment are correlated with changes in PTSD-SUD symptoms.

10.6 Exploratory Aim: Suicidality

We hypothesize that MSC will decrease suicidal ideation. This aim will be evaluated by examining clinically meaningful change pre-to post-treatment.

10.7 Intention-to-treat vs. Treatment-exposed Analyses

Initial analyses of the primary hypotheses will be conducted on the full sample of assigned participants, regardless of actual exposure to treatment (intention-to-treat sample). It is possible that we will then analyze the subset of participants who were sufficiently exposed to treatment (the treatment-exposed sample). The need to conduct both types of analyses depends on the rate and nature of participation in the treatment. The intention-to-treat sample will include all participants for whom we have follow-up data, even if partial. To accommodate missing values on both outcome and covariates, we will conduct multiple imputation as needed. These analyses are an important gauge on the effectiveness of the interventions under real-world conditions.

10 Quality assurance, monitoring & safety

Data Safety and Monitoring

This study involves low risks to study participants. The PI is responsible for study monitoring and ensuring the safety of participants and the validity and integrity of the data. Research team meetings will be held weekly. The PI will supervise the project coordinator in structured diagnostic interviews, assessments, and data entry.

The PI will ensure that all research team members are familiar with the data and safety monitoring plans, systems for adverse event reporting, data integrity, confidentiality, and the

protection of participants' safety. All study personnel will complete the required training and education on the protection of human subjects and the study will receive initial review and ongoing monitoring by the PVAMC IRB.

Data monitoring will be performed on an ongoing and regular basis. The project coordinator will collect data via interviewer- and self- administered formats, generating both paper and electronic data. All paper data collection forms will be reviewed for accuracy and completeness prior to data entry. Onsite at the PVAMC, paper data will then be entered into a purpose-designed client-server database, and each item will be subject to range testing and validity checks as provided by the data system. We will use a double-entry method whereby data are entered twice and entries are matched against each other to flag inconsistencies, which are then corrected prior to data analyses. Data collected via the computer will also be reviewed by the PVAMC project coordinator for accuracy and completeness before data are compiled for analyses, and will have built-in range testing and validity checks.

11 Finance and resource use*

12.1 Funding

This research is funded by Rehabilitation Research and Development (RR&D) at the Providence VA Medical Center.

Table 4. Project Budget

Project Year	Direct and Indirect Costs
1	74,974
2	75,731
Total	150, 705

12.2 Resources

The research team has sufficient resources available to conduct the proposed study. Dr. Eaton's primary clinical and research office space is on site at the PVAMC where the study will be conducted, and includes telephone/email and internet service, access to photocopier, shredder, fax machine, printers, and adequate storage space to securely store study related data. Co-Investigators Capone and Shea also have office space on site at the PVAMC.

The Providence VA Medical Center (PVAMC) provides health care for Veterans in Rhode Island, southeastern Massachusetts and eastern Connecticut. The PVAMC is a major teaching and research affiliate of the Brown Medical School, with 238 acute care beds and more than 250,000 outpatient visits per year. The PVAMC provides a full range of patient care services with state-of-the-art technology and active affiliations with Brown University and Boston University Medical Schools. It has established patient-oriented research programs in mental health and substance use disorders, dermatology, oncology, gastroenterology, hypertension, and cardiac and

pulmonary diseases. Over 300 University residents, interns, students and fellows are trained at the PVAMC each year.

The proposed research will be conducted in designated research space in Building 32. Available resources include exam rooms, a gait and motion lab, a virtual reality lab, a large conference room, several meeting rooms, a large physical therapy area, and offices used by investigators and research staff. Building 32 is a secure space for research-related equipment and files. Project personal computers are password protected, behind the VA firewall, and are located in locked temperature-controlled offices. The building can only be accessed with limited electronic passkey access. In addition, the IRM of the Medical Center houses a secured research server with ample storage to house the data used by investigators. The database management facilities are built with multiple levels of security. Access to the data is limited to persons with IRB approval and appropriate VA privacy, human subjects, and security training. Access privileges to research project directories on the server are monitored on a quarterly basis by research personnel.

Dr. Eaton also has access to resources in the Department of Psychiatry and Human Behavior (DPHB) at Brown University. Dr. Eaton has full access to Brown's library facilities and on-line access to research materials. Brown University and PVAMC have forged a strong alliance in regard to research and training. The faculty at PVAMC and Brown University include many outstanding psychologists and psychiatrists who are widely recognized for their scientific contributions. There are numerous opportunities for intellectual connections with other investigators including Grand Rounds, Visiting Guest Lecture Series, and monthly faculty meetings. This scientific environment and strong institutional support will undoubtedly contribute to the success of this project. The research team, already well qualified to carry out the proposed work, will have access to other leaders in clinical research to consult with as indicated.

12 Dissemination of Results and Publication policy

The principal investigator will share de-identified datasets, statistics, and results collected from this proposal by depositing these data at the National Library of Medicine (NLM) PubMed Central website repository as this is a VA supported data repository. Additional documentation including metadata that will include information about the methodology and study procedures used to collect the data, details about code, and `definition of variables will also be included.

We will also register with clinicaltrials.gov, which contains over 100,000 trials sponsored by a variety of federal and private industry sources, and receives over 50 million page views per month and over 65,000 visitors daily. Study findings will be submitted to a peer-reviewed journal and presented at professional conferences, such as the International Society for Traumatic Stress Studies, the APA, and appropriate VA and DoD conferences. Dr. Eaton will work with the research team to analyze and disseminate publications.

If we find evidence for the feasibility and acceptability of MSC among the Veteran population, these data will be used to submit a larger RCT.

13 Human Subjects

14.1 Risks/ Benefits Assessment

In previous and current studies of the assessment and SC treatment procedures, no serious adverse events have been observed or reported. Regardless, several protections will be in place regarding the risk of emotional discomfort and every effort will be made to minimize risk of the potential for participant emotional distress. In addition to the training of assessment and therapy personnel to observe and monitor, participants themselves are clearly informed about the risk of emotional upset, are encouraged to let us know if they become upset, and several options for handling this are discussed and detailed in the consent form. Crisis and relapse plans are formulated as standard procedure by the PVAMC programs for all patients, and participants will be encouraged to utilize emergency services, including presenting at the PVAMC Urgent Care clinic or calling the Veterans Crisis Hotline, should the need arise. Any issues that arise are discussed in research team meetings so that all members of the team are aware of potential participant reactions and appropriate responses to them. This also allows us to monitor adverse events, evaluate them according to federal regulations and IRB policies, and decide on an action plan for reporting them when appropriate.

Depressive symptoms will be assessed via the Patient Health Questionnaire (PHQ-9) and Beck Scale for Suicide Ideation (BSSI) at baseline and follow-ups. The project coordinator will administer the PHQ-9 and BSSI and review the participant's responses. If a participant endorses current self-harm thoughts, the project coordinator will notify the PI (Dr. Eaton). The PI will meet with the participant to further assess risk of self-harm, and consult with the research team if necessary. If the participant is deemed at imminent risk, standard procedures for addressing SI will be followed – the participant will be escorted to the Urgent Care Clinic at the Providence VA (equivalent of a walk-in urgent care clinic for crisis management) and, if appropriate, will be offered hospitalization. If Dr. Eaton is not available, the project coordinator will escort the participant to Urgent Care for further evaluation by licensed clinicians.

The proposed research could potentially involve pregnant women and persons with limited literacy. The involvement of pregnant women in the study is clearly within the bounds of the federal regulations (45 CFR 46.204) and poses no additional risk to the woman (or her fetus) beyond what would normally be encountered in a clinical therapy or addiction treatment setting. The additional monitoring, evaluation, and contact provided through the research context will likely offer more protection or support than would a typical treatment setting.

<u>The Risk of Worsening Symptoms or Lack of Improvement during/after MSC:</u> Risks associated with participation in this trial include possible lack of positive response to MSC. There is no guarantee that the MSC program will lead to improvement of symptoms. During the program or after finishing the final session, symptoms may worsen. Although MSC is considered a very safe intervention, it is possible that difficult emotional material will surface during practice. Adverse

events that are identified by spontaneous report and direct query during or after MSC sessions will be referred for appropriate follow-up care according to good clinical practice.

Furthermore, there are potential risks and challenges that may arise during the MSC group sessions and during home practice. These challenges include attuning to and an increased awareness of difficult emotions and body sensations. There is a possibility that participants may experience things more intensely, have an increase in traumatic memory reexperiencing, or relaxation-induced panic or anxiety. It is estimated that these effects occur at rates approximately equal to what happens generally in psychotherapy. Should any of these concerns arise, we encourage participants to discuss with their trained MSC clinician and/or contact the principal investigator. The research team is staffed with licensed clinical psychologists trained to treat such conditions, and the staff will attempt to minimize any discomfort participant's may feel throughout the course of the study.

The Risk of Inconvenience and Burden of Required Time/Travel: Participants may engage in screening procedures and learn they are not eligible for participation in the research treatment trial. Frequent visits to the research clinic, for the MSC training (1 day per week) for 8 weeks, may represent an inconvenience, especially if a participant travels a great distance or has other constraints on their time or transportation.

Psychiatric Interview and Questionnaires: Emotional discomfort may be associated with completing the assessments and questionnaires. Subjects will be informed that if they experience discomfort during symptom assessment, study personnel will take appropriate measures, including debriefing and referral to the principal investigator or co-investigators for further evaluation. If the presence of a mental health concern arises, participants will be referred for appropriate care according to VA guidelines.

The Risks Associated with Using Virtual Platforms to Conduct Video Groups:
Veterans will be informed prior to their first group session, that attending group sessions via remote video platforms can present some privacy issues as other group members will be able to see into the Veteran's home environment during group sessions. Study staff will advise Veterans to choose the location in which they connect to the group wisely, stressing the importance of finding a private quiet space to participate in the group virtually as doing so will reduce the risk of people in the Veteran's home seeing or hearing fellow group members group participation and possibly disclosing any personal information. Suggestions to reduce these risks will be made to the Veteran by asking him/her to remove all pictures of loved ones, discussing the importance of privacy and confidentiality with the people who they live with and stress the importance of these people not interrupting the group sessions, walking into the camera's field of vision or talking to the Veteran during the group session as overhearing what is being discussed breaks confidentiality. Additionally, if the Veteran is unable to find a private room, study staff will help find locations where the Veteran could be present for the group sessions while not disclosing any personal information (e.g., their car, office, finished basement). In an effort to prevent disclosure, the use of headphones and hanging a sign on the door to "please not disturb" during

group sessions will be recommended to those who are having a difficult time finding private space for the group sessions.

Confidentiality: To minimize the risks of confidentiality violation, all data will be obtained by trained staff. Because of the sensitive nature of some of the data gathered, several precautions will be taken to prevent disclosure of information to unauthorized parties. Specifically: (1) Data sheets will be stored in the investigator's locked office (Building 32, Providence VA Medical Center as assigned); (2) data will be entered in coded form; (3) data will be stored in computer files protected from unauthorized access by passwords; (4) information that might potentially allow an individual participant to be identified will not be allowed in any publications or reports sent to individuals outside the study; and (5) all employees who are to handle data will be trained in confidentiality policies and procedures. Access to data will be limited to study investigators and staff.

Confidentiality issues related to Using Virtual Platforms to Conduct Video Groups:
Additional risks of confidentiality are associated with conducting group therapy via Video VA Chat or Zoom for Healthcare. We will ask participants in the group to respect everyone's privacy and confidentiality, and not to identify anyone in the group or repeat what is said during the group discussion. However, while group leaders will not disclose any participant communications or information, group participant communications are not protected. As such, confidentiality within the group setting is often based on mutual trust and respect. Confidentiality issues related to persons outside the group (e.g. family members and roommates present during the group sessions) will be addressed with participants as well. Plans to mitigate these risks include informing participants that others should not be able to overhear the group visit. Participants will be informed that study staff will help them find solutions (e.g. private space, use of headphones) in order to protect the privacy of other group participants. Suggestions will be made to the Veterans that they put a sign on the door of the room they are in to "please not disturb", alerting others in the house to provide privacy to the Veteran and other group members during group sessions. Participants will be informed that if they cannot find a private space to meet with the group virtually, they will not be able to participate in the group sessions.

As always, the participants' well-being will always be placed above research considerations. Participants will understand that they can refuse to answer any question and to stop an interview at any time. The participants will be clearly informed that they are free to terminate participation in the study at any point.

14.2 Potential Benefits of the Proposed Research

As described earlier, Veterans with co-occurring posttraumatic stress and substance use disorders are at greater risk for negative outcomes for both disorders, and for treatment attrition. This intervention has potential to improve outcomes for both substance use and posttraumatic stress disorders, and to improve the effectiveness of treatment by increasing retention. Both addiction treatment and PTSD therapy practitioners have expressed the need for assessment and treatment strategies for co-occurring substance use and other psychiatric disorders. This study has the clear

potential to add to the existing options for practitioners to more effectively help their patients with this challenging co-morbidity.

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