RESEARCH STRATEGY

A. SIGNIFICANCE

Posttraumatic stress disorder, substance use disorders and comorbidity: Post traumatic stress disorder (PTSD), a chronic condition that develops following an extremely distressing traumatic event, is characterized by a set of symptoms resulting in significant functional impairment (APA, 1994).

Comorbid PTSD and substance use disorders (SUD) commonly co-occur and is associated with a more complex clinical presentation with poorer clinical outcomes when compared with either disorder alone, including increased chronic physical health problems, poorer psychosocial functioning, higher rates of depression and suicide attempts, higher rates of other comorbid psychiatric disorders, and high treatment attrition (Brady et al., 2000; Brown, 2000; Harned et al., 2006; Najavits et al., 1999,Ouimette et al., 2007; Read et al., 2004)). In the majority of cases, the PTSD precedes the development of the SUD, providing temporal support for the use of substances to cope with PTSD symptoms (Back et al., 2006; Back et al., 2005; Chilcoat & Breslau, 1998; Compton et al., 2000; Jacobsen et al., 2001; Stewart & Conrod, 2003). The need to treat PTSD in this comorbid population has become evident as untreated PTSD predicts relapse to substance use (Back, 2010; Brady et al., 2001; Hien et al., 2011; Ouimette et al., 1997; Reed et al., 2007).

Women with PTSD and SUD: Women are twice as likely to be diagnosed with PTSD as compared to men. While the reasons for these gender differences are multi-factorial, the greater frequency of sexual abuse and the higher rate of comorbid conditions in women, including SUD likely play a large role (Breslau et al.,1999; Cortina et al., 2006, Najavits et al., 1997). Community SUD treatment programs typically address trauma in gender-specific groups recognizing the differences both in trauma history and substance use issues. Women-only groups provide an emotionally safe and supportive environment that allows women to address sensitive issues such as domestic violence and victimization (Ashley et al., 2003; Bloom 1998; Greenfield et al., 2010; Grello 2008; Pendegrast et al., 2011). Women specific substance abuse groups have been shown to be more effective in reducing drug use in women with high psychiatric severity than mixed gender groups (Greenfield et al., 2008). In summary, further research focused on treatments for women with comorbid PTSD and SUD, particularly in group format and delivered in front line community substance abuse programs are needed to fill the gap in knowledge and expand the evidence-based treatment alternatives for this comorbid population.

Integrated Treatment Models for comorbid PTSD and SUD: A number of integrated treatment approaches addressing symptoms of both PTSD and SUD concurrently have been explored in the past decade. Support for integrated treatment comes from several studies that have shown improvements in PTSD result in improvements in substance use but PTSD symptoms do not necessarily improve with substance use reduction (Back et al., 2006; Hien et al., 2011). These treatments typically consist of psychoeducation, exploring the relationship between PTSD symptoms and substance use, self-management of symptoms and negative emotions, and development of cognitive behavioral coping skills (Donovan et al., 2001; Hien et al., 2009; Najavits et al., 1998; Triffleman et al., 1999). Integrated treatments that include exposure techniques for PTSD and CBT for SUD have also shown promise in improving both PTSD and substance use symptoms (Brady et al., 2001; Mills et al., 2012). *However, attrition remains problematic with patients attending on average about half the prescribed study sessions (Brady et al., 2001; Hien et.al, 2009; Mills et al., 2012). Both emotional reactivity and avoidance are major features of PTSD, resulting in treatment dropout and/or use of substances to cope. Thus, addressing emotional reactivity early in treatment may increase retention, reduce substance use and importantly, facilitate engagement in trauma focused work (Foa, 2007). Innovative approaches such as mindfulness meditation that address this avoidance and emotional dysregulation delivered early in treatment may offer a less threatening, more amenable way of engaging in emotionally charged trauma thoughts, emotions and memories. Additionally, patients demonstrating improvements in emotional regulation are better able to implement more adaptive coping skills. Other considerations when implementing integrated therapies in community programs include the preferred group therapy treatment delivery method and resources needed for training and ongoing fidelity supervision.*

Mindfulness Meditation: Mindfulness meditation (MM), with roots in Eastern philosophy, has been explored in stress-related medical conditions, depression, anxiety and addictions in clinical and non-clinical populations

(Fjorback et al., 2011; Hoffmann et al., 2010; Roemer et al., 2002; Tacon et al., 2003;Teasdale et al., 2000). MM can be defined as a self-directed practice of intentionally attending to present-moment experiences (physical sensations, perceptions, affective states, thoughts and imagery) in an accepting, non-judgmental, observational manner with the intent of increasing non-reactive awareness (Kabat-Zinn 1992;1990;1982). Consciously exposing oneself to such experiences leads to better emotional processing and thus, improved emotion and self-regulation skills (Lau & Grabovac, 2009*). Bishop et al., (2004) proposes two essential components of MM; sustained attention to the present moment experience, and an orientation to that experience that involves curiosity, openness and acceptance. Noticing how thoughts, feelings and sensations change moment to moment and not getting attached to any one specific experience is acquired through MM practice. Acceptance is an important part of the MM process. Specifically, MM is concerned with approaching and changing one's relationship to the internal experience of thoughts, emotions, and sensations without attempting to change or suppress them. Participation in MM has been associated with decreases in experiential avoidance, a major factor in PTSD (Baer, 2003; King et al., 2013; Roemer et al., 2002). Reductions in stress and anxiety associated with MM are mediated through reductions in intrusive ideation and worry, another major feature of PTSD (Carmody et al., 2008). Jain et al. (2007) demonstrated that the mechanism for reduction in distress were different for MM and relaxation training. Specifically in MM but not relaxation, improvement in distress was mediated by reduced rumination and distraction.*

MM may provide a way for individuals with PTSD and SUD to experience a greater sense of control in relation to craving *triggered by trauma-related intrusive* thoughts, memories and sensations. *Individuals able to modulate these internal experiences are less emotionally reactive or prone to relapse in order to escape/avoid distressing symptoms.* During MM practice, when distressing trauma memories/thoughts emerge into consciousness, no attempt is made to change or suppress them; rather, it is simply noticed as one part of a broader range of experiences in that moment. Thought meanings are not internalized, accepted as reality, or escalated into self-inflicted preoccupations that lead to increases in negative emotional states with subsequent substance use or other maladaptive coping (Carmody et al., 2009; Teasdale et al., 2000,1995). Experiencing repeated exposure to PTSD and SUD triggers through MM without the associated emotional or behavioral reactivity, individuals practicing MM may habituate to these experiences resulting in diminished trauma symptoms and craving. *Several studies incorporating MM as an adjunctive therapeutic approach for altering maladaptive ways of emotional processing have demonstrated improvements in problem solving, decision making and more adaptive behavioral responses (Hayes et al., 1999; Linehan 1993; Marlatt, 1994, Teasdale et al., 1995; Williams, 2000). There is also emerging evidence from fMRI studies demonstrating that MM practice is associated with down regulation in the amygdala and activation of the anterior cingulate cortex, posterior insula, ventromedial prefrontal cortex, areas of the brain involved with emotional processing and regulation (Desbordes et al., 2012; Lutz et al., 2013; Zeidan et al., 2013).*

***Conceptual Framework**: The proposed study will use the multidimensional conceptualization of "emotional regulation" as a mental process of awareness, understanding and acceptance of emotions, and the ability to act in desired ways regardless of emotional state (Bishop et al., 2004; Grantz & Roemer. 2004; Hayes & Feldman, 2004; Watt, 2004). Rather than attempting to eliminate, control or react to emotions, adaptive emotional regulation involves modulating internal experiences through observation, attention in the present moment, awareness and nonjudgmental acceptance. Experiencing internal and external events from a more objective, informational and 'de-centered' perspective can change the representation of the event (Johnson, 1999; Shapiro et al., 2006)). An individual's increasing tolerance and acceptance for his/her internal experiences may lead to reductions in emotional reactivity and improved cognitive flexibility, enabling more effective coping responses (Bishop et al., 2004). Both PTSD and SUD have been conceptualized as disorders of emotional dysregulation (Watts, 2004). Disrupted emotional regulation and intolerance to negative internal and external experiences may be an important mediating factor between trauma exposure and subsequent SUDs. Studies show that the most common precipitant of relapse to substance use is negative emotional states (Baker et al., 2004; Cooney et al., 1997; Stewart et al., 2000). With comorbid PTSD and SUD, the emotional distress triggered by intrusive trauma associated thoughts and painful memories may serve as a cue for craving and subsequent substance use (Coffey et al., 2002). Interventions that address emotional*

dysregulation can better enable patients to make less reactive decisions, problem solve, and cope more adaptively in high risk situations. In a recent study, changes in emotional regulation mediated the link between MM skills and PTSD symptom improvement (Reber et al., 2012). As such, emotions can function as important informational cues that can alter habitual maladaptive ways of coping commonly seen in PTSD and SUD.

Mindfulness-Based Relapse Prevention (MBRP): MBRP integrates coping skills from cognitive-behavioral relapse prevention therapy with MM practices, raising awareness of substance use triggers and reactive behavioral patterns, and teaching skillful coping responses (Bowen et al., 2010).

The MBRP program is a manualized intervention consisting of eight group sessions. In a pilot study (N= 168), MBRP, delivered as aftercare following inpatient or intensive outpatient treatment, was compared to treatment as usual (TAU) in patients with SUDs (Bowen et al., 2009). Individuals in TAU participated in 12-steps processing and psychoeducation groups. MBRP sessions were implemented in closed cohort groups of eight weekly two-hour sessions. Participants attended more hours in the MBRP than in the TAU intervention (12.8 $\pm$ 4.9 versus 9.8 $\pm$ 8.2 hours; $p \leq 0.001$) and 86% of MBRP participants reported practicing meditation during follow-up. Acceptance and acting with awareness was significantly higher and craving was significantly lower in the MBRP participants. At two month follow-up, participants in the MBRP had significantly less days of alcohol and drug use than participants in the TAU group (2.1 versus 5.4 days; $p \leq 0.02$), however, these differences were no longer found at four months. One of the important findings of this study that is pertinent to the proposed study targeting SUD and PTSD is the impact of MBRP in altering reactivity to negative emotional states. Following treatment, craving was found to mediate the relationship between depressive symptoms and subsequent alcohol/drug use at four months post intervention in the TAU but not the MBRP group. This was not an unexpected finding in that the goal of MBRP is to allow individuals to experience negative emotions and challenging situations without reacting automatically or impulsively (Witkiewitz & Bowen 2010). A recent large randomized control study (n = 286) comparing MBRP, relapse prevention (RP) and TAU delivered as aftercare following SUD intensive treatment explored long term alcohol and substance use outcomes. Both MBRP and RP had greater reductions in drug use and heavy drinking than TAU at 6 month follow-up ($p<0.5$). At 12 months, MBRP resulted in a 31% greater reduction in drug use days among those participants who used (IRR = .69; $p<.05$) and a greater probability of not engaging in heavy drinking (OR 1.51 $p<.05$) than RP participants (Bowen et al., 2014). In another small uncontrolled pilot study, 14 court-mandated women with alcohol use disorder and aggression participated in Mindfulness and Modification Therapy (MMT), an adaptation of MBRP, in 12 weekly sessions to evaluate feasibility, acceptability and impact on behavioral dysregulation. There was a significant decrease in mean number of drinking days (11.3 $\pm$7.23 to 1.36 $\pm$ 3.27; $p = 0.001$) and number of drinks per drinking day (4.21 $\pm$ 1.42 to 0.68 $\pm$ 1.39; $p = 0.001$) from the four weeks prior to the intervention to the last 4 weeks of treatment. Days of drug use significantly decreased and no reported engagement in physical aggression was reported by the end of treatment. The program was well received with a 93% completion rate and self-reported improvements in self-esteem and family relationships. Most of the women felt the treatment could be improved by extending the duration (Wupperman et al., 2012)

Mindfulness Meditation and PTSD: There have been only a few small studies exploring MM for the treatment of PTSD. Twenty seven women with history of childhood sexual abuse who received 8 weeks of mindfulness based stress reduction (MBSR) were followed over 24 weeks for PTSD symptom severity and depression. There were sustained improvements in all outcomes with large effect sizes ($d = 0.8$) in PTSD symptom severity, most notably in avoidance/numbing PTSD symptoms. The intervention was acceptable and well tolerated by the women, with high adherence for at home meditation practice (Kimbrough et al., 2010). Another recent larger study explored depression, PTSD symptoms and quality of life in 92 veterans who received 8 weekly MBSR sessions. PTSD checklist scores were significantly more improved from baseline to 2 and 6 months follow-up (52.4 $\pm$16.3 versus 43.4 $\pm$ 16.3 and 41.9 $\pm$ 16.8, $p< 0.001$, respectively). Of importance, MM practice outside of sessions was associated with sustained improvements in PTSD outcomes with 40% having significant PTSD improvements at 2 months and 46% at 6 months (Kearney et al., 2012).

Although MM interventions have shown promise in reducing symptoms of PTSD, there are no studies investigating MM in patients with comorbid PTSD and SUD, particularly in women who represent a high percentage of patients being treated in community programs.

In summary, substance use can be conceptualized as a harmful dysregulated behavior used as a coping mechanism to avoid negative emotions associated with PTSD/ trauma triggers. MM may benefit patients with comorbid PTSD and SUD in an approach similar but more acceptable to exposure-based therapies in that patients are not directly instructed to confront or focus on trauma related stimuli (emotions, thoughts, sensations) but rather allow these experiences to emerge into consciousness without the interference of associated evaluative or judgment content. Through regular practice of mindfulness, patients habituate to the impact of emotional distress associated with PTSD symptom distress (Carmody et al., 2009; Wupperman et al., 2012). MM may be particularly useful in community programs that treat a large number of women with comorbid PTSD and SUD where gender specific group treatment is common practice.

B. INNOVATION

The proposed study is innovative in several ways. Mindfulness meditation (**MM) introduces a new approach for patients with SUD to deal with emotions, thoughts and behaviors that trigger substance relapse.** It is widely accepted by patients, particularly women, who continue to practice MM outside of treatment. Another unique aspect of MM is that both therapist and patient engage in MM practice such that therapists role model a practice that they perceive beneficial to their own health. In the proposed study, a MM-based treatment which has shown promise in the treatment of individuals who have either SUDs or PTSD **will be tailored for the treatment of co-occurring PTSD and SUDs and tested for the first time in women with PTSD/SUDs. MM addresses emotional dysregulation and resulting behavioral control deficits that are not well addressed by standard psychosocial interventions.** In order to conduct this trial, the Mindfulness Based Relapse Prevention (MBRP) manual developed by Bowen, Chawla and Marlatt (2011) for the treatment of individuals with SUD will be adapted in several innovative ways. **First**, *the MBRP manual is focused primarily on SUDs, so it will be tailored to address PTSD symptoms and the relationship between PTSD and SUDs* (see Initial Manual Modifications for details). *These modifications are based on modifications made in other MM (MBSR and MBRP) interventions that address PTSD, as well as other comorbid PTSD/SUD integrated interventions (Killeen et al., 2012; Kimborough et al., 2012; King et al., 2013).* Throughout the eight sessions, participants will engage in MM practice, whereby they are trained to approach thoughts, feelings and physical sensations including awareness of trauma related triggers, in an observational, non-judgemental, present moment manner versus use of suppression or avoidance coping. Following in-session MM practice, patients process the MM experience and adaptive coping responses, including alcohol/substance use relapse prevention, in group discussions. Participants are asked about the experience, what did they notice or what came up for them during the experience and what was learned from the experience that they can apply to their addiction and trauma recovery (corrective feedback). The experience often can elicit a different perspective or cognitive reframe. Several examples include: Thoughts are transient and not a self- representation. Memories are past events and can no longer cause harm. Anxiety is just a feeling that is tolerable and will not last indefinitely. *The cognitive behavioral component addresses cognitive conflicts and behaviors that maintain PTSD symptoms and substance use.* **Second,** the intervention will take place in a community-based treatment setting, so several innovative adaptations of the manual are needed to enhance feasibility in this setting. Feasibility is an important part of behavioral therapy development as it increases the likelihood of adoption. *Unlike trials reported to date, **groups will use a hybrid open enrolment**, a more typical mode of treatment delivery in community programs versus a closed cohort (see Feasibility Modifications)*. **Third**, MBRP, originally developed as an aftercare program, will be adapted to be introduced **earlier in the continuum of care**. Several studies with substance abuse populations have successfully introduced MM early in treatment (Bowen et al., 2006; deBois et al., 2012; Wupperman et al., 2012). Both of these adaptations will decrease wait time and risk of attrition. **Finally**, procedures for training and monitoring fidelity of treatment for community-based therapists will be developed. Provider acceptability, feasibility and ease of implementation will be monitored to increase the potential for program adoption and sustainability in community-based settings. Thus, this project will result in the development and testing of an innovative approach to be used in community-based treatment settings for a common and costly comorbidity, PTSD and SUDs.

C. APPROACH

1. Research Team

A multidisciplinary research team with relevant and complementary expertise and skills has coalesced to plan and conduct the proposed project. ***Therese Killeen, APRN, PhD*** *has been involved in the conduct of community-based clinical trials in the area of PTSD and SUD for 20 years. She has been PI and Co-I on numerous studies related to PTSD and SUD .Specifically, Dr. Killeen has been the lead investigator on 3 studies conducted in the same community program as the proposed study. One study was a multi-site randomized trial comparing seeking safety and women's health education interventions in women with comorbid PTSD and SUD. Importantly, recruitment and retention for this study exceeded the expectations set by the lead National team. More recently, Dr. Killeen conducted a study in the same community program in adolescents with marijuana use disorders (R21 DA020798, Killeen PI). Dr. Killeen was also the PI on a multisite pharmacotherapy study exploring the efficacy of risperidone as an adjunct to sertraline for treatment resistant PTSD (Rothbaum, Killeen et al., 2009). She has served as a co-investigator, trainer/supervisor in several studies of exposure-based treatment for co-occurring PTSD/SUD (*R01 DAO30143, PI/ Back; R01 *DA023187, PI/Hien). Over the last five years, Dr. Killeen has worked on adaptations to exposure-based treatment for co-occurring PTSD/SUD (Killeen, Back & Brady, 2012; Back, Killeen, et al., 2012), She is co-author on the manualized exposure based treatment for PTSD and SUD entitled "COPE: Concurrent Treatment for PTSD and SUD using Prolonged Exposure" (Back, Foa, Killeen et al., in press, Oxford Press)*. In addition, Dr. Killeen has practiced MM for over 15 years and was trained in MBRP by Dr. Sarah Bowen. Since that time, she has been using MBRP in the treatment of individuals with SUDs. **Sarah Bowen**, PhD., University of Washington, will serve as a study trainer and expert consultant. Over the past 5 years, Dr. Bowen's work has focused on development, efficacy and mechanisms of change in mindfulness-based treatments for addictive behaviors. She currently is PI on the ARRA-funded randomized trial of MBRP. In addition to authoring over 20 peer reviewed articles and several book chapters in this area; she is lead author on both the Mindfulness-Based Relapse Prevention (MBRP) therapist manual and the primary outcomes paper resulting from the initial pilot and long term follow-up study. Importantly, Dr. Bowen has conducted numerous national and international trainings in MBRP (letter of support included). **Kathleen Brady, MD, PhD** is a nationally-recognized expert in both SUD and PTSD research. As PI of the Southern Consortium Node of the NIDA Clinical Trials Network (CTN), she has supervised the conduct of over 25 clinical trials in the SUD area conducted in community settings over the past 12 years. In particular, much of her work is focused on the PTSD/SUD interface. **Nathan Baker, MS** is a biostatistician who has worked with Drs. Brady and Killeen for the past 5 years. He has extensive experience in treatment outcome studies in the SUD area. **Chanda Brown, PhD** has served as the Charleston Center (CC) Executive Director since 2010, after serving for 5 years as the official CC liaison to the CTN and coordinating 2 CTN trials, including a trial exploring outcomes for women with comorbid PTSD/SUD. She is firmly committed to research and the successful implementation of evidence based practices within the agency and has a solid working relationship with Drs. Killeen and Brady (letter/scope of work included). **Mark Hamner, MD** is a nationally recognized expert in the area of PTSD, and specifically clinical trials testing innovative therapies for PTSD. He is currently the PI of a trial of MM in the treatment of PTSD in veterans.

Relevant Experience:

CTN Trials: As above, Drs. Killeen, Brown and Brady have collaborated for the past 12 years in conducting clinical trials in community-based settings through the CTN. Specifically, they have conducted three trials at CC. Two studies focused on contingency management and the other focused on the same population to be recruited for the proposed study, women with PTSD and SUDs. In the conduct of both studies, this investigative team surpassed recruitment goals and had excellent metrics with regard to regulatory and fidelity/integrity monitoring.

Therapy Development: Drs. Brady and Killeen have worked together closely in developing a treatment manual focused on exposure-based treatment for individuals with co-occurring PTSD and SUDs (COPE, Back et al, in press). This process followed the same "staged" approach to therapy development that is proposed in the current protocol. The initial study was focused on Stage 1 therapy development, pilot testing and manual

modification. A subsequent Stage II trial of the manual has been published (Mills et al., 2012) and two other Stage II trials are in progress. Dr. Killeen has been involved in all phases of this process from manual modification through development of fidelity/integrity monitors and training/supervision of therapists. *Dr. Bowen is an expert in MM and will help with supervision and issues related to the implementation of meditation. She will also be able to consult with any revisions to the manual.* **Mindfulness Meditation Trials:** Dr. Sarah Bowen has completed a long term randomized study exploring the efficacy of MBRP (Bowen et al., 2014). As previously mentioned, Dr. Mark Hamner is currently the PI on an investigation of MM in the treatment of PTSD in veterans. Study recruitment went extremely well and retention/satisfaction with treatment has been high. We have assembled a team of investigators and experts in both MM and comorbid PTSD and SUD who have previously worked together and are committed to exploring innovative evidence based treatments for this complex comorbid population. We anticipate successful completion of our target goal as scheduled.

2. Research Design and Methods

Overview: The proposed study is a *Stage 1b* study in that an existing evidence-based treatment targeting SUD, MBRP, will be modified to address both PTSD and SUDs to be delivered in a community-based treatment setting. The purpose of the proposed intervention is to evaluate the feasibility and preliminary efficacy of the modified MBRP with treatment as usual for women with comorbid PTSD and SUD in a community-based SUD treatment program. The execution of the project will take place in three phases: 1) manual revisions to address PTSD and feasibility in community programs, 2) training, certification of therapists, piloting in 2 patient groups with further manual revisions, and 3) manual tested *in a randomized controlled pilot trial comparing MBRP plus treatment as usual (TAU less trauma focused group) to TAU alone in 80 patients enrolled in the intensive outpatient and New Life programs at the Charleston Center. Process assessments will include measures of manual adherence, therapist competence, therapeutic/patient alliance and therapist/patient acceptability and satisfaction. Comprehensive evaluation on measures of mindfulness meditation (MM), PTSD symptom severity and substance use outcomes will be done at baseline, weekly throughout the intervention, post treatment 3- and 6- month follow-up. Changes in emotion regulation as measured by the emotional regulation scale and components of MM (attention, awareness to present moment and acceptance) will be explored to determine impact on PTSD symptoms, craving and substance use.* If promising, results from this pilot study will provide an effect size estimation for a Stage II randomized clinical trial. This pilot project will also allow for the testing of training and fidelity monitoring procedures for community clinicians and assess acceptability, knowledge and adherence/competence.

Manual Modifications: In **Phase 1** of the project, the existing manual will be modified in several ways: Feasibility Modifications: There are two feasibility modifications that will increase the potential for adoption in community substance abuse programs. 1*) Delivery in a hybrid open enrolment format: Participants will begin their involvement in MBRP with an introductory individual session, which will include: a) psychoeducation regarding PTSD symptoms and the relationship between substance use and PTSD, b) orientation to the overall intervention and the sequence of the group sessions into which they will enter, and c) initial MM practice. The goal of the sessions is to facilitate the transition of new participants into the larger on-going groups. To adhere to a strict sequential order of therapy session delivery, a cohort of group participants would need to be assembled before any participants can begin the group. This can impact recruitment feasibility as participants may be asked to wait for several weeks before beginning the group. We have created a hybrid system that allows participants to enter their therapy group in an open enrolment format, yet maintains the essential elements of treatment delivery in an order that makes sense. Each participant will begin with one introductory session that is delivered individually (or in a small group when several participants enroll within the same week) prior to joining the larger groups. The two therapists delivering the group intervention will stagger the delivery of therapy sessions such that in any given week, one therapist will be delivering early sessions (2-4) and the other therapist will be delivering the later sessions (5-8). The early sessions are designed to focus on problems encountered early in recovery and sequential delivery is not essential. In these sessions the therapists will be working with participants to establish their MM practice. The later sessions focus on more recovery maintenance issues and how to incorporate MM into routine daily life. Participants will participate in these group sessions after they have completed the initial three group sessions.* 2) Introduction of MBRP

earlier in the treatment continuum as opposed to delivering the intervention in the aftercare phase: This will improve recruitment and retention rates and, more importantly, expose participants to meditation practice early in treatment when emotional distress is high. The intervention will begin no sooner than 7 days after clinic treatment entry. This will allow time for improvement in cognitive function, particularly attention and concentration which are commonly affected by active substance use. These two modifications are more applicable to standard community practices and will increase the potential for adoption.
Initial Manual Modifications: 1) *Revision of the MBRP manual to address PTSD will be done in accordance with theoretical underpinnings, therapy techniques and modifications made in other MM interventions (MBSR and MBCT) for patients with PTSD (King et al., 2013; Kimborough et al., 2012; Lang et al., 2012).* Mindfulness meditation (MM) rationale, key concepts, in- session meditation practice and importance of home practice will be included in the initial introductory individual session. The PTSD/SUD interface will be discussed in this session and participants will be given a handout of common reactions to trauma. The first session is entitled "Automatic Pilot and Relapse." Participants discuss the tendency to act 'automatically' without full awareness. Participants will also practice breath meditation and instructed to practice this at home on a daily basis. *In MM the breath is not used as a distraction but rather as one of the primary anchors for attention, particularly when thoughts are becoming difficult to approach and observe in a mindful manner.* They will be given a CD (and player or mp3 player if indicated) and a practice tracking log to facilitate the practice. Following the individual session in the second week, participants will join the larger ongoing group for the remaining sessions. Each session has a central theme/topic (see Appendix A) and consists of in-session experiential meditation practice, discussions related to MM experiences, coping responses and homework assignments. Specifically, the sessions start with a check in, followed by a 15 to 20 minute meditation. The therapist reviews homework practices and discusses any challenges. Common challenges that can occur include aversion experiences and the desire to 'fix' the discomfort, cravings, restlessness and agitation, drowsiness and sleepiness, doubt and trauma related avoidance. Examples of MM practices include mountain meditation, awareness of hearing, sober breathing space, sitting meditation, lovingkindness, walking or movement meditation. These MM practices invite a different approach to deal with cravings and trauma related intrusive thoughts and memories. In processing these exercises, therapists ask participants to describe experiences during the exercises. Participants note differences before and after the meditation practice and how prior traumatic experiences have shaped maladaptive beliefs and subsequent behavioral reactions. Thus, interpretations assigned to events are seen as not necessarily factual. To attend to trauma issues, therapists create a safe and supportive environment for the emergence of trauma thoughts and memories. On a practical level, during MM practices participants may choose to keep their eyes open and stay in a preferred sitting position for the meditation exercises (Bowen, Marlatt & Chawla, 2011). The second session, "Awareness of Cravings and Triggers," involves a discussion of common drug/alcohol stimuli that elicit cravings. Many different stimuli become triggers for drug use in the same way that stimuli present during the traumatic experience can become subsequent triggers for the anxiety/fear response observed in PTSD. Drugs/alcohol are commonly used as coping mechanisms or negative reinforcers to avoid trauma related stimuli (thoughts, feelings and physical sensations) and activities/situations that elicit the PTSD fear/ anxiety response. MM techniques use the concept of allowing oneself to consciously experience these avoided thoughts and feelings rather than the use of escape, distraction and suppression. MM is introduced as a new approach to coping that will offer more long term benefits with practice. In- session practice includes urge surfing, a different way of experiencing craving, and body scan exercises. Participants are assigned MM exercises with a practice tracking sheet. They will also complete the "noticing the triggers" worksheet, identifying both drug/alcohol and PTSD related thoughts, emotions and bodily sensations that they experience throughout the week. The third session focuses on 'being with' day to day physical sensations and emotions without reaction, which will enable participants to expand their awareness of behavioral responses and make better choices. "Acceptance and Skillful Action" is another session where PTSD content is integrated into the session discussion. Meeting life struggles generated from past experiences with acceptance and self-compassion can allow greater freedom, flexibility and space to make changes. The lovingkindness MM practice can be particular useful for participants with PTSD who feel emotional numbness and have trouble with positive emotions. Session six is relevant to PTSD as participants

are asked to welcome and become aware of thoughts and the relationship between thoughts, emotions and sensations. Attention is focused not on the content of the thoughts but rather the on the presence of thinking in the moment. Through this practice of 'awareness of thinking' participants learn that thoughts and memories are harmless and powerless. The last two sessions focus on lifestyle changes that support both PTSD and substance use recovery. Participants are asked about their own MM practice and how they have incorporated it into their lifestyle. Noticing daily activities that are either 'nourishing' or 'depleting' help with understanding life choices. Often individuals with PTSD expend so much of their physical, cognitive and emotional resources managing symptoms (i.e. hyperarousal, avoidance, re-experiencing) that there is a deficit of nourishing activities. Participants are assigned to engage in 'nourishing' activities which are also activities that are avoided due to PTSD anxiety/fear response. Finally, participants explore support systems and future plans to sustain addiction/trauma recovery and MM practice.

Training and certification of therapists and piloting. In phase 2, master's level therapists will receive training in the MBRP with PTSD components integration. Over 90% percent of therapists at the CC have Master's degrees. Training will take place at a central location and include (1) didactic review of intervention-specific theory (cognitive behavioral therapy and mindfulness meditation techniques); (2) manual review with initial PTSD revisions; (3) observation and practice within trainer-conducted mock intervention sessions; and (4) trainee-conducted mock intervention sessions. Two therapists and one supervisor will be trained by Dr. Sarah Bowen from the University of Washington who developed the MBRP manual. All therapy sessions (described below) will be audiotaped and reviewed by Dr. Bowen and/or Dr. Killeen for therapists' certification. Competency and adherence ratings on audiotaped sessions using the Mindfulness-Based Relapse Prevention Adherence and Competence Scale (MBRP-AC scale/ see Appendix) with PTSD component revisions will be used during the training phase to determine certification status (Chawla et al., 2010). The supervisors will obtain inter-rater reliability on the MBRP-AC scale with Dr. Bowen and Dr. Killeen. Dr. Bowen will be available as the expert trainer for supervision consultation. Therapists will be certified once they complete all the sessions at a level of proficiency of at least a 3 on a scale of 1= low to 5 = high on item ratings consisting of key MBRP concepts, therapist style/ approach subscales and overall performance). Supervision, Therapist Competence and Manual Adherence: Throughout the study, therapists will receive weekly supervision focusing on fidelity to the treatment model, the quality of the intervention, and clinical concerns about particular participants. Each session with be audiotaped and randomly selected sessions (approximately 1/3 for each therapist) from each group will be evaluated using the MBRP-AC Scale with PTSD component revisions. Adherence ratings evaluate the degree to which therapists employ individual components of MBRP and discuss of key concepts. The competence ratings will be used to assess therapist style/approach and performance. Competency and adherence ratings will be used to assess therapist "drift" and to determine whether remedial training procedures are necessary. In addition, treatment-specific Therapist Checklists completed by the therapists will assess their use of specific interventions. These checklists are intended both to (a) provide a regular reminder to therapists of the key elements or interventions specific to their form of treatment and (b) to estimate the overall level of treatment-specific interventions provided to each participant in the study. In preparation for weekly supervision the supervisor will review taped therapy sessions and therapist rating forms. The supervisor will provide feedback to reduce therapist departure from structured treatment protocol and to assist the therapists in identifying issues to be addressed in subsequent sessions. If during the course of the study it is determined upon review of taped therapy sessions and supervisory sessions that a therapist is not competent or does not adhere sufficiently to the manual the therapist will be re-trained. Every attempt will be made to correct problems through weekly supervision. The decision to replace a therapist will be a decision made by the supervisor and PI after consultation with Dr. Bowen. Treatment Integrity: To maintain treatment integrity throughout the study we will do the following: 1) use manualized treatments; 2) provide intensive weekly supervision by experts; 3) audiotape all treatment sessions for supervisors to regularly review; and 4) conduct independent ratings of treatment competence and adherence. Manual adherence and therapist competence will be assessed throughout the project as previously described. Therapists will receive ongoing supervision and training throughout the project to reinforce and sustain their skills in therapy delivery. These methods parallel those used to sustain integrity in other integrated treatment

outcome research projects at our sites. Following training and certification, therapists will pilot the intervention with two groups consisting of approximately 3 to 6 women per group. Careful monitoring of therapists and participants during the delivery of the therapy will help address questions concerning the best match of trauma related components with the MBRP techniques. Weekly monitoring of PTSD, emotion regulation, craving and substance use will provide information concerning the timing, impact and duration of the intervention effects. One focus group will be conducted with clinicians and one focus group with each group of participants following the completion of the intervention. For clinicians, the focus groups will address issues such as safety, ease of delivery, feasibility, participant interest and engagement, perceived effectiveness and intent to continue intervention. For participants, the focus group will address interest, acceptability, usefulness, duration and timing of intervention in treatment program and ability/willingness to practice meditation outside of the sessions. Both clinicians and participants will be asked about what was most helpful and suggestions for improving the intervention. Interviews will be audio-recorded and then transcribed to identify common themes. We expect interviews to last 30- to 45- minutes. These focus group discussions will contribute to manual revisions prior to the randomized pilot study.

3. Procedure

Design: *This randomized controlled pilot study will evaluate the feasibility and preliminary efficacy of MBRP* ***plus*** *usual community treatment (TAU) compared to TAU alone (TAU) for women with SUD and PTSD enrolled in community substance abuse treatment. Participants will be randomized to eight weekly 90-minute, mixed individual and group-based MBRP in addition to TAU or TAU alone. The eight sessions of MBRP will replace 8 sessions of seeking safety (SS); a trauma focused integrated therapy currently implemented in TAU. Outcomes assessed will be: (1) PTSD symptom severity as measured by the Clinician's Administered PTSD Scale (CAPS) and Post Traumatic Stress Disorder Symptom Scale-Self Report (PSS-SR); (2) Alcohol and substance use as measured by the Timeline Follow Back (TLFB) assessment and corroborated with urine drug screens; The Clinical Trials Network (CTN) Treatment Effect and Assessment Measures Task Force (2010) recommended making UDS/self- report discrepancy corrections based on an algorithm that takes into account self-reports from the 2 days prior to the UDS test day (3)) Psychosocial functioning; (4) Measure of emotional regulation and mindfulness awareness, attention and acceptance.*

Recruitment: Recruitment of participants will primarily take place from the CC women's Intensive outpatient and New Life programs. Program description and patient flow is described below. We have had a long-standing collaboration with the CC and have worked together in previous and ongoing clinical trials, including 2 multisite NIDA Clinical Trials Network studies in which the site exceeded the recruitment expectations set by the MUSC investigative team. Thus, procedures for study recruitment and conduct are well-established. The PI and research staff are located adjacent to the CC and interact frequently with clinic staff. Patients who are scheduled for a clinic intake assessment will be approached by the research staff, and given a description of the study and invited to participate. Research staff will attend staff meetings on a regular basis to discuss study recruitment and potential participants. There are currently no other studies recruiting from the CC women's programs so overlap with other studies will not present a problem.

Additional Recruitment Methods: In order to increase study enrollment, recruitment of participants may also take place from other sites/sources, including but not limited to referral from professional treatment facilities, referral from within the community, through therapist referral, or through self-referral.

Screening: Following therapist training, certification and piloting, eligible women enrolled in intensive outpatient and New Life treatment will be invited to participate in the study. Interested potential participants will be screened for major inclusion/exclusion criteria including age, alcohol/substance use, history of trauma and psychiatric/health/medication status. If potentially eligible, an IRB approved informed consent will be obtained and participants will be scheduled for a screening followed by a baseline assessment appointment if eligible. If an individual is ineligible to participate in this research protocol, she will continue in her usual community treatment program and/or if indicated, be referred for additional treatment services within or outside the CC. We decided to limit the study group to women because they represent the largest percentage of patients with comorbid PTSD and SUDs and most have experienced sexual and/or physical trauma. So when trauma-

focused treatment is delivered in a group setting for this population, single sex groups create a safe, comfortable and open atmosphere that is required for MM-based treatment and trauma focused work.
Community Program Description: The Charleston Center, one of the largest SUD treatment agencies in South Carolina, provides a full continuum of prevention, intervention, and treatment services for people suffering from SUDs. Services provided include medical and clinical detoxification, inpatient programs and programs specifically designed for pregnant and parenting woman (see Facilities and Resources).
Outpatient programs serve adolescents and adults and the CC houses a Therapeutic Childcare Program for children of addicted parents. The outpatient programs serve Charleston County and the inpatient programs accept referrals throughout South Carolina. The proposed study will take place within the women's intensive outpatient program (WIOP) and New Life program which served a total of 398 women, with a primary alcohol or substance dependence, between July 2012 and June 2013. Women in the New Life residential program scheduled to attend the WIOP will also be invited to participate. The proposed study will recruit approximately 3 patients per month for a total of 100 participants over the approximate 36 month recruiting period. This is a feasible recruitment goal as previously 72 women were recruited in this program over a 19 month period for the multisite CTN Women and Trauma study. The CC WIOP is approximately 12 weeks long and provides groups and classes focused on psychoeducation, relapse prevention, 12-step and parenting up to 20 hour/ four days a week program. The program includes weekly 90 minute SS groups, a cognitive behavioral integrated trauma intervention. Women meet individually with a counselor prior to SS group entry.

Table 2 Assessment Schedule

	SC	BL	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	Months 3 and 6
MINI	X										
Urine pregnancy	X										
UDS		X	X	X	X	X	X	X	X	X	X
LEC	X										
ASI-Lite		X								X	X
CAPS	X					X				X	X
TLFB	X	X	X	X	X	X	X	X	X	X	X
UDS		X	X	X	X	X	X	X	X	X	X
PSS-SR		X	X	X	X	X	X	X	X	X	X
OCDS-R-Brief		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
FFMQ-SF		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
CAMS-R		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
DERS		*X*				*X*				*X*	*X*
MAAS		*X*				*X*				*X*	*X*

Participants: A total of 100 women meeting *DSM-V* criteria for PTSD and SUD will be enrolled and randomized in the study. Inclusion Criteria: 1) Women between 18 and 65 years of age enrolled in the CC intensive outpatient and New Life program treatment. 2) Able to comprehend English. 3) *Meets DSM-V criteria for current alcohol or substance use disorder and have used alcohol/substances in the 60 days prior to clinic treatment entry. 4) Meets DSM-V criteria for current PTSD with a score of ≥ 25 on the CAPS.* 5) Participants may also meet criteria for a mood or anxiety disorder. *Participants on psychotropic medications for a mood or anxiety disorder must have been stabilized on medications for at least 4 weeks before therapy initiation.* 6) Able to adequately provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments. 7) Willing to commit to 8 therapy sessions, baseline, weekly and follow-up assessments. Exclusion Criteria: 1) Current primary psychotic or thought disorder (i.e. Schizophrenia or schizoaffective disorder, mania), major depression with suicidal ideation, dissociative identity disorder and/or homicidal ideations. 2) Present a serious suicide risk, such as those with severe depression, or who are likely to require hospitalization during the course of the study. 3) In ongoing therapy for PTSD either within or outside of the CC, who are not willing to discontinue these therapies for the duration of the study therapy, 4) Unstable medical condition or one that may require hospitalization during the course of the study. 5) Women who are pregnant or planning to become pregnant.

Assessments: The assessment schedule is displayed in Table 2. The urine pregnancy test will be done at the screening visit. If the pregnancy test is positive, the patient will not be eligible to participate in the study and no further study procedures will be conducted. Mini-International Neuropsychiatric Interview (M.I.N.I.): The M.I.N.I. is a brief structured interview that was designed to assess DSM-V diagnoses using a series of questions in dichotomous format (yes/no). Earlier studies have found that the M.I.N.I. is similar in sensitivity, specificity, and inter-rater reliability to other more lengthy diagnostic interviews, such as the SCID-I/P (Sheehan et al., 1998). This instrument will be used to assess inclusionary/exclusionary psychiatric and alcohol/substance use disorder diagnoses. Addiction Severity Index-Lite (ASI-LITE) is a structured interview that assesses problem severity in seven domains commonly affected by alcohol/substance abuse: medical, legal, drug, alcohol, work, family/social, and psychiatric. The patient reports number, extent and duration of symptoms in each domain for the time frames of lifetime and the past 30 days (McLellan et al., 1992). Time Line Follow Back (TLFB) is a semi-structured interview which uses a calendar to prompt participants to provide retrospective estimates of their daily alcohol and drug use over a specified time frame. The TLFB was originally developed to track daily alcohol use but has been adapted for use of other drugs. Memory aids are used to enhance recall and facilitate accurate recollection of use behavior. The TLFB has high test retest reliability (inter-rater correlation coefficients ranging from 0.7 to 0.94), good discriminant and convergent validity, and acceptable agreement with urine drug screens. We will use the TLFB to assess alcohol and drug use patterns 60 days prior to community treatment entry, then administer the TLFB weekly during the treatment, post treatment, 3- and 6- month follow-ups (Sobell & Sobell 2000,1992,1995). Urine toxicology Urine drug testing (UDS) will be performed with the 7 panel on-site rapid drug test (clia-waived) which includes built in adulterant checks. It will test for the presence of cocaine, opiates, methadone, THC, methamphetamine, benzodiazepines and oxycodone. UDS will be obtained at baseline, weekly during the intervention and at follow-ups. Life Events Checklist for DSM-5 (LEC-5; Weathers et al., 2013): The LEC-5 assesses lifetime exposure to trauma. It includes the list of 16 different events from the original LEC (Gray et al., 2004). In addition, two items screen for military sexual trauma. The primary addition to the LEC-5 is a category involving occupational exposure (e.g., paramedic, police, military, or other first responder"). The psychometric properties of the LEC-5 have not yet been established, however the measure is nearly identical to the original LEC, which has been shown to demonstrate good convergence with the Traumatic Life Events Questionnaire (average kappa = 0.55) and correlate with the Posttraumatic Stress Disorder CheckList (reliability coefficients 0.34 to 0.48), and it demonstrates good test-retest reliability over 7-days.

Clinician Administered PTSD Scale (CAPS) is a structured, clinical interview for assessing the frequency and intensity of signs and symptoms of PTSD. The CAPS measures DSM-V symptoms of PTSD, validity of responses, impairments in social and occupational functioning, and overall symptom severity. It also measures the degree of improvements since an earlier rating. The CAPS has excellent diagnostic usefulness against the SCID PTSD diagnosis. The CAPS has also been found to have sound psychometric properties (Blake et al., 1990). The CAPS will be administered at baseline, week 4, post treatment, and follow-ups. The LEC lists Post-Traumatic Stress Disorder Symptom Scale-Self Report (PSS-SR) is a 17-item self-report inventory, which assesses the frequency and severity of PTSD symptoms corresponding to the diagnostic criteria listed in the DSM-V. Both internal consistency and test-retest reliability are high among women with assault histories (Foa et al., 1997). Cronbach's alpha for the total score is .91. Alpha coefficients for the symptom cluster subscales were .78, .80 and .82 for re-experiencing, avoidance, and arousal scales, respectively. The PSS-SR will be administered at baseline, weekly throughout the intervention, post intervention and at follow-ups. This assessment will be monitored throughout to assess adverse events (symptom worsening).

The Obsessive Compulsive Drinking Scale-Revised (OCDS-R) is a 10 item self- report measure revised to measure global urges to use substances. Patients complete the assessment based on the substance for which they presented for treatment. The OCDS-R has good reliability and concurrent validity (Morgan et al., 2004).

The Mindfulness Acceptance and Awareness Scale (MAAS) is a 15-item instrument designed to assess a core characteristic of mindfulness, namely, open or receptive awareness of and attention to what is taking place in the present. The scale asks participants to rate the frequency with which they experience impaired moment to-moment attention on a 6-point Likert scale from 1(almost always) to 6 (almost never). Higher scores reflect

higher levels of mindfulness (Brown & Ryan, 2003). Difficulties in Emotion Regulation Scale (DERS) is a 41-item self-report measure developed to assess clinically significant difficulties in emotion regulation. Responses range from 1 – 5 with higher scores indicating greater difficulties in emotion regulation. DERS items reflect difficulties within the following dimensions of emotion regulation: a) awareness and understanding of emotions; b) acceptance and emotions, c) the ability to engage in goal-directed behavior, and refrain from impulsive behavior, when experiencing negative emotions; and d) access to emotion regulation strategies perceived as effective. Preliminary findings suggest the DERS has high internal consistency, good test-re-test reliability, and adequate construct and predictive validity. Importantly and pertinent to MM, the subscales focus on difficulties controlling behavior when emotion is present (i.e. avoidance, substance use), rather than on difficulties controlling emotion (Grantz and Roemer, 2004). The 24 item Five Factor Mindfulness Questionnaire – Short Form (FFMQ-SF) is a reliable and valid self-report instrument for assessing different aspects of mindfulness in both community and clinical samples (Bohlmeijer et al., 2011). Component skills include observing, describing, acting with awareness, nonjudging of inner experience, and nonreactivity to inner experience. The FFMQ was shown to have good psychometric properties and is able to distinguish meditators from non-meditators (deBruin et al., 2012). Cognitive and Emotion Regulation Scale-Revised (CAMS-R) is a brief 10 item self-report questionnaire that captures a multi-faceted conceptualization of mindfulness with four factors (attention, present-focus, awareness, and acceptance. The CAMS-R demonstrates evidence of discriminant as well as convergent validity in that the CAMS-R is more strongly associated with theoretically consistent emotion regulation and problem-solving styles (i.e., awareness of feelings, cognitive flexibility) than with other potentially adaptive but less theoretically consistent styles (i.e., distraction, problem analysis, and plan) Higher mindfulness scores were associated with lower levels of maladaptive emotion regulation, including experiential avoidance, thought suppression, worry, rumination, and overgeneralization, which is commonly seen in patients with PTSD and SUD (Feldman et al., 2007). Helping Alliance Questionnaire (HAQ-II-C/T). (Luborsky et al., 1996), a well-validated measure of agreement on tasks and development of bonds between therapist and participant, will be completed by each participant and therapist at weeks 4 and post treatment. Participant and therapist satisfaction surveys will be collected at 4 weeks and post treatment to assess acceptability, feasibility and other therapy feedback.

Randomized Pilot Study Intervention: After having at least 7 days in standard TAU screening and baseline assessments will be collected. This will allow time for improvement in cognitive function, particularly attention and concentration which are commonly affected by active substance use. Women meeting inclusion with no exclusionary criteria will be randomized to MBRP plus TAU or TAU alone control. Both groups will attend their standard TAU program. The eight MBRP therapy sessions (one individual/small group and 7 groups) will be integrated into the standard TAU program and replace 8 TAU SS sessions (one individual and 7 group sessions). Participants will be introduced to the therapists and scheduled for their first individual/small group session. If there is more than one participant enrolling within the same week, both will receive the first session together prior to joining the larger ongoing groups. Both therapy sessions and weekly research assessments will be scheduled with consideration of the clinic treatment program and participant's schedule and preference.

Retention: Every attempt will be made to engage participants for the duration of the therapy period. Individuals will be considered drop-outs from treatment if they fail to attend five consecutive therapy sessions and without any contact with research staff. Throughout the course of the study we will have adequate personnel to track participants, manage the scheduling of appointments, and have close supervision of therapy procedures. Research staff will gather locator information at screening and baseline (i.e. phone numbers, contacts), which they will update on a weekly basis. Therapists and research assistants will be trained in the importance of this aspect of the protocol and in techniques used in other studies to enhance retention. We will also provide transportation or transportation reimbursement vouchers for fuel to minimize this potential obstacle and burden. Of note, the CC offers some free transportation as part of its women's IOP clinical services. Comparable to other studies, compensation for time it takes for completion of assessments will be in the form

of cash, vouchers, gift cards, or reloadable debit card and includes the following: Participants will receive $35 for the screening assessment; $20 for the baseline assessment, $20 for completion of weekly assessments, $35 for completion of week 4 assessments, $40 for completion of 8 week post intervention, $50 for the three month follow-up and $75 for the six month follow-up assessment. Thus, the total participants may receive for completion of all the study assessments is $375. Participants who are non-adherent or drop out of treatment will be invited to participate and receive compensation for completion of follow-up assessments. W*e will make every effort to continue assessments for the entire course of treatment and follow-up, even among those who fail to adhere to randomized assignment or stop participating in the assigned intervention. If a participant is not physically able to come to the site to attend a follow-up visit and she agrees, follow-up assessments including the CAPS, TLFB and the ASI-lite, as well as the self-report PSS-SR and the OCDS forms and excluding urine drug screen and breathalyzer may be conducted by phone. All other self- report forms may be mailed to participants with a stamped return envelope for completed forms to be sent back to the research staff, or may be sent to the participant via an emailed survey link. Gift card compensation for the visit will be mailed to the participant, or if using a reloadable debit card, funds will be loaded to the card upon completion of the assessments and return of completed self-report forms.*

Statistical Considerations

Outcome Measures: The primary outcome measures for the efficacy portion of this study are 1) the effective reduction in PTSD symptom severity through the total score on the CAPS at the end of treatment between the two study groups and 2) the effective reduction in the proportion of days using and amount of use of alcohol/substances during the final 30 days of treatment as measured by the TLFB verified by UDS (*see Procedures for discrepancy correction*). In addition, secondary endpoints will include CAPS scores at the 3 and 6 month post-intervention follow-up visits, the 7 day point prevalence abstinence rates at each treatment, post treatment and follow up visits. Also, PSS-SR, OCDS-R, ASI-Lite, DERS, MAAS, KIMS and CAMS-R will also be secondary endpoints and used to gain insight into potential effect modification and mediation. Secondary analysis will also include the proportion of days using alcohol/drugs, craving, psychosocial functioning and emotional regulation at 3- and 6- month follow-ups.

Study Power: this study is powered to assess the efficacy of MBRP versus TAU in the reduction of CAPS scores from baseline to the end of treatment (8 wks). In addition, the study aims to estimate the precision of the variance estimates by calculating effective differences and 95% confidence interval for the squared sample standard deviation of mean responses and their differences. In a similar study design, King et al (2013) found a clinically significant difference in CAPS score reductions following 8 weeks of mindfulness based cognitive therapy as compared to TAU in participants suffering from combat PTSD (Completers: Hedge's g=1.01). Assuming an attenuated effect size in an intent to treat analysis (Hedge's g=0.80), for a 1:1 randomization allocation, a sample of 60 participants will provide 80% power with a type 1 error rate of 5% to detect this meaningful difference in reduction of PTSD symptoms. With a similar attrition rate of 25%, the inflated sample size of 90 participants (45 per group) would maintain adequate power to detect such a difference. Hien et al (2011) also found a significant correlation between reduction in PTSD severity and co-occurring reductions in substance use; while results from an intervention study of a similar population (Hien et al., 2009) estimated that baseline percentage of days using stimulants was 16 ± 23% and following a 7 week intervention decreased to 6 ± 16% (30day TLFB; g=0.50). Assuming a similar baseline percentage of drug using days, the proposed sample of MBRP subjects will have ample power (87%) with a type 1 error rate of 5% to detect this clinically relevant reduction in frequency of use. We will also have 80% power to detect an effect size of 0.79 for the difference between percentage of alcohol/substance using days (final 30 days of the study) between the MBRP and TAU groups.

Statistical Methods: The primary aims of the proposed study is to assess the feasibility of MBRP in the proposed population and to estimate effect sizes and their 95% confidence intervals in order to inform a larger study sample size calculation for a clinically relevant treatment effect. PTSD severity will be assessed prior to treatment, at the end of treatment, and at the 3 and 6 month post-intervention follow up visits using the Clinician Administered PTSD Scale (CAPS). The frequency and amount of substance use will be assessed using the 60 day Time line

follow back (TLFB) prior to treatment, during the last 30 days of treatment, and at both follow up visits. Abstinence will be assessed at weekly intervals during the treatment phase of the study and at the follow up visits. Estimates of between group difference in CAPS score and substance use frequency and the associated variances will be calculated using model based estimates and their 95% confidence limits. PTSD Symptoms (CAPS, PSS-SR) as well as substance use quantification (TLFB, % days using) will be examined using a linear mixed effects model to estimate the treatment effect and variance in the change from baseline to the end of treatment and 3- and 6- month follow-ups. Effect modification of secondary measures of craving, mindfulness and emotional regulation on the primary outcomes of PTSD symptom severity and substance use will be tested with interaction terms included in the models. Normality of the model residuals will be assessed (where appropriate) both graphically (Q-Q plots) and through the use of statistical normality tests (Shapiro-Wilk test). Deviations from normality will be corrected with alternate functional forms of the dependent variable (natural logarithm or square root transformations). Where normality cannot be reasonably obtained, non-parametric models will be used to test the hypothesis. Treatment effects estimated using the results of the general linear models in combination with the confidence intervals of the variance will be used to estimate power for a larger efficacy clinical trial of MBRP for the treatment of comorbid PTSD/SUD.

Data Interpretation/Future Studies: This study will evaluate the utility of a potentially effective psychosocial intervention, MBRP, in reducing PTSD symptom severity and alcohol/substance use as compared to TAU. Further, this will be the first study to incorporate MBRP in a community substance abuse treatment program in a population of women with PTSD and SUD. Results from the proposed study will provide an effect size estimation for a larger stage II randomized community effectiveness study. Adaptations made to the MBRP for implementation in a community setting will increase the likelihood of successful adoption, as well as provide another treatment option for patients with comorbid PTSD and SUD.

Randomization: Urn randomization will be used in assigning participants to the MBRP or TAU groups (Stout, Wirtz, Carbonari, & DelBoca, 1994) in a 1:1 allocation while balancing treatment assignment on two variables. To maximize the power for a comparison of effect across groups and minimize confounding, intensity of drug use and baseline CAPS scores will be balanced during the randomization. Days of drug use and severity of PTSD symptomology at baseline (pre-study involvement) is a likely prognostic factor on the primary outcome measure, and as such, will be controlled during randomization.

Safety Procedures

Patients will be monitored for adverse events (AEs) throughout the study as described in the protection of human subjects section. Emergency procedures are in place in the event of worsening of symptoms or other life threatening events. The PI, Co-Is will be available to assess all AEs and make appropriate decisions regarding study termination and referrals to more intensive treatment.

Non-Participant MBRP Group Members

MBRP group sessions may be populated with non-participant group members to ensure the MBRP group sessions have sufficient participants to run continuously throughout the study. Non-participant group members are not considered MBRP or TAU participants in the study. Essentially, they are “auditing” the MBRP group sessions similar to how students audit a college course; they are not truly “enrolled” in the group but they could gain a benefit from the experience. Non-participant group members may attend all nine of the weekly MBRP group sessions along with regular research participants, and may participate fully just as they would with any other recovery group. Non-participant group members do not have to meet all eligibility requirements. These individuals are women aged 18 – 65, with symptoms of PTSD and SUD, who are in treatment at Charleston Center but were not enrolled in the study due to being ineligible for study participation for a variety of reasons (did not meet DSM-V criteria for PTSD with a score ≥ 25 on CAPS, did not have alcohol/substance use within 60 days prior to clinic entry, pregnant, not staying locally in the Charleston area). Non-participant group members are not randomized, do not complete research visits or study assessments, and are not compensated for their participation. However, they will receive group materials associated with the intervention, such as an mp4 player downloaded with meditation practice exercises. Non-participant group members will meet with research staff only for the consent process and to determine the next available group session to attend. Interested clients will provide informed consent with an approved non-participant group

member informed consent form and an approved HIPAA consent form. They will be made aware of the risks and benefits of group participation. Consent forms will be kept in a locked file cabinet and all group session recordings will be stored securely in a locked file cabinet or on a secure and encrypted server. Only the project staff and supervisors will have access to the recordings. They will be destroyed after the study has been completed. Research staff will attend CC staff meetings on a regular basis to discuss recruitment of non-participant group members and any other issues that arise.

Telehealth Option

Participants in this research study may choose to complete this study via telehealth, which may improve retention by avoiding financial barriers, transportation issues, and public health risks associated with traveling to MUSC for in-person sessions.

Electronic Consent:

Participants will have the option to complete the informed consent process electronically. Research staff will contact the participant to thoroughly explain the research study and to answer any questions the participant may have. The participant and the research staff will then sign the informed consent form and HIPAA authorization electronically via a MUSC approved application. The signed copy of the informed consent form and HIPAA authorization will be mailed/emailed to the participant based on their preference. Research staff will document the electronic informed consent process in the participant study file in REDCap and retain records of the electronic informed consent document and HIPAA authorization. Alternatively, participants will have the option to complete the informed consent process via the mail/phone method. Prior to the informed consent process, research staff will mail/email two copies of the informed consent form and HIPAA authorization to the participant. Once received, research staff will contact the participant to thoroughly explain the research study and answer any questions the participant may have. The participant will sign both copies of the informed consent form and HIPAA authorization, keep one copy for their records, and mail the second copy back to the research team in a stamped return envelope provided by the research team. The final signed copy of the informed consent form and HIPAA authorization will be mailed/emailed to the participant based on their preference. Research staff will document the informed consent process in the participant study file in REDCap and retain records of the informed consent document and HIPAA authorization.

Study Sessions:

Study sessions will be delivered via a standard desktop computer, laptop computer, tablet, or smartphone running MUSC approved applications. Participants who choose telehealth will be required to have their own computer, tablet, or smartphone. Study participants will be given a tutorial on the MUSC approved applications by the research team prior to participation in the first study session, and will then be invited to join the session at a pre-scheduled time. The therapist will begin the session and lead the session through to completion. Study sessions will occur in this fashion until completion of the study session portion of the study. Research staff will document visit attendance in the participant study file in REDCap. Additional research staff will always be available to assist the therapist and/or participants with any technological issues that may occur throughout the study.

Screening:

Prior to the screening appointment, research staff will mail pregnancy tests and urine drug screens to the participants to test for pregnancy and substance use. After the informed consent process is complete, participants will be asked to complete a pregnancy test and must provide verbal and/or virtual confirmation of a negative pregnancy test prior to proceeding with the screening appointment. Research staff will be available to provide instructions on how to provide a urine sample, how to use the dipstick to test, and how to differentiate between a positive and negative result. Ability and willingness to perform a pregnancy test is required for telehealth participants. Participants will be asked to complete weekly urine drug screens and provide verbal and/or virtual results as part of the weekly assessments. Research staff will be available to provide instructions on how to provide a urine sample and how to differentiate between a positive and negative result.

Other Study Supplies:

Research staff will mail any additional study supplies to the participants prior to the start of the first study session. Additional study supplies may include handouts, MP4 players, yoga mats, and any additional items deemed necessary to facilitate completion of the study.

Operational Plan and Research Timetable

Funding for five years is requested.

Year 1: Manual modification; hiring and training research personnel; submitting regulatory documents; preparing for study initiation (standard operating procedures); training and certifying community clinicians who will be delivering the intervention.

Year 2: Pilot eight session intervention with two groups of approximately 6 patients; focus groups with participants and clinicians following completion of sessions; revisions to manual as indicated per feedback. Enroll first eight participants in randomized pilot

Year 3: Enroll 36 participants in randomized pilot; data collection/entry and management; complete 36 post treatment and 48 (28 three months and 20 six months) follow-ups.

Year 4: Enroll 36 participants in randomized pilot; data collection/entry and management; complete 38 post treatment and 73 follow-ups (37 three month and 36 six month) follow –ups.

Year 5: Enroll 10 participants in randomized pilot; complete 16 post treatment, 25 three month and 34 six month follow ups, data clean and analysis, final manual revisions, publication, dissemination in community program (train trainers).

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