I. BACKGROUND AND SIGNIFICANCE

A. Overview

Substance use disorders (SUDs) are chronic and relapsing conditions (Connors et al., 1996). Compared to the general population, military personnel and Veterans are at increased risk for developing SUDs (Hoge et al., 2004; Hoge et al., 2006; SAMHSA, 2005; Brady et al., 2009). A recent study found that nearly 50% of active duty service men reported binge drinking in 2008 and misuse of prescription opiates increased from 2% in 2001 to 11% in 2008 (Bray et al., 2010). The Office of National Drug Control Policy (2010) found that prescription drug misuse among military personnel was more than twice that of the general population and more than four times the rate of the general population for women. A recent study of military personnel within one year of return from deployment in Iraq or Afghanistan found that 39% screened positive for an alcohol use disorder and 3% positive for drug abuse (Eisen et al., 2012). These findings suggest that the need for improved treatment for SUDs in VA settings will increase. The rates of relapse associated with alcohol, cocaine, heroin and other SUDs are estimated at over 60% following any single treatment episode (Macay and Marlatt, 1990; McLellan et al., 2000). Psychiatric comorbidity is commonly found in Veterans with SUDs and increase the risk of relapse following treatment (Hasin et al., 2002; Greenfield et al., 1998; Kodl et al., 2008). A recent IOM report (2012) recommended that the Military Health System shift focus from acute care to an outpatient chronic care model for SUDs, encouraging individuals to remain connected to recovery-based systems. Thus, new continuing care strategies targeting life-style changes and improved coping strategies are critical to maintaining abstinence, rehabilitation and functional improvement for Veterans with SUDs.

B. Mindfulness Based Relapse Prevention

Mindfulness Meditation: Mindfulness meditation (MM), with roots in Eastern philosophy, has been explored in the treatment of stress-related medical conditions (e.g. chronic pain), depression, anxiety and addictions (Bishop et al., 2004; Fjorback et al., 2011; Roemer et al., 2002; Teasdale et al., 2000). MM is a self-directed practice of attending to present-moment experiences (physical sensations, perceptions, affective states) in a non-judgmental manner to increase non-reactive awareness and improve emotional processing, affect regulation and self-management skills (Lau & Grabovac, 2009). Increasing tolerance and acceptance of experiences may lead to reductions in emotional reactivity and improved coping strategies, enhanced self-efficacy, self-control and emotional well-being (Astin et al., 1997; Carmody et al., 2009). Thus, MM can allow individuals with SUDs to experience greater control over cravings, thoughts and memories, making them less likely to use substances.
Mindfulness in SUD Treatment: In a systematic review of MM-based treatment of SUDs, Zgierska and colleagues (2009) concluded that the overall preliminary evidence was positive, but significant methodologic limitations including small sample size, lack of standardized outcomes and heterogeneity of interventions, prevented conclusions about efficacy. Recommendations included further studies using high-quality research methods including a written treatment manual. Mindfulness-Based Relapse Prevention (MBRP) is a manualized, eight-session group-based therapy integrating cognitive-behavioral relapse prevention therapy and mindfulness practices, raising awareness of substance use triggers and reactive behavioral patterns, and teaching skillful coping responses (Bowen et al., 2010). Individuals are taught to experience and monitor cravings and urges in a non-judgmental manner with the goal of self-regulation of thoughts, emotions, sensations and behavior. In a randomized trial comparing MBRP to usual continuing care in 168 individuals who had completed acute care treatment for SUDs (Bowen et al., 2009), the MBRP group reported significantly fewer days of drug or alcohol use (2.1 versus 5.4 days) and significant reductions in craving in the two months following intervention. Reductions in craving partially mediated decreased substance use and the MBRP group were less likely to crave in response to depressed mood (Witkiewitz and Bowen, 2010) but the MBRP impact was not explained by improvements in depression. Using MBPR as part of the continuing care strategy for military Veterans who are in the recovery and rehabilitation phase following successful primary treatment for SUDs makes sense for the following reasons: (1) there is a significant unmet clinical need; (2) relapse risk is highest immediately following treatment and improved approaches to continuing care are needed; (3) minimizing relapse is critical to improved morbidity, mortality and functional recovery; (4) MBRP addresses emotional dysregulation and control deficits

that are not well-addressed by other standard SUD interventions.

II. SIGNIFICANCE AND RELEVANCE TO VHA

A. Priority Illness

SUDs are prevalent in military populations. A recent report found that 43% of Army personnel reported past month binge drinking (Department of Army, 2012) and a recent DoD survey revealed significant increases in prescription opiate use and binge drinking between 1998 and 2008 (Bray et al., 2010). SUDs are commonly associated with suicide in Veterans (Ilgen et al., 2010). Relapse following treatment is common and the need for new continuing care approaches to improve long-term outcomes, recovery and rehabilitation is critical.

B. Priority Novel Treatments and Continuing Care

Despite a substantial number of trials focused on SUD treatment, most have focused on acute care. Novel approaches with the potential to facilitate lasting changes in lifestyles and coping strategies are needed. MM-based treatment has been well received by Veterans with PTSD. Expanding on these promising findings to explore the use of MBRP in SUD treatment is a logical next step.

III. PRELIMINARY DATA

A. Research Team

A multidisciplinary research team with relevant and complementary expertise and skills has coalesced to plan and conduct the proposed project. **Kathleen Brady, MD, PhD** (PI) has been conducting clinical trials for over thirty years. As PI of the Southern Consortium Node of the NIDA Clinical Trials Network (CTN), she has supervised the conduct of over 25 SUD clinical trials, many of them multi-site trials, in the past 12 years. Much of her work is focused on the PTSD/SUD interface. **Karen Hartwell, MD** (Charleston VAMC Site PI)**,** an addiction psychiatrist, is a staff psychiatrist in the Substance Abuse Treatment Clinic (SATC) at the Charleston VAMC, one of the sites for the proposed study. She has been active in clinical research with Dr. Brady for 7 years, has served as a PI and Co-I for a number of clinical trials and is experienced in assessment, recruitment, retention, safety and quality control issues in clinical trials. **Lori Davis, MD** (Tuscaloosa VAMC Site PI) has been conducting clinical trials in psychiatric disorders at the Tuscaloosa VAMC for 15 years. She is the PI on a multi-site VAMC study of MM in PTSD being conducted at the Tuscaloosa and Charleston VAMCs. Drs. Brady and Davis have served on advisory groups together and have been colleagues for over ten years. Drs. Davis and Hamner have successfully collaborated on a number of VA multi-site trials. **Therese Killeen, RN, PhD** has served as the site PI for a number of NIDA CTN-sponsored multi-site trials, including a trial of exercise in SUD continuing care conducted in the Charleston SATC. She has served as a trainer/supervisor in several therapy-based SUD studies and was the site PI on a study of 12-Step Facilitation, which used the same treatment manual to be used in the proposed study. Dr. Killeen has practiced mindfulness meditation (MM) for over 25 years and was trained in MPBR by Dr. Sarah Bowen. **Mark Hamner, MD** is a nationally recognized expert in psychiatric clinical trials and has been conducting research at the Charleston VAMC for over 20 years. He is currently the site-PI of a multi-site trial of MM in the treatment of PTSD in veterans. **Elizabeth Santa Ana, PhD,** staff psychologist in the Charleston SATC, has experience in the conduct of randomized clinical trials investigating psychosocial interventions for SUDs. She is an experienced therapy trainer/supervisor and is proficient in monitoring adherence/competence to manualized therapy protocols. **Sarah Bowen, PhD,** Assistant Professor of Psychiatry at the University of Washington is one of the primary developers of MBRP, lead author on the MBRP manual to be used in this study and lead investigator on a pilot study of MBRP in SUDs (Bowen et al., 2009; 2010). She will assist in training and supervising the MBRP therapists. **Nathan Baker, MS**, study biostatistician, has worked with Drs. Brady, Killeen and Hartwell for the past 5 years and has extensive experience in treatment outcome studies in addictions. In summary, the proposed study team has experience in conducting clinical trials in VAMC settings, in treatment research in addictions and in mindfulness-based

treatment of psychiatric disorders. They have a history of successful collaboration and are well equipped to carry out the proposed work with the highest degree of scientific integrity and quality.

B. Relevant Clinical Trials Experience

Drs. Brady, Killeen and Santa Ana are currently collaborators on a psychotherapy treatment trial for Veterans with co-occurring PTSD and SUDs at the Charleston VAMC. Of particular relevance to the proposed trial, Drs. Brady and Killeen recently completed a multisite trial at the Charleston VAMC comparing exercise to health education in Veterans with stimulant dependence as an adjunct to residential aftercare treatment. Participants were required to attend three sessions per week for the first 12 weeks followed by weekly visits for six months. Recruitment, treatment exposure (62 sessions) and follow-up for the Charleston site was exemplary, meeting the national recruitment expectation of approximately two patients per month over 15 months despite strict inclusion criteria. The retention rate was 86% for the acute intervention (first three months) and 80% in the continuation phase (3-9 months), highest of all of participating sites. This study demonstrates the ability of the research team to successfully recruit an adequate number of participants, insure excellent treatment exposure to a fairly high intensity alternative therapy and successfully follow participants over time in the same population that will be recruited for the proposed trial. Dr. Davis is the PI on a multi-site VAMC trial of MM treatment of PTSD in which Dr. Mark Hamner is the Charleston site PI. Study recruitment has gone extremely well and retention/satisfaction with treatment is high. Acceptance has been high in OEF/OIF Veterans. As such, both sites have trained therapists and investigative teams experienced in the implementation of a clinical trial investigating MM-based therapy in a VAMC setting.

IV. RESEARCH DESIGN AND METHODS

A. Overview

The primary objective of this prospective, randomized, controlled trial is to evaluate the efficacy of mindfulness-based relapse prevention (MBRP) compared to 12-Step Facilitation (TSF) in military Veterans following completion of intensive outpatient treatment for SUDs at the Charleston or Tuscaloosa VAMC, *residential treatment programs or intensive outpatient programs similar to the programs at the Charleston or Tuscaloosa VAMC.* . The trial will be conducted at two sites to allow recruitment of an adequate number of participants to address critical study questions within a four-year timeframe. The eight weekly 90-minute, group-based MBRP or TSF sessions will be followed by a *10-month follow-up period* with assessments of alcohol/drug use, mood/anxiety symptoms, quality of life and functional outcomes.

B. Subjects

Subjects will be 308 Veterans who have completed the intensive SUD outpatient program at the Charleston or Tuscaloosa VAMC, residential treatment programs or intensive outpatient programs similar to the programs at the Charleston or Tuscaloosa VAMC. Males and females with mood, anxiety and other psychiatric disorders will be included. There will be no exclusion based on race, ethnicity, or gender. A stratified urn randomization procedure using the prognostic covariates gender and anxiety/mood disorders will be used. Additional stratification variables (e.g. primary substance of abuse) were considered, but because of excessive division among multiple cells, these variables will be explored as covariates in efficacy analyses (see Data Analysis Section). Specific inclusion/exclusion criteria are listed in the Human Subjects Section.

C. Procedures

C.1 Recruitment: The primary recruitment sites are the VAMC SATC Intensive Outpatient Programs (IOP) in Charleston, South Carolina and Tuscaloosa, Alabama. No other treatment outcome projects are projected to recruit from these programs during the time of proposed study conduct, so there should be no problem recruiting approximately 10 subjects total per month for study completion within the timeline proposed. The availability of VA-supported housing for participants in these IOP programs will enhance the feasibility study of recruitment and retention. The secondary recruitment sites are residential treatment programs or other Intensive Outpatient

Programs that are similar to the IOP at the Charleston or Tuscaloosa VAMC.
Charleston: Over the past year, approximately 446 veterans participated in the VAMC SATC-IOP with a 68% completion rate. Approximately 38% met criteria for alcohol dependence, 11% for drug dependence, and 51% for both. The majority were male, approximately 50% Caucasian and 50% African-American.
Tuscaloosa: In 2012, the Tuscaloosa VAMC enrolled 102 veterans in the substance abuse treatment intensive outpatient program. The majority were male, approximately 36% Caucasian, 62% African American and 2% Hispanic *with* primary diagnoses of alcohol, cocaine and cannabis dependence.
Intensive Outpatient Programs (IOP): Both programs provide individualized treatment planning, medical/psychiatric evaluation and group-based treatment for 3 hours per day, 5 days per week. Groups include psychoeducation, cognitive behavioral therapy, relapse prevention and introduction to AA/NA. Individuals are enrolled in pre-treatment groups for 1-2 weeks and then participate in the IOP for approximately 4 weeks. Follow-up generally consists of 6 months of group aftercare meetings, individual case management, treatment for comorbid conditions and ongoing medication management as needed.

C.2 Screening, Eligibility and Randomization: Study representatives will present a study overview during IOP groups and collect contact information from those Veterans who wish to be contacted about the study. A quick screen (inclusion/exclusion criteria) by phone or in person will be used to determine initial eligibility of interested individuals and a face-to-face assessment will be scheduled as appropriate. Potential subjects will be given a full study description and asked to read and sign an IRB-approved informed consent form before study procedures/assessments are conducted. Eligible subjects will complete assessments and randomly assigned to either MBRP or TSF. Subjects will begin the MBRP or TSF intervention after completion of the IOP program. Subjects who are ineligible will continue in the VAMC IOP and aftercare treatment.

We will also receive referrals from the clinical staff of the SATC IOP. The SATC clinical staff will ask their patients if they are agreeable to being contacted by the research staff to discuss a research study. If an SATC patient is agreeable to being contacted about a research study, the SATC staff member will make a note in CPRS stating that the Veteran is agreeable to being contacted and will then forward the patient's name and contact information to the research staff. Permission to be contacted may also be documented by the Veteran's signature on a contact information form. The SATC clinical staff will give these forms to the research staff so the Veteran can be contacted about the study.

Respondent-Driven Sampling (RDS) will be used to enhance recruitment of the sample. The RDS sampling methodology is based on recruiting the eligible friends and acquaintances of each participant so that the sample "snowballs". Each eligible participant who is randomized into the study, and agrees to take part in this recruitment assistance, will be given coupons to pass on to other potential participants. The coupons will have a unique code linked to the person who passes them out. A referral will be instructed to call the study team for screening. If that person successfully completes a screening assessment and is randomized, the participant who referred them can redeem the coupon for $10.

C.3 Assessment Instruments: After the informed consent procedure, subjects will complete a battery of assessments. The assessment instruments (Table 1) were selected because they are standardized, have good psychometric properties, are widely used and have been used by our research group in the past. A multimodal assessment strategy measuring change across several dimensions will be utilized. Unless otherwise stated, assessments will be administered at baseline, weekly during treatment, post-treatment, and *at 3, 6 and 10-month follow-up visits.* Weekly TLFB, UDS and alcohol biomarkers will provide a valid trajectory for imputation of treatment dropout data for intent-to-treat analyses. Independent assessors (IA) performing end of treatment and follow-up assessments should to the extent possible be blind to participant's treatment assignment.

General Diagnostic and Inclusion/Exclusion Criteria

Demographic Data: At the baseline assessment, demographic data (e.g., age, race/ethnicity, marital status, employment) will be collected using a form designed for this study.

Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998): The MINI is a well-standardized structured interview which is similar in sensitivity, specificity, and inter-rater reliability to other more lengthy diagnostic interviews, such as the Structured Clinical Interview for DSM-IV. The DSM 5 version of the MINI will be utilized. The MINI will be used at baseline to assess psychiatric diagnoses for inclusion/exclusion and urn randomization purposes.
Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2012): This brief, well-validated instrument will be used at baseline to screen for cognitive impairment that could interfere with ability to benefit from MBRP. A cut-off of 26/30 is considered normal. The research team will use their judgement in determining eligibility for any participant who scores below 26 on the MOCA.
Urine pregnancy test: A urine pregnancy test will be performed on all females at the baseline visit. Pregnancy testing will be conducted prior to the urine drug screen. If a woman is found to be pregnant, she will be excluded from the study and no further study procedures will be conducted.

Substance Use
Timeline Follow-Back (TLFB; Sobell & Sobell, 1992): The TLFB will be used to obtain retrospective self-report of alcohol, nicotine, illicit drug (e.g., cocaine, marijuana, stimulants, sedatives, opioids), and prescription drug use using calendar and memory prompts to stimulate recall. The TLFB yields consistently high test-retest correlations and correlates well with other self-reports and collateral reports (Carey, 1997). Quantity and frequency assessments as well as time-to-event measures can be obtained. At baseline, drug/alcohol use in the 30 days before enrollment in treatment will be assessed. We will use a modified TLFB to collect detailed information about treatment and work activities (described below).
Urine Drug Screen: Urine samples will be collected with an on-site multi-drug 12-panel test, which allows detection of THC/marijuana, cocaine, phencyclidine, opiates, methamphetamines, methadone, amphetamines, barbiturates, benzodiazepines and uses concentration levels established by SAMHSA. Osmolality and temperature will be assessed at collection time to insure sample validity.
Alcohol Breathalyzer Test: Breathalyzer tests will be used to measure subjects' blood alcohol concentration (BAC) before treatment sessions. Study staff and/or counselors will decide if individuals who test positive will be allowed to attend group sessions. Samples >0.01 g/dl will be considered positive.
Laboratory Evaluations: The conjugated alcohol metabolite ethyl glucuronide (EtG) remains positive in urine for several days following cessation and is a useful biomarker of recent drinking in outpatient settings (Dahl 2011). This will be used as the primary biologic assessment of drinking status as breathalyzer tests only assess very recent alcohol use. The on-site EtG urine test will be done on samples collected at baseline, end of treatment and 3-, 6-, and 10-month follow-up visits.

Reconciliation of Self-report and Laboratory Evaluation
UDS, breathalyzer and EtG will be used to corroborate self-report. Results will be used to correct discrepant self-reports within the timeframes appropriate to each substance's half-life following protocols currently in use.

Associated Areas of Functioning
Mindfulness Acceptance and Awareness Scale (MAAS; Brown and Kasser, 2005): This is a 15-item self-report instrument rating the frequency of experiencing impaired moment-to-moment attention on a 6-point Likert scale. This measure will be done at baseline and end of treatment and used to explore the relationship between MAAS scores and treatment response.
Beck Depression Inventory 2nd Edition (BDI-II; Beck et al., 1996): This 21-item self-report scale will be used to assess for worsening depression/suicidality in safety monitoring.
Beck Anxiety Inventory (BAI; Beck & Steer, 1993): This 21-item self-report scale has symptom clusters reflecting neurophysiological, subjective, panic, and autonomic dimensions.
Concomitant Medications: Dosage/frequency of all medications will be assessed.

Other Functional Outcomes/Quality of Life Indices
Addiction Severity Index, Lite (ASI-Lite; Cacciola et al., 2007): This standardized, multidimensional, semi-structured interview provides information concerning functioning in six domains commonly impacted by

substance abuse: alcohol/drug, medical, psychiatric, legal, family/social and employment. Composite scores for each domain can be used to assess functional outcomes.

Days Engaging in Structured/Productive Work Activities (PWAC; Based on the TLFB): The PWAC will be used to assess self-reported days engaged in structured, volunteer, or employed work activity of at least 1 hour in duration. A review of VA medical records in CPRS will be used for medical record corroboration. Activities outside of the VA will be included.

Treatment Engagement: Treatment Attendance Calendar (TAC; based on TLFB): The TAC will be used to assess number of days treated for a substance abuse/mental health problem in the VA or any other outpatient aftercare setting, number of 12-step or self-help group meetings attended and physician contact and/or hospitalization. Treatment utilization will also be examined through CPRS.

Quality of Life Scale (QUOLS; Burchardt and Anderson, 2003): This 16-item scale, used to assess satisfaction with major areas of life function, has convergent and discriminant construct validity in chronic illness as evidenced by high correlations between the QOLS total score and Life Satisfaction Index.

Process Variables

Treatment Adherence: Completion of "homework assignments" will be monitored weekly during treatment. The percent of completed assignments will be computed as an indicator of treatment adherence.

Session Attendance and Study Attrition: Records of session attendance will be assessed. Treatment completion will be defined as completion of at least five of the eight treatment sessions.

Helping Alliance Questionnaire (HAQ-II; Luborsky et al., 1996): Therapeutic alliance is a promising construct for predicting treatment outcomes in SUD psychotherapy (Connors et al., 1997). This well validated measure will be completed at weeks four and eight.

Table 1. Assessment Instruments and Timeline

Instrument	Purpose/Domain	Length	Baseline	Weekly (treatment phase)	Week 8/EOT	3 Months from EOT	6 Months from EOT	10 Months from EOT
Informed Consent	Obtain informed consent from subject	10-20 min	X					
Demographics	Characterize sample	5 min	X					
MINI-International Neuropsychiatric Interview	Assess DSM-V psychiatric disorders	40 min	X					
Montreal Cognitive Assessment	Screen cognitive deficits	10 min	X					
Timeline Follow-Back (TLFB)	Primary outcome, substance use severity and frequency	10-30 min	X	X	X	X	X	X
Addiction Severity Index-Lite (ASI-Lite)	Assess alcohol/drug; family and social	20 min	X		X	X	X	X
Urine Pregnancy Test	Determine eligibility	5 min	X					
Urine Drug Screen (UDS)	Biomarker drug use	5 min	X	X	X	X	X	X
Alcohol Breathalyzer (if indicated)	Recent alcohol use	1 min	X	X	X	X	X	X
Ethyl Glucuronide (EtG)	Biomarker alcohol use	5 min	X		X	x	x	X
Beck Depression Inventory-II (BDI-II)	Assess depression	10 min	X	X	X	X	X	X
Beck Anxiety Inventory (BAI-II)	Assess anxiety	10 min	X		X	X	X	X

Helping Alliance Questionnaire (HAQ-II)	Assess therapeutic alliance	5 min			X			
Mindfulness Acceptance and Awareness Scale	Mindfulness	1 min	X		X	X	X	X
Quality of Life Scale	Life satisfaction	5 min	X		X	X	X	X
Treatment Adherence	Homework completed	1 min		X				
Productive Work Activities	Self-reported days engaged in work activities	10 min	x	x	x	x	x	x
Treatment Attendance Calendar	Assess number of days treated for substance abuse/mental health problems	10 min	x	x	x	x	x	x
EOT = End of Treatment								

C.4 Compensation: *The compensation plan, designed to be fair and devoid of undue inducements, includes the following: $25 for the completion of the baseline visit, $20 for each of the weekly assessments completed at weeks 1 – 7 during the active treatment phase, and $40 for completing week 8 (end of treatment) of the active treatment phase. Subjects will receive $45 for completing the 3-month follow-up visit, $50 for completing the 6-month follow-up, and $60 for the completion of the 10-month follow-up. Subjects are also eligible to receive an additional $10 once they complete a total of 3 weekly assessments and an additional $30 for completing a total of 5 weekly assessments. Thus, the total amount subjects may receive for the baseline assessment, treatment and follow-up visits is $400.*

C.5 Treatment Interventions:

Both the Charleston and Tuscaloosa VAMC continuing care programs have "open enrollment" treatment groups, so that participants enter treatment groups when they are ready rather than waiting for a new group cycle to begin. For both MBRP and TSF therapies, participants must be exposed to introductory materials first, so consideration to the order of presentation of material is needed. To adhere to strict sequential session delivery, a cohort would need to be assembled before beginning treatment and the wait time involved can negatively impact recruitment. To address this, *we created a hybrid system to allow group entry within a week of completing assessments, yet maintain treatment delivery in coherent order. Participants begin MBRP with an introductory session delivered individually (or small group if several participants enroll in same week) prior to joining the larger group. Participants begin TSF session 1 as a group with an introduction to the 12-step view of addiction and therapy overview. Therapists in both conditions will stagger therapy session delivery such that in any given week, one therapist will be delivering early sessions (1-4) and the other therapist will be delivering later sessions (5-7). In both therapies, early sessions focus on early recovery problems and later sessions focus on recovery maintenance issues, so sequential delivery within subgroups is not essential as long as subjects participate in the early sessions first. The TSF termination session will be delivered individually or in a small group when several participants finish treatment in the same week. The MBRP termination session is delivered in a group and covers social support and continuing practice.* The table of contents and introductory chapter from both manuals can be found in the appendix material. The TSF manual in the appendix material is focused primarily on stimulant dependence as this was the focus of the recent CTN trial. This will be easily converted to address SUDs more generically for the proposed trial.

Mindfulness Based Relapse Prevention (MBRP): The Introductory session provides an orientation to the intervention, basic mindfulness techniques and general description of group sessions. Each session has a central theme/topic (Table 2 below) and consists of in-session experiential practice, discussions and homework assignments. Sessions begin with a check-in followed by a 20-30 minute meditation (i.e. body scan). The therapist reviews homework assignments, discusses challenges and participants are taught a variety of MM practices such as breath meditation, urge surfing, walking or movement meditation.

Table 2. Mindfulness-Based Relapse Prevention Sessions

Introduction to the Manual: Delivered individually or in a small group
Sessions 1-8

Session 1:	Automatic Pilot and Relapse
Session 2:	Awareness of Triggers and Craving
Session 3:	Mindfulness in Daily Life
Session 4:	Mindfulness in High Risk Situations
Session 5:	Acceptance and Skillful Action
Session 6:	Seeing Thoughts as Thoughts
Session 7:	Self-care and Lifestyle Balance
Session 8:	Termination Session: Social support and continuing practice

Twelve-Step Facilitation Intervention (TSF): The Introductory session (session 1) covers the 12-Step view of addiction and therapy overview. The manual, originally developed for individual sessions, has been adapted for group delivery (Brown et al., 2002). The eight selected sessions include four topics chosen by the manual developers as core topics and four elective topics (Table 3). The intervention involves helping participants understand and incorporate core principles of 12-Step approaches while encouraging active participation in 12-Step meetings and related activities. The primary goal is to promote abstinence by facilitating the patient's acceptance and surrender of addiction. Sessions begin with a check-in during which participants introduce themselves, report on meeting attendance and participation in related activities, any alcohol/drug use or craving to use. The remainder of the session focuses on discussion of the topic content followed by a "take home" summary and homework assignment. In a multisite randomized study comparing TSF to treatment as usual, the TSF group was significantly more likely to be abstinent at the end of treatment (OR 2.44, $p<0.05$) (Donovan et al, 2013).

Table 3. Twelve-Step Facilitation Intervention Group Sessions

Sessions 1-8

Session 1:	12-Step Recovery (Introduction)
Session 2:	Acceptance
Session 3:	People, Places and Things
Session 4:	Surrender
Session 5:	Getting Active in 12-Step Programs
Session 6:	Emotions: Hunger, Anger, Loneliness and Tired (HALT)
Session 7:	Enabling
Session 8:	Termination: To be delivered individually or in a small group

D. Therapists Training and Supervision

Therapist training sessions will be held in Charleston. Sarah Gainey, MSW served as the therapy supervisor in the CTN TSF trial (discussed above), and will oversee TSF training and supervision. Drs. Bowen and Killeen will oversee MBRP training and supervision. Training will include (1) didactic review of intervention-specific theory; (2) manual review; (3) observation and practice; and (4) mock intervention sessions. Competency and adherence ratings will be used to determine certification status. Training materials and rating forms developed for prior trials will be utilized.

Ongoing Supervision: Therapists will receive every other week supervision via teleconference focused on treatment model adherence, intervention quality and clinical concerns about particular participants. Feedback to reduce departure from treatment protocol and assist therapists in identifying issues for subsequent sessions will be provided. In preparation for weekly supervision, the supervisor will review taped therapy sessions and rating forms. If it is determined that a therapist is not competent or does not adhere sufficiently to the manual, additional training sessions will be scheduled. Every attempt will be made to correct problems through training and supervision. The decision to replace a therapist will be made by the therapy supervisors and the PI.
Therapist Competence and Manual Adherence: *To assure that therapy is delivered in a manner consistent with manual guidelines, all therapy sessions will be audiotaped and randomly selected sessions (approximately 1/3 for each therapist) will be evaluated using the MBRP Adherence and Competence Scale (MBRP-AC: Chawla et al., 2010) and the TSF Adherence, Competency and Empathy Scale (TSF ACES: Campbell et al., 2012). In addition to supervisors review of tapes for supervisory purposes, experienced therapists not otherwise involved in the study will also rate tapes to insure objective assessment of adherence and competence.* Adherence ratings evaluate employment of individual components of MBRP or TSF and discussion of key concepts. Competence ratings assess therapist style, approach and performance. Inter-rater reliability on measures of adherence and competence between independent raters will be established. To provide a regular reminder of key treatment elements and estimate level of treatment-specific interventions provided, treatment-specific therapist checklists will be completed by the therapists weekly.
Treatment Integrity: Treatment integrity will be maintained through: 1) manualized treatments; 2) expert supervision; 3) regular review of audiotaped sessions; and 4) independent competence/adherence ratings. These methods parallel those used to sustain integrity in other MUSC treatment research projects.

E. Safety and Monitoring Plan

Every attempt will be made to engage participants for the duration of the therapy and follow-up. Individuals will be considered for treatment termination if they fail to attend three consecutive weeks of therapy in spite of attempts by phone and mail to engage them in treatment. On certain circumstances as determined by the PI/Co-Is participants may be considered to resume sessions in another ongoing cohort. If at any point during the assessment, treatment or follow-up period, participants need medical management, psychiatric consultation or hospitalization, they will be evaluated and referred as necessary. If a participant becomes suicidal, emergency psychiatric assessment will be arranged and they will be clinically monitored until they are no longer suicidal or an appropriate care plan is in place. Both the Charleston and Tuscaloosa VAMC programs have well-established protocols for emergency psychiatric evaluation, crisis intervention and/or psychiatric hospitalization for suicidal, homicidal, psychotic or acutely distressed patients. During evenings or weekends, the PI/Co-Is will be on-call for emergencies. At these times, acutely distressed patients will be instructed to go to the VAMC urgent care for evaluation. The PI/Co-Is will have notified the physician on call in advance of the patient's situation. Acute psychiatric hospitalization is available for emergencies. Therapists will be instructed to use their best clinical judgment regarding day-time emergencies and inform the site PI, Co-Is or therapy supervisor as soon as possible. In addition to relying on clinical judgment, SUD and depression symptoms will be monitored weekly using standardized measures to detect symptom worsening requiring further evaluation. Participants will be encouraged to discuss worsening SUD and depression symptoms with their therapist. If a patient has relapsed to substance use (return to pretreatment use or more), this will be dealt with therapeutically during the session or within their standard treatment. If, in the judgment of the therapist/supervisor and/or PI/Co-I's, it is determined that symptoms are worsening and a participant would not benefit from further MBRP/TSF treatment, appropriate referrals will be made. These decisions will be dealt with in training and supervision and monitored carefully.

Patients will be discontinued from the study and referred for more intensive treatment if there are:

1. Increases in alcohol or drug use leading to the need for a more intensive level of care
2. Suicidal or homicidal ideation accompanied by a plan
3. Inability to manage the patient within the inclusion/exclusion criteria of the study (i.e., need for the initiation of maintenance psychotropic medications; development of psychosis)
4. Inability to return for therapy appointments due to incarceration or hospitalization

F. Strategies to Minimize Attrition
We have extensive experience with research scheduling and subject tracking. Techniques used successfully in other studies to improve engagement and retention include appointment reminder cards, appointment verification 24h in advance, immediate contact of subjects who miss appointments. We have budgeted to minimize the impact of transportation problems on treatment compliance. Our team consists of clinical researchers familiar with the military culture and following study participants within VAMC settings.

G. Research Integrity and Confidentiality
To ensure confidentiality, a participant number will code all data and records will be kept in a locked cabinet in a locked room with access limited to the investigators and research staff assigned to this protocol. A certificate of confidentiality was obtained prior to initiation of the study.

H. Statistical Analysis and Data Management

H.1 Data Management Plan: Data will be collected by the appropriate individual (research assistant, PI, Co-I) using standardized paper forms. Data will only be identified with participant study IDs. The codes linking the name of the participant to the study ID will be kept confidential in a secured cabinet in a secure office. Data will be transferred to and managed in the VA REDCap system. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. These procedures are effective in minimizing data entry errors (e.g., missing or errant data). Quarterly database management and data integrity audits will be conducted. In order to conduct data integrity audits across sites, randomly chosen CRFs will be uploaded to the VA REDCap database for auditing by the Charleston VAMC research staff.
H.2 Statistical Analysis: *Specific Aim:* To evaluate the efficacy of MBRP as a continuing care treatment to promote sustained abstinence and recovery in Veterans following primary treatment for SUDs.

<u>Hypothesis 1: Individuals randomized to the MBRP group will have less substance-using days during treatment and during the 10-month follow-up period as compared to individuals assigned to the TSF group.</u>

The primary hypothesis will be assessed using the number of substance-using days during the eight-week treatment and *10-month follow-up period*. A mixed effects modeling framework will be specified with the number of substance-using days as the primary outcome. A Poisson distribution will be assumed with a logarithm link function to assess the effects of treatment, time, the appropriate interaction, and baseline number of substance-using days. Over-dispersion due to a wider than expected distribution in discrete count models (from heterogeneity) can have a significant impact on parameter inference, thus when detected, a negative binomial (NB) distribution will be specified. In addition to over-dispersion, data collected in SUD studies, particularly count data, often contain a preponderance of zeros. Since all study subjects are in SUD treatment prior study initiation and can be considered at risk for substance use during the study, zeros in the distribution can be considered sampling zeros in the Poisson process (Bandyopadhyay et al., 2011). *If this excess is present in the distribution, two part Hurdle models (Poisson and NB) (Mullahy, 1986) will be explored. These models will allow simultaneously estimation of the effect of MBRP on abstinence and the frequency of substance use during the study. The hurdle part of the model will allow estimation of the probability of abstinence during the test period (odds ratio) while the Poisson/NB portion will assess risk of an increase in using days beyond zero during the test period (risk ratio). Model fit of the Poisson (Hurdle Poisson) model will be compared to the Negative Binomial (Hurdle NB) model by practical examination of both the deviance and Pearson chi-square values (Likelihood Ratio) with respect to degrees of freedom. As the standard and hurdle models are not nested models, goodness of fit comparisons from these models will be done using Vuong's test statistic (Vuong, 1989). Due to clustering within multiple sites and treatment group assignments, random effects of site and group assignment will be specified in the final model (Min and Agresti, 2005). Model-based estimates will be used to test group differences*

at the pre-specified time points of interest. All statistical models will be implemented using SAS PROC NLMIXED in SAS v. 9.3.

Secondary Outcome Analysis*:* The effect of MBRP on quality of life, depression and anxiety symptomology, emotional regulation and other functional outcomes such as employment will be assessed. Generalized linear mixed-effect models will be used to assess differences between treatment arms. For continuous outcomes, a Gaussian distribution will be used to assess the effects of treatment, time and the appropriate interaction. Model-based means will be used to test group differences at the pre-specified time points. For binary or count outcomes, a framework similar to that developed for the primary aim of the study will be developed with appropriately determined distributions (Logit, Poisson/ NB, and Hurdle models).
Baseline Analysis*:* Contrasts of baseline characteristics and clinical predictors of substance use will be performed between groups. Continuous and ordinal characteristics will be compared using a Wilcoxon Rank-Sum test, while categorical characteristics will be compared using a Pearson Chi-Square test. If a baseline characteristic is significantly associated with the outcomes of interest, the corresponding variables will be used as initial covariates in the analyses. Secondarily, possible covariates will be tested for confounding effects on the models specified. When present, they will be included in the final adjusted model.
Missing Data and Attrition: Missing data and attrition can introduce bias in the treatment group parameter estimate and reduce power, precision, and generalizability. To minimize missing data and study attrition, enhanced communication between study coordinators and participants will be emphasized including telephone reminders, meeting with subject in community, and reinforcing adherence at each visit. In addition, appropriate analysis methods will be employed to accommodate missing data. Mixed-effects models yield valid inferences assuming ignorable attrition (i.e., attrition is accounted for by covariates or dependent variable measured prior to dropout). We propose a sensitivity strategy to examine the ignorability assumption. A pattern mixture model will be used to examine treatment response among participants with various dropout patterns and implemented in the mixed-effects framework (Little 1993; 1995; Hedeker and Gibbons, 1997) in which subjects are classified by attrition pattern (e.g., early, middle or late dropout, completer). In addition, we 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 able to come to the site to attend a study visit and (s)he agrees, some assessments and/or visits (excluding the baseline assessments) may be conducted by phone.
H.3 Power and Sample Size: The study is powered on the primary hypothesis that there will be a clinically significant decrease in the number of days of substance use during the treatment and follow-up period for those receiving MBRP as compared to a TSF continuing care approach. The primary outcome is the number of days of substance use during the eight-week treatment and *10-month follow-up period*. The two treatment arms will be tested using a generalized estimating equations framework for repeated count data (Assuming a Poisson process). The study will be powered to detect the least of the effect sizes determined to be clinically meaningful for the study hypothesis. In a study of MBRP treatment, Bowen and colleagues (2009) found that those receiving MBRP has significantly less days of substance use than those receiving TAU during eight weeks of treatment (MBRP 0.1 ± 0.3 vs. TAU 2.6 ± 9.1; RR=0.02, $p<0.001$). Two months after treatment completion, the MBRP group continued to demonstrate reductions in days of substance use (MBRP 2.1 ± 7.2 vs. TAU 5.4 ± 14.7; RR=0.39, $p<0.001$). Because we will be dealing with a more complex population (Veterans) and a longer follow-up period, we anticipate an increased rate of substance-using days during treatment and follow-up as well as an attenuated risk ratio as compared to the Bowen study. Assuming that a 30% decrease in risk (RR=0.7) of a substance-using day during treatment is clinically meaningful, with 80% power and a 2-sided type I error rate of 5%, 131 subjects per treatment arm will be needed to detect a 30% reduction at the end of treatment. Niles and colleagues (2012) conducted a small MM study in Veterans with PTSD and found a retention rate of 82% at the end of the treatment and 73% at follow-up assessment. The current study focuses on SUD rather than PTSD, but the population is similar and 15% attrition during treatment is assumed. Thus accounting for study attrition, we should achieve adequate power to detect clinically meaningful risk reductions at the pre-specified time points by randomizing 154 subjects to each arm of the study (N=308 total subjects).

I. Cross-Site Coordination and Communication

Dr. Brady will be the Lead PI and the Charleston site will have the overall responsibility for training and supervision, operational issues, data management and analysis. A face-to-face meeting in Charleston with all co-investigators will be scheduled when the grant is approved for funding. A secure Skype connection will be available for individuals unable to travel. Plans for staff training, data collection, quality assurance, quality control monitoring, and randomization will be discussed. Any revisions to the study suggested by reviewers will be discussed and implemented, based on group consensus. A second face-to-face meeting will be held in Year-4 for in-depth discussion of the therapeutic outcome, adverse events and next steps. There will be yearly (or more frequently as indicated) Skype meetings to discuss trial progress, adverse events and review the DSMB reports. At each site, the site PI (Drs. Hartwell and Davis), study coordinator, and support staff will manage day-to-day operations and protocol-specific functions, including recruitment, data collection, scheduling and tracking. The teams will meet weekly (via teleconference) with Drs. Brady and Killeen during the first 4 months of the trial and monthly thereafter to discuss study conduct and problems related to training, supervision, and/or implementation. Dr. Killeen will oversee intervention training and supervision. Drs. Brady and Killeen will work with the Project Manager to ensure that recruitment, assessment, intervention, follow-up and data collection are conducted similarly across sites. As the site PI on a number of CTN studies, including a study of TSF, Dr. Killeen has experience in coordinating the efforts of large groups working across distant sites and is well versed in conflict resolution. Nathan Baker will oversee randomization schemes, data management and statistical analyses. Drs. Brady, Killeen and Davis have all had experience leading multi-site trials and have worked well together.

Once the grant is approved for funding, a Standard Operating Procedures (SOP) manual and working protocol will be written by Drs. Brady, Davis, Hartwell, Killeen and relevant staff. The SOP manual will include common procedures to train staff, monitor and ensure protocol compliance, report severe adverse events, and site-specific problem solving. Developing one SOP manual provides a common document from which to implement the study, minimize errors, clarify procedures, and ensure consistency across sites. The Charleston investigators have recently developed SOP's for a trial they are leading in the CTN (CTN-052), so they are experienced in this process. Following document finalization, a detailed Data and Safety Monitoring Program will be submitted to the VAMC, and the appropriate materials will be submitted to the IRB at each site and to the Data and Safety Monitoring Board.

Dr. Killeen and the Project Manager will be responsible for Quality Control/Quality Assurance including staff training, regulatory and overall clinical practices, source documentation, consent forms and casebook data collection. In order to conduct quality assurance checks across sites, signed informed consent documents and HIPAA authorizations will be uploaded to the VA REDCap database with limited access. The Project Manager will work with Mr. Baker in quality checks on data entry. Initial training will take place in a face-to-face meeting in Charleston and will include training in assessments, randomization, data collection, follow-up procedures. Following the training, a site initiation visit will be conducted at each site to insure operational readiness. Computer programs will be run on the database to detect values outside the ratings scale parameters and direct inspection and rechecking of all safety data will be required. Written reports will be generated and a tracking system will be implemented to prevent systematic errors. Dr. Brady will serve as the medical monitor and oversee adverse event reports and medical questions for both sites. These procedures meet FDA standards of Good Clinical Practice and are being utilized in ongoing studies.

J. Study Timeline

YEAR 1: SOP manual/procedures established, training and site initiation; enroll 40 subjects/site
YEAR 2: Enroll 52 subjects/site; complete 62 subject follow-ups; ongoing data entry and management
YEAR 3: Enroll 52 subjects/site; complete 62 subject follow-ups; ongoing data entry and management
YEAR 4: Enroll 10 subjects/site; complete 30 subject follow-ups; data entry, management, analysis and report preparation

K. Summary

Attention to continuing care, recovery and rehabilitation for SUDs in military Veterans is critical. A recent IOM report recommended that the Military Health System shift its focus from acute care to an outpatient, chronic care model that encourages individuals to remain connected to a recovery-based system. New continuing care strategies targeting life-style change and improved coping mechanisms are critical for maintaining abstinence, promoting rehabilitation and functional recovery for Veterans with SUDs. MBRP has shown promise as a continuing care strategy in SUD treatment. We have assembled a multi-disciplinary team with exceptional relevant experience to conduct a randomized trial exploring MBRP as a continuing care strategy in Veterans following completion of primary treatment for SUD. If this trial demonstrates that MBRP improves substance use outcomes, quality of life, and functional outcomes, it will provide a valuable intervention to facilitate rehabilitation and recovery for Veterans with SUDs

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PROTECTION OF HUMAN PARTICIPANTS
1. Risks to Participants

A. Human Participants Involvement and Characteristics

The PI and Co-Is have all completed the University of Miami computer-based CITI Human Participants Research Education Course. A total of 308 men and women military Veterans meeting DSM–V criteria for a substance use disorder (SUD) will be will be recruited over a 37-month period. Additional inclusion and exclusion criteria are described below.

Inclusion Criteria

1) Men and women military Veterans who have completed the Charleston or Tuscaloosa Veterans Administration Medical Center (VAMC) intensive outpatient substance abuse treatment program, a residential treatment program, or an intensive outpatient program similar to the Charleston or Tuscaloosa VAMC program.

2) Able to comprehend English.

3) Meets DSM-V criteria for a current substance use disorder and have used substances in the 30 days prior to treatment entry. Participants on medications targeting their substance use must be stabilized on medications for at least 2 weeks before therapy initiation.

4) May meet criteria for a mood, anxiety or other psychiatric disorder. Participants on maintenance medications for a mood or anxiety disorder must be stabilized on medications for at least 2 weeks before therapy initiation.

5) Able to adequately provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments.

6) Willing to commit to 8 group therapy sessions, baseline, weekly and follow-up assessments for 10-months after the end of treatment (12-month total).

Exclusion Criteria

1) Active suicidal or homicidal ideation with a plan as this is likely to require hospitalization or other interventions that could interfere with study participation.

2) Unstable psychiatric condition likely to require hospitalization or other interventions that would interfere with study participation.

3) Unstable medical condition or one that may require hospitalization during the course of the study.

4) Meets criteria for nicotine dependence only

5) Women who are pregnant

B. Sources of Materials

1. Research material obtained from individual participants includes self-report questionnaires, structured interviews with study personnel, taped therapy sessions as well urine samples.

2. The research material will be obtained specifically for research purposes. Written research material obtained will be stored in a locked file cabinet in an office that is locked when not in use. The master list of participants linking study numbers to any source identifying information will be in a separate locked file cabinet at the VA Mental Health Research Building. Urine samples will be discarded after results are documented.

3. Therapy sessions will be digitally audio-recorded to be used for supervision and adherence monitoring. They will be transferred electronically and stored on a dedicated server maintained by and accessible only to project

staff. Centrally storing all recordings on a password- and firewall-protected computer enhances security and integrity (e.g., automatic 128-bit AES encryption and backup).

C. Potential Risks
Risks to the patients include feeling distress being interviewed regarding substance use and other sensitive information, adverse events related to the study intervention (see adverse event definitions below) and risk of loss of confidentiality regarding the information obtained during the assessment and follow-ups and taped therapy sessions. Potential psychological risk of the treatment includes exacerbations of distress and increase in substance use during the assessment and/or treatment sessions.

2. Adequacy for Protection Against Risk and Harm to Participants

A. Recruitment and Informed Consent

Participants will be recruited from the Charleston or Tuscaloosa Veterans Administration Medical Center (VAMC) intensive outpatient substance abuse treatment programs. Research staff will approach patients in the Intensive Outpatient Program, inform them about the study and elicit interest. We will collect names and contact information from interested potential participants. They will be screened by phone or in person for major inclusion/exclusion criteria including age, substance use, and psychiatric/health/medication status. Prior to any study procedures being performed, the Institutional Review Board (IRB) approved informed consent will be obtained by research staff trained in informed consent procedures. Informed consent will be collected at the study research offices, in a private and interruption-free environment. Explanation of the informed consent document will include a detailed description of the study in easy to understand detail with the participant, along with statements regarding participants' rights to withdraw from the procedure at any time without consequences. The participant will be asked to read the document and if he or she has any questions, they will be answered prior to participant signature. Consent will be documented by the date and signature of the participant on an informed consent agreement and by the date and signature of the individual obtaining the consent. A HIPAA authorization form will also be signed, and copies of both documents will be provided to the participant. Potential participants may decide to discuss participation with their families and/or significant others prior to making a decision to sign consent.

The secondary recruitment sites are residential treatment programs or other Intensive Outpatient Programs that are similar to the IOP at the Charleston or Tuscaloosa VAMC. SATC clinical staff will refer patients from these programs with the patient's permission.

Respondent-Driven Sampling (RDS) will be used to enhance recruitment of the sample. The RDS sampling methodology is based on recruiting the eligible friends and acquaintances of each participant so that the sample "snowballs". Each eligible participant who is randomized into the study, and agrees to take part in this recruitment assistance, will be given coupons to pass on to other potential participants. The coupons will have a unique code linked to the person who passes them out. A referral will be instructed to call the study team for screening. If that person successfully completes a screening assessment and is randomized, the participant who referred them can redeem the coupon for $10.

B. Protection against Risk

All investigators and project personnel have completed a certified program of instruction in the protection of human participants in research, the University of Miami CITI course. These courses in responsible conduct of research and the protection of human research participants will be completed on a regular basis, in compliance with MUSC institutional and VA-ORD regulations. All research activity, informed consents and continuing reviews will be reviewed by MUSC's IRB in compliance with 45CFR46 and compliant with the VA 38CFR before the research is started and continuing review will occur annually. The research staff will ensure that all information needed for the continuing review is at the IRB in accordance with IRB requirements.

We will take careful precautions to maintain confidentiality for all participants, using procedures we have used with similar previous studies. All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers in the Study Coordinator's or RA's research office) so as to protect the confidentiality of participant information. Access to research records (paper and computerized) will be restricted to the project staff. Specifically, access to de-identified study data will be limited to named project investigators, the Project Manager, the Study Coordinator, and the VA Research Compliance Auditor. Binders with study data will have a study number that will be kept locked separately from any source documents with identifying information. The master list of participants linking study numbers to any source identifying information will be kept in a separate locked file cabinet at the Ralph H. Johnson VAMC. When study results are published or presented, only aggregate reports of the results will be used and participants' identity will not be revealed. All analyses will be conducted on de-identified data only.

Therapy sessions will be digitally audio-recorded to be used for supervision and adherence monitoring. They will be transferred electronically and stored on a dedicated protected server maintained by and accessible only to project staff. All recordings will be centrally stored on a password- and firewall-protected computer to enhance security and integrity (e.g., automatic 128-bit AES encryption and backup).

Exclusion criteria are crafted to exclude potential participants at higher risk for adverse effects, including those with co-occurring medical or psychiatric disorders where they may be more likely not to benefit from the intervention and/or to be hospitalized during the course of the study. The informed consent document specifically reviews potential psychological distress as a potential outcome of participation.

Measures to avoid potential risk associated with psychological distress/substance use include exposure to the intervention that has as one of its primary aims, reduction of distress and substance use through meditation and cognitive-behavioral interventions (e.g., breath meditation, coping with negative affect). Additional measures include informing participants that they are free to terminate treatment sessions at any time. Risks associated with assessment include the possibility that participants might be upset by questions pertaining to their emotional functioning. Some participants might be offended by detailed questions about health status and impairment. Our past research suggests that data collection using many of these measures can be conducted without undue psychological distress or exacerbation of symptoms among adult participants. This experience includes substantial research with younger and older adults, rape victims, victims of other forms of violence, substance abusing individuals and work on large scale studies asking questions about similar topics with general population samples.

Social risks are present if another person or parties observe participants attending treatment clinics or learn by other means of participants receiving treatment. Participants will not be overtly identified as research participants or participants for psychological intervention.

In the event participants experience extreme psychological distress secondary to participation, they will be encouraged to telephone the Principal Investigator (PI) or the Co-I's. In addition, they will have access to the VAMC treatment services. Any such adverse effects noted by any project personnel in response, or in potential response to any project intervention, assessment protocol, or study involvement will be immediately reported to the PI and Co-I's. Participants will also be given the PI's name and telephone number and the on-site Study Coordinator's contact information. Moreover, if research or clinical staff believes that a participant is significantly distressed by participation, the PI will be notified and will contact the participant to assess distress and assure participant safety. If called by participants, the PI will attempt to address all participant concerns and if indicated, set up an alternate referral for counseling for those who desire it from outside the project.

If at any point during the assessment, treatment or follow-up period, participants are in need of medical management, psychiatric consultation or psychiatric hospitalization, they will be evaluated and if indicated, referred to a more intensive level of treatment. If a participant becomes suicidal, emergency psychiatric

assessment will be arranged. The participant will be closely monitored clinically until they are no longer suicidal or an appropriate safety plan is in place. A procedure for clinical deterioration has been established based upon our experience with previous studies. Therapists will be instructed to use their best clinical judgment regarding emergencies and inform the site PI, Co-I's or therapy supervisor as soon as possible. In addition to relying on clinical judgment on the part of the treating therapists(s) who are experienced with this population, substance use, mood and anxiety symptoms will also be monitored weekly through standardized measures (TLFB, BSI) in order to detect any symptom worsening requiring further evaluation. Additionally, participants are advised to observe any signs of worsening substance use, depression and anxiety symptoms and to discuss these with their therapist. If a patient has relapsed to substance use (defined as a return to pretreatment use or more), this will be dealt with therapeutically during the session or in their standard treatment as usual program. Therapists will use their clinical judgment and supervision with regard to treatment in the face of relapse. If in the clinical judgment of the therapist in collaboration with the supervisor and/or PI/Co-I's, it is determined that the participant symptoms are worsening and he would not benefit from further MBRP treatment, appropriate referrals will be made. These decisions will be dealt with in training and supervision and monitored carefully.

Patients will be terminated from the study and referred for more intensive treatment if there are:

a. Increases in alcohol or drug use leading to the need for a more intensive level of care (i.e., medical detoxification, inpatient).

b. Active suicidal or homicidal ideation.

c. Inability to manage psychiatric symptoms within the inclusion/exclusion criteria of the study (i.e., need for the initiation of maintenance psychotropic medications; development of psychosis). If it is determined, based on clinical criteria, that a participant needs to be started on maintenance medications for anxiety, mood or psychotic symptoms during the course of the study, they will be discontinued from the treatment trial.

d. Inability to return for therapy sessions due to incarceration or hospitalization lasting longer than four weeks.

At the VAMC, there is a well-established protocol for emergency psychiatric evaluation, crisis intervention and/or psychiatric hospitalization for suicidal, homicidal, psychotic or other acutely distressed patients. Immediately on detection of these needs, the assessor/research therapist will page the PI/Co-I's to review the patient's situation. If appropriate, PI/Co-I's will personally evaluate the patient. During evenings or weekends, the PI/Co-I's will be on call for emergencies. At these times, acutely distressed patients will be instructed to go to the psychiatric emergency room for evaluation by the psychiatric resident. The PI/Co-I's will notify the resident in advance of the patient's situation. Acute psychiatric hospitalization is available for emergencies.

3. Potential Benefits of Research to Subjects and Others

The benefit to participants is a potential reduction in substance use and related problems. In addition, they may benefit from the cognitive realization that, through their volunteer efforts, they are helping to advance the state of knowledge as it applies to mental health care for substance use disorders.

4. **Importance of Knowledge to be Gained**

The proposed study has the potential benefit of developing an effective rehabilitation intervention for substance use disorders delivered in group format. The study will help inform critical questions about rehabilitation options for individuals with substance use disorders. Such a finding would have the potential benefit of (1) improving long-term outcomes for Veterans with substance use disorders and (2) reducing functional impairment and related health care costs associated with substance use disorders in Veterans.

5. Inclusion of Women and Minorities

Both male and female subjects will be recruited. There will be no exclusion based on race or ethnicity. Subjects will be recruited without preference for gender, race, ethnicity or socio-economic status. Based on estimates from the Substance Abuse Treatment Center (SATC) at the VAMC where recruitment will take place, we estimate that approximately 46% of the sample will be comprised of African Americans, 15% minorities and 11% women.

6. Inclusion of Children

Per the current VA-ORD definition that "children" refers to all participants under the age of 21, children will be included in this study if they 18 years of age or older. Children ages 18 to 21 will be included in representative proportion to their prevalence in the target recruitment sites. The intervention has not been tested in children less than 18 years of age. Children under the age of 18 will not be included in this study because the focus of this investigation is to determine the effectiveness of the intervention in veterans over the age of 18 with SUD.

7. Data Monitoring and Safety Plan

This section is based on the recommendations in NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan" (www.drugabuse.gov/funding/dsmbsop.html).

Protocol Summary: This application proposes to test an existing evidence-based treatment for relapse prevention in SUDs in men and women military Veterans with SUDs who have successfully completed the first part of a VAMC SATC treatment program. The primary outcome of interest is reduction in substance use over a 10-month follow-up period.

Trial Management: The study will be managed from the Division of Clinical Neuroscience within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina. The target population is described above in the inclusion/exclusion criteria.

Data Management and Analysis: A data analysis plan is outlined in the Data Analysis section. Briefly, the primary outcome will be percent days using drugs of abuse. Secondary outcome measures will be associated areas of functioning (i.e., depression, anxiety, quality of life, employment), process variables (e.g., participant satisfaction, treatment adherence rates, retention rates, therapist fidelity). Estimates of treatment group variance will be calculated using model based estimates and their 95% confidence limits will be determined using the 2.5^{th} and 97.5^{th} percentiles of the chi-square distribution. Substance use quantification (TLFB, % days using) will be examined within participants using a general linear model to estimate the variance in the change from baseline to the end of treatment and 3-, 6- and 10--month follow-ups. Models will be adjusted for significant predictors of change in the frequency and amount of substance use. Treatment effects will also be estimated using the results of the general linear models, in combination with the confidence intervals of the variance and will be used to appropriately power a larger efficacy clinical trial of MBRP for relapse prevention in SUDs.

Quality Assurance*:* Data quality will be monitored by random inspection of the completed forms by research staff and any irregularities or problems detected will be discussed with the PI. Therapists will receive standardized training and adherence will be monitored using audiotapes and individual supervision. If therapy drift is observed the therapists will be re-trained.

Regulatory Issues: All unexpected Adverse Events (AEs) and Serious Adverse Events (SAEs) will be reported to the appropriate authorities according to the local Institutional Review Board and VA R&D Committee reporting guidelines. Follow-up of all unexpected and serious AEs will also be reported. All AEs are reviewed weekly by the PI or a Co-I, biannually by the Data Safety Monitoring Board (DSMB) and yearly by the IRB. Any significant actions taken by the local IRB and protocol changes will be relayed to the funding agency. AEs and SAEs occurring during the course of the trial will be collected, documented, and reported in accordance with protocol

and IRB reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting. The research assistant, Study Coordinator, or Project Therapists will identify any potential AEs during the course of the study from participant self-report and administration of assessments and procedures. This information will be provided to the PI, Co-I's (MD, PhD), who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness.

A. Adverse Events Reporting and Documentation

Adverse events will be monitored throughout the study and all events will be followed to resolution or stabilization. All serious adverse events will be collected and reported immediately to the local IRB, VA R&D Committee, and the federal funding agency. If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for review by the PI and for forwarding to the program officer as appropriate within 2 weeks of the initial SAE report.

We will report adverse events to the MUSC and Tuscaloosa IRBs online as soon as possible, but no later than 10 working days after the investigator first learns of the event. The MUSC IRB AE reporting requirements are as follows: All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the MUSC IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the MUSC IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. Reportable AEs are reviewed by the IRB Chair and reported to the IRB Board at the next meeting.

An adverse event (AE) is defined as any reaction, side effect, diagnosis or untoward event that either a) occurs during the course of the clinical trial and was not present at baseline; or b) was present at baseline and appears to worsen during the study. All AE's will be assessed by the PI, Co-I (MD, Ph.D.) from baseline through the last follow-up assessment. During weekly assessments the research assistant (RA) will inquire about AEs. In the event that the participant is experiencing a worsening of symptoms, the RA will inform appropriate study and clinical staff. The PI, Co-I and the participant's therapist should determine if the AE places the participant at risk if study treatment is continued. The risks expected from trials employing behavioral interventions are presumed minimal relative to pharmacologic interventions. However, for this trial specifically, the population studied is a vulnerable population and possibly high risk given the nature of the disorders (i.e. SUDs). Thus, in accordance with OHRP and NIH requirements for human participant protection, the collection and reporting of AE/SAEs are specified below. All adverse events, with the exception of clinically insignificant events and minor common illnesses and injuries (e.g., cold/flu, scrapes, upset stomach, low-grade headaches) will be documented on the *AE Log.* The AE Log is a source document and this information will not be entered into the study database. The PI, Co-I (MD, Ph.D.) will regularly review the AE Log. Any AEs determined to be serious and/or study-related by the PI, Co-I will require the completion of an *AE CRF in REDCap*. The RA may gather much of the information but the PI, Co-I must review the CRF information, make all medical determinations and sign the CRF. If an AE is determined to be serious, an *SAE Form* and an *SAE Summary Report* containing the event narrative must also be completed and signed by the study clinician. Study staff will be trained to provide crisis intervention and referral to standard operating procedure within the VAMC for such situations, should they become dangerous or life-threatening (i.e. suicidal ideation or attempts). The PI, Co-I (MD, Ph.D.) will be available to respond to a need for consultation in order to fully assess untoward reactions or severe symptoms, including suicidality.

Adverse events will be categorized using severity codes of mild, moderate or severe. In this protocol potential study related AEs include 1) worsening of SUD symptoms, and 2) worsening of depressive/anxiety symptoms.

For this reason, participants will be assessed weekly on current symptom measures of SUD and anxiety/depression (TLFB, BDI, BAI) to observe any signs of severe symptoms of SUD and anxiety/depression. Additionally, participants are advised to observe any signs of worsening SUD and anxiety/depression symptoms and to discuss these with study staff. If the level of symptom worsening becomes dangerous or life threatening (e.g. drug overdose or suicidal ideation or attempt, any symptom worsening requiring inpatient hospitalization) these will be classified as SAEs and require further documentation. Study staff will be trained to provide crisis intervention and referral for such situations. In the case that a participant is worsening over the course of treatment, consideration for early termination or study discontinuation will be conducted.

Serious Adverse Events: Each Adverse Event will be categorized as serious or not. Serious adverse events are defined as any fatal, life-threatening, permanently and/or substantially disabling condition; or one that is a congenital anomaly, requires an initial hospitalization or prolongs a hospitalization, or is an event which requires intervention to prevent permanent impairment or damage. The PI, Co-I (MD, Ph.D.) should be consulted if questions arise as to whether an AE should be categorized as serious. Initial notification of an SAE to the IRB is to be followed by submission of the Serious Adverse Event Form within 24 hours. Failure to comply with reporting requirements can result in serious negative consequences, including criminal and/or civil penalties.

Trial Safety: The potential risks and benefits and methods to minimize these risks are outlined above. Protocols for reported AEs and SAEs are outlined above. All unexpected AE and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research staff. At the weekly team meetings (or before if urgent), the research staff will report any premonitory symptoms of clinical deterioration.

Study procedures will follow as much as possible the FDA's Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Any outside requests for information or any breaches in confidentiality will be reported to the PI. All requests by participant's physicians and other medical providers will be referred directly to PI.

DSM Plan and Administration: The research assistant and research coordinator will be responsible for data collection, entry and checking. The research staff will examine data for errors or gaps on the day of collection, and immediately make the correction. The data manger will be responsible for conducting and supervising coding, entry, cleaning and processing of raw data. Data will be collected by the appropriate individual (research assistant, PI, Co-I) using standardized paper forms. Data will be transferred to and managed in the VA REDCap system. Quarterly database management and data integrity audits will be conducted.

The PI will be responsible for monitoring the study. The PI will regularly examine the outcomes database for missing data, unexpected distributions or responses, and outliers.

B. Data Safety and Monitoring Board

The data safety and monitoring plan will include a Data and Safety Monitoring Board (DSMB). The purpose of the DSMB is to ensure the safety of participants and the validity of the data. The DSMB will be made up of professionals with appropriate expertise, who are willing to participate and who do not have any conflict of interest. The DSMB will include: a) experts in the areas of substance abuse; b) a biostatistician with clinical trial expertise; and c) members with expertise in treatment of Veterans. The board may be called at any point if needed for unexpected AEs, etc. Modification will be made in the procedures and/or the protocol if necessary based on the recommendations of the board. A DSM report will be filed with the IRB and reported to VA R&D Committee on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report results at the end of the trial.