Medical University of South Carolina
Protocol

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Study Title: **Approach bias modification for the treatment of cannabis use disorder.**

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A. SPECIFIC AIMS

Effective and durable treatments for cannabis use disorder remain elusive. Given the increasing prevalence rates of cannabis use and CUD nationwide, investigation of novel treatments is warranted. Implicit cognitive processing is an emerging, and potentially critical therapeutic target.

Cognitive models of addiction posit an override of explicit control-related cognitive processes by implicit reward-driven processes resulting from chronic drug exposure. One form of implicit cognitive processing is *approach bias*, or, the automatic tendency to approach rather than avoid drug cues, which has been identified for alcohol, nicotine, opioids, and cannabis. Cannabis approach bias predicts increased cannabis use, dependence severity, and cannabis-related problems among heavy cannabis users. Approach bias modification (ABM) is a novel treatment approach that seeks to reduce approach bias by attenuating the incentive-salience of drug cues, and subsequently, drug cue reactivity and drug use. ABM has been shown to reduce relapse rates in alcohol dependent adults by 10-13% at one-year follow-up, and dependence severity in nicotine dependent adults. Our pilot data suggests that ABM may also reduce cannabis craving and that gender may moderate the effect of ABM on cannabis sessions per day in non-treatment seeking adults with CUD. A recent fMRI study with alcohol-dependent adults found decreased mesolimbic activation in participants who received ABM compared to sham-control participants. ABM appears to target implicit reward-driven processes, and could be an effective adjunct to traditional psychosocial and/or future pharmacological interventions that target explicit control-related processes.

Building on our promising feasibility data, the proposed K23 research study will examine the effects of ABM on cue-reactivity and cannabis outcomes in a four-session randomized, double-blind, sham-controlled pilot treatment trial. One-hundred and six (106) treatment-seeking adults with moderate to severe CUD will be randomized to receive either MET/CBT plus ABM or Motivational Enhancement Therapy/Cognitive Behavioral Therapy(MET/CBT) plus sham-ABM. An equal number of men and women will be recruited and randomization will be stratified by gender. ABM sessions will occur following each of the four weekly MET/CBT therapy sessions. Primary outcomes will include cannabis cue-reactivity and cannabis use.

Aim 1: Evaluate the efficacy of ABM combined with MET/CBT on reductions in cannabis cue-reactivity in adults with cannabis use disorder. Using a cue-reactivity paradigm, we will evaluate the efficacy of approach bias modification on physiological (i.e. skin conductance) and subjective (i.e. cannabis craving) cue-reactivity.

Hypothesis 1: Participants receiving ABM will demonstrate blunted cue-reactivity compared to control participants.

Aim 2: Evaluate the efficacy of ABM combined with MET/CBT on end of study cannabis use outcomes in adults with cannabis use disorder. Using self-report and urine toxicology we will evaluate the efficacy of ABM on cannabis use outcomes.

Hypothesis 2: Participants receiving ABM will demonstrate greater percent days abstinent and lower creatinine corrected cannabinoid levels compared to control participants.

Exploratory Aim 1: Explore gender as a potential moderator of ABM, cue-reactivity, and cannabis outcomes. Given existing evidence of gender differences in cannabis use, cannabis-related cognitive impairment, and

treatment outcomes, it is important to investigate the role of gender in interventions targeting cognitive processing, such as ABM. Pilot data suggests potential gender modification on cannabis outcomes in response to ABM.

B. BACKGROUND AND SIGNIFICANCE

B1. Cannabis use is increasing and existing treatments are inadequate. Cannabis use among the United States general population has more than doubled from 2002 to 2013 with a corresponding increase in rates of cannabis use disorder (CUD) from 1.5% to 2.9%[1]. Myriad consequences of cannabis use have been identified including cognitive impairment, structural and functional brain changes, increased risk of psychosis, physical health problems, and poor psychosocial outcomes[2,3]. Approximately 17% of all substance use treatment admissions are for primary cannabis use disorder[4], yet treatments remain inadequate. There is no approved pharmacotherapy to date, and while psychosocial treatments have shown effectiveness in reducing frequency and quantity of use, abstinence rates remain modest and decline over time[5]. Cognitive-behavioral and motivational approaches are the most effective treatments available, but their durability is limited. Augmentation of existing psychosocial treatments is an important next step to improving CUD treatment outcomes. As the prevalence of cannabis use continues to rise, so will the public health and individual burden. Evaluation of novel adjunctive treatments for CUD is warranted.

B2. Cognitive mechanisms of addiction. Cognitive models of addiction identify two distinct yet interactive types of mental processes, implicit and explicit[6-8]. Implicit refers to automatic, reward-driven, contingency-based learning processes, while explicit refers to reflective, inhibitory, executive control-related processes[7,9]. Chronic drug use results in neuroadaptations that strengthen the implicit reward-driven system and weaken the explicit control-related system, resulting in compulsive drug use despite negative consequences[9,10]. Cannabis use is associated with explicit processing deficits including working memory, attention, and abstract reasoning[12], as well as maladaptive implicit processes, such as attentional bias[13] and approach bias[14]. These implicit cognitive biases develop when drug-related stimuli acquire incentive-motivational properties following repeated exposure and sensitization of meso-corticolimbic reward pathways[15]. Cognitive biases are associated with heavier cannabis use, dependence severity, and more cannabis-related problems[16,17], and quantity of cannabis use has been associated with reward pathway hypersensitivity[18]. A review of twenty-four clinical fMRI studies found that attenuation of reward pathway sensitivity through cognitive interventions is a common factor associated with positive treatment outcomes across substances[19], and therefore, is an important therapeutic target. Cognitive bias modification is a novel approach that targets reward pathway sensitivity using computerized tasks to reduce the incentive-salience of drug stimuli.

B3. Approach bias modification may improve cannabis treatment outcomes. Approach bias is one form of implicit cognitive bias whereby highly salient drug cues unconsciously capture an individual's attention and elicit a tendency for approach behavior. Approach bias is associated with poor clinical outcomes in alcohol and cannabis using populations[11-14]. *Approach bias modification (ABM)* is a novel treatment that involves retraining the implicit action tendency to approach a drug cue by manipulating contingencies in a stimulus-response paradigm[15]. In two recent clinical trials, ABM effectively reduced alcohol relapse rates by 10-13% at one-year follow-up[13,14]. Likewise, ABM has shown promise in reducing cigarette consumption and dependence severity among nicotine-dependent individuals[16,17]. A recent fMRI study found decreased neural activity in the mesolimbic region and reduced subjective craving among alcohol-dependent individuals who received ABM compared to controls[18], suggesting ABM may directly target reward pathway hypersensitivity implicated in addiction. ABM holds great therapeutic potential, yet to date, it has not been investigated for CUD.

B4. Sex/gender may moderate the effect of ABM on cannabis outcomes. Evidence suggests that the endocannabinoid system plays a critical role in neurodevelopment[19] and that the effect of cannabis on neuropsychological functioning is sex-dependent[20]. Sex differences in cannabis users compared to healthy controls have been found in visuospatial and psychomotor performance[21,22], as well as in prefrontal cortex and amygdala volumes[23,24]. Moreover, our pilot data suggests that gender may moderate the efficacy of ABM on cannabis use outcomes, with men showing significant reductions in sessions per day compared to women (Sherman et al., In revision). In contrast, neuroimaging evidence suggests that women may be more responsive to cognitive bias retraining as they showed an association between craving and activation of cognitive control circuitry during a subliminal cue task, and thus may experience additive effects of ABM on existing cognitive control potential[25]. The role of sex/gender in CUD treatment is yet unclear, but may be related to differences in cognitive functioning. It is therefore critical to consider sex/gender as a potential moderator of treatments that target cognitive functioning.

C. PRELIMINARY STUDIES

Experience with recruitment and retention of adults with CUD: Dr. McRae-Clark (primary mentor), has completed multiple NIH-funded studies involving individuals with CUD. Of immediate relevance to the proposed project, the candidate recently completed a 4-session human laboratory pilot study in non-treatment seeking adults with CUD. Over the course of approximately 8 months, a total of 61 patients were consented, of which, 49 were randomized, 39 (80%) completed all 4 study sessions, and 33 (67%) completed through follow-up. These studies demonstrate the ability to effectively recruit and retain individuals with CUD for brief interventions.

Experience with adjunctive treatments for psychosocial interventions: Developing adjunctive treatments for CUD has been a career research focus of primary mentor Dr. McRae-Clark. Most recently, she completed a pilot study on oxytocin-enhanced MET for cannabis dependence[26]. Participants who received MET plus oxytocin demonstrated reductions in amount (grams) used daily (p=0.012) and number of cannabis sessions per day (p=0.003), while those who received MET plus placebo did not. In addition to Dr. McRae-Clark's experience, off-site mentor Dr. Sofuoglu also has considerable expertise integrating psychosocial interventions with novel adjunctive treatment approaches (see *Biosketch*).

Experience with the ABM paradigm: The candidate recently completed a randomized sham-controlled pilot study investigating the effect of ABM in non-treatment seeking adults with CUD (N=33). Results showed a trend of blunted cannabis cue-induced craving at end of treatment among ABM participants compared to controls (p=0.051) (see Figure 1), and preliminary evidence of gender modification of cannabis outcomes; men receiving ABM reported fewer sessions per day at the end of treatment (EOT) compared to women (p=0.022), while there was no gender difference in the sham-control group (Figure 2). These pilot findings suggest that ABM may be efficacious in reducing cue-reactivity and improving cannabis outcomes, and that gender may moderate this effect. As proposed in this K23 application, further investigation into the feasibility and efficacy of ABM as a potential adjunct to psychosocial treatments is warranted.

Figure 1: Cannabis craving by group and visit adjusted for baseline.

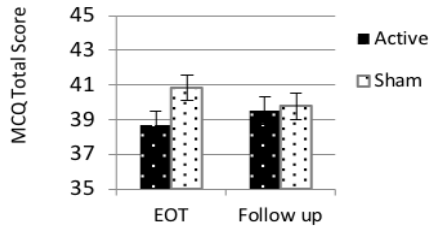
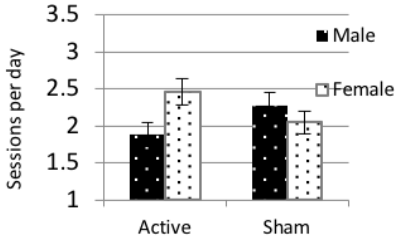


Figure 2: Cannabis use by gender and condition at EOT.



Summary. Our research group has significant experience with administration of human laboratory studies involving cue-reactivity. Further, we have successfully recruited this patient population and we anticipate no issues with rapid study implementation and conduct of the proposed project.

D. RESEARCH DESIGN AND METHODS

D1. Study overview: The proposed four-week randomized double-blind sham-controlled pilot study will investigate the efficacy of ABM combined with MET/CBT on cue-reactivity and cannabis outcomes. An equal number of treatment-seeking men and women will be recruited, and all participants will receive four sessions of MET/CBT. Following each therapy session half of the participants will receive ABM training sessions, while the other half will receive sham ABM sessions. The primary outcomes will be cannabis cue reactivity, creatinine-corrected cannabinoid levels, and self-reported cannabis use. Cue-reactivity will be assessed at baseline (BL), end of treatment (EOT), and at a one-month follow-up visit (FU); cannabinoid levels and self-report data will be collected at every study visit.

D2. Recruitment: Cannabis-using adults will be recruited from the community based on previously successful techniques used over the past 20 years by primary mentor Dr. McRae-Clark. This will include a mix of community, print, radio and online advertising. Through Facebook and Instagram ads, individuals can choose to enter their contact information if they are interested in participating. Contact information is stored in an excel file that only the study staff will have access to. Ads may also contain a link to a restricted access, secure RedCap database where interested people can enter contact information.

D3.a. Inclusion criteria:

1. Be age 18-65 and must be able to provide informed consent.
2. Meet DSM-5 criteria for current moderate to severe CUD (past 60 days).

3. Identify cannabis as their primary substance of choice.
4. Express an interest reducing marijuana use.
5. Consent to remain abstinent from alcohol and cannabis for 12 hours immediately prior to study visits and other drugs of abuse (except nicotine) for three days prior (see Additional Instrumentation below for methods); by restricting cannabis and other substance use as proposed, participants should not be under the acute effects of cannabis or other substances.

D3.b. Exclusion Criteria:

1. Evidence of, or a history of serious medical or neurological disease that may affect cognitive processing.
2. History of, or current psychotic disorder, bipolar disorder, or current untreated major depressive disorder or attention-deficit hyperactivity disorder (ADHD) as these may interfere with subjective measurements.
3. Current use of psychotropic medications because these may affect subjective measurements (individuals taking antidepressants, or psychostimulants for ADHD will be allowed).
4. Current suicidal ideation. Individuals who endorse suicidal ideation will be seen by a psychologist or psychiatrist in the office and will be referred to treatment as necessary.
5. Women who are pregnant, nursing or of childbearing potential and not practicing an effective means of birth control.
6. Moderate to severe DSM-5 substance use disorder within the past 60 days (other than nicotine or cannabis).

D4. Participant Procedures.

D4.a. Consent and screening interview: Participants will be screened either by telephone or in person by trained study personnel. A quick screen will be used to initially determine study eligibility. Potential participants will then be given a full description of the study procedures and asked to read and sign an IRB-approved informed consent form. The Mini-International Neuropsychiatric Interview (M.I.N.I.)[27] will assess exclusionary psychiatric diagnoses, DSM-5 substance use disorders, and substance use history.The SCID-R/V Externalizing Disorders Module[55] will be used to confirm self-reported ADHD in individuals who are not receiving treatment.. Females will be tested for pregnancy. After all inclusion and no exclusion criteria have been met, participants will complete a descriptive assessment of cannabis use and will then be randomly assigned to either the experimental or control condition and stratified by gender.

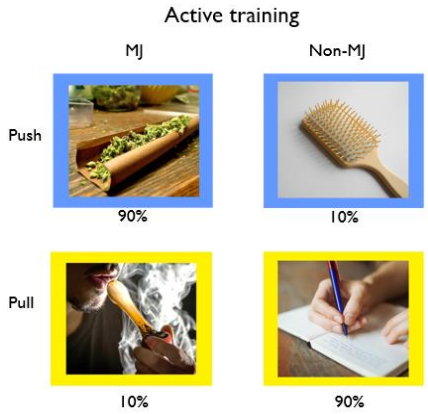
Remote screening visit:. Patients may also complete the initial visit remotely if warranted. In this case, participants will be electronically consented using Doxy.me or REDCap. The informed consent will be emailed to the participant prior to the video call. The participant will have the opportunity to ask questions on the call and will electronically sign the document. A signed copy will be emailed to the participant. The M.I.N.I. interview will then be conducted, also via Doxy.me Participants will be advised to find a private location during these procedures to protect privacy and confidentiality. Participants will be sent survey links to complete self-report questionnaires. Females will have a pregnancy test completed at Study visit 1.

D4.b. Session preparation: Participants will present to the Addiction Sciences Division research clinic for all study visits. The participant will be breathalyzed and will provide a urine sample which will be tested for pregnancy (females). If the pregnancy test is negative or the subject is male, the sample will be tested for the presence of cocaine, opiates, benzodiazepines, THC, and stimulants. A saliva sample will also be collected to verify cannabis abstinence for 12 hours prior to study procedures. If test results are within study inclusion/exclusion criteria, study visit procedures will begin.

D4.c. Approach Bias Modification (ABM): ABM procedures will use a cannabis adaptation of the Approach Avoidance Task[28] designed to assess and modify cannabis approach bias. *Approach bias assessments:* During the assessment phase, participants are presented with marijuana (MJ)-related and neutral images on a computer screen and are asked to push or pull a Logitech Extreme 3D Precision joystick in response to an irrelevant stimulus feature (i.e. image border color). Joystick movement activates a zooming feature, which has been shown to effectively model approach (pull: zoom in) and avoidance (push: zoom out) behavior[29]. Participants are asked to respond to stimuli as quickly and accurately as possible and reaction times (RTs) are calculated from image onset to action completion (zoom off-screen). Approach bias is computed by subtracting median “approach MJ” RTs from median “avoid MJ” RTs ($RT_{avoid} – RT_{approach}$); a positive value thus indicates greater approach bias. Assessments will occur at three time points: Baseline (BL), End of Treatment (EOT), and Follow-Up (FU). Each assessment

consists of 2 blocks of 96 trials and participants are presented with an equal number of MJ and neutral trials across response condition (i.e. approach/avoid).

ABM (or sham) training sessions consist of 2 blocks of 192 trials. Active training involves the manipulation of response contingencies favoring the "avoid MJ" response. In the active condition, 90% of MJ images are presented in the avoid (push) format and 10% approach (pull). Control (sham) training involves continued presentation of equally distributed approach/avoid MJ pictures. ABM training sessions will occur following each MET/CBT session, as per previous research on ABM for nicotine use[16]. Two stimulus sets of 16 MJ and 16 neutral images will be used and counterbalanced to test for generalizability. For example, if subject 101 receives Set A for pre-assessment and trainings, their post-assessments will use Set B; if subject 102 receives Set B for pre-assessment and training, they will be tested using Set A at post-assessments.



D4.d. Psychosocial treatment: All participants will receive three individual sessions of motivational enhancement/cognitive-behavioral therapy (MET/CBT). Sessions will incorporate a personalized feedback report summarizing cannabis use patterns, problems related to use, and reasons for quitting. Session 1 will focus on building rapport, enhancing motivation, and developing an action plan. Session 2 will focus on skill building exercises including managing life stressors, problem solving, coping with urges and cravings, and discussing barriers to goal achievement. Session 3 will focus on reinforcing effective use of skills and reviewing their action plan. The research team has successfully used a similar psychosocial intervention in previous studies[30-32]. All sessions will be 30-45 minutes and will be conducted by Sherman (PI) or the masters level study coordinator, who are both trained in MET/CBT for substance use disorders.

D4.e. Cue Reactivity: Cue reactivity will consist of physiological (skin conductance) and subjective (self-reported craving) components and will be assessed at three time points: BL, EOT, and FU. Participants will be connected to a finger sensor and then exposed to a neutral cue set, followed by a cannabis cue set. Each cue set contains tactile, auditory, and olfactory cues. Cannabis craving will be assessed prior to neutral cues, after neutral cues, and after cannabis cues to account for any carryover effects[33]. Skin conductance will be assessed continuously with time markers of cue onset/offset noted by study personnel to be used for subsequent analysis. Cue reactivity will be assessed following approach bias assessments.

D4.f. Additional instrumentation:

Descriptive assessment of cannabis use: Cannabis use in the 30 days prior to baseline will be assessed using urine drug screens and the Timeline Follow-Back (TLFB)[34]. The TLFB is a calendar-based instrument used with specific probes to ascertain detailed information about amounts of substance use. Number of discrete cannabis using sessions per day and quantity (hits) used per day will be recorded.

If necessary to limit person-to-person exposure, certain items such as the HAM-A, HAM-D and questions about substance use may be completed remotely. Participants may also be sent survey links to complete questionnaires remotely throughout study participation.

Menstrual History Diary: Subjects will be asked to estimate the timing of their cycle for the 90-days prior to study entry and to track their cycle during study participation.

Substance-related instruments: *TLFB:* Described above. In addition to cannabis use, participants will be asked about daily alcohol use (standard drinks), as well as instances (yes/no) of other substance use. *Urine Drug Screening*: Drug screens will be performed using the One Step Multi-Drug Test Dip Card (Drugconfirm™), a lateral flow chromatographic immunoassay for the qualitative detection of drug or drug metabolite in the urine at the following cutoffs (ng/ml): cocaine (300), amphetamines (1000), methamphetamine (1000), THC (50), opiates (2000), and benzodiazepines (300). Samples will then be sent to MUSC laboratory for cannabinoid quantification

and creatinine correction processing. Results will be used to ascertain abstinence prior to study procedures, cannabinoid levels, and to substantiate self-reports of all substance use. *Saliva Drug Screening*: In addition to urine testing, participants will provide a saliva sample to verify past-12-hour abstinence from cannabis. *Breathalyzer:* To ascertain abstinence from alcohol prior to study visits, subjects will have their breath sampled for the presence of alcohol (Alco-Sensor III, Intoximeters Inc., St. Louis, MO). *Skin Conductance:* Physiological cue-reactivity will be assessed using the eSense Skin Response System (Mindfield Biofeedback)®.
Self-report instruments: The Marijuana Use Summary Sheet, Self-Efficacy Questionnaire (SEQ), Marijuana Problem Scale (MJPS), and Reasons for Quitting Questionnaire (RFQ)[35] will be used to gather information from subjects to prepare personalized feedback reports (PFRs) as part of the MET/CBT component. The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES)[36], will be used to assess motivation to change along 3 dimensions: Ambivalence, Readiness, and Taking steps and the Marijuana Ladder[56], a 10-point Likert-type scale assessing overall motivation to quit marijuana. The Pittsburgh Sleep Quality Index (PSQI)[37] will be used to assess sleep function as a potential time-varying covariate. The Cannabis Withdrawal Scale (CWS)[38] will assess changes in cannabis withdrawal and the Marijuana Craving Questionnaire (MCQ)[39] will be used during cue-reactivity paradigm to assess cannabis craving. The Marijuana Motives Measure **(**MMM)[46] is a 25-item questionnaire assessing five motives for marijuana use: enhancement, coping, social, conformity, and expansion**.** The Brief COPE is a self-completed questionnaire measuring coping strategies. It comprises 14 subscales for which psychometric properties are described.[47] The Barratt Impulsiveness Scale (BIS11)[48] is a validated questionnaire designed to assess the personality/behavioral construct of impulsivity. The Hamilton Anxiety and Depression Rating Scales (HAM-A & HAM-D)[49,50] are validated scales to assess the severity of anxiety and depressive symptoms. The Rand 36 Item Short Form Health Survey[51] is a validated self-report to assess quality of life. The Difficulties in Emotion Regulation Scale – Short Form (DERS-SF)[52] is a widely used self-report measure of subjective emotion ability, as defined by a prominent clinically derived model of emotion regulation. The Effortful Control subscale of the Adult Temperament Questionnaire-Short (ATQ)[53] assesses constructs of attentional control, activation control, and inhibitory control. The Positive and Negative Affect Scale (PANAS)[57]will assess affective states. **Coronavirus Impact Scale:** 12 item questionnaire assesses life changes that have occurred as a result of the coronavirus (Stoddard & Kaufman, 2020). We will also ask how substance use has been impacted.

Neuropsychological assessments: Cognitive functioning will be assessed at BL, EOT, and FU to examine whether cognitive functioning is improved following the intervention or whether changes in cognitive functioning mediate treatment effect. To obtain additional measures of implicit cognitive bias, a cannabis adaptation of the dot-probe task that has shown sensitivity across substances of abuse[40,41] will be used to assess cannabis attentional bias and a cannabis adaptation of the Implicit Association Task[14] will be used to assess cannabis memory bias. Multiple forms of executive function shown to be impacted by SUDs will be assessed and which include: inhibitory control (Go No-Go task[42]), working memory – verbal (WAIS-IV Digit Span Subscale) and nonverbal (N-Back[43]) tasks. The Symbol Digit Modalities Test (SDMT)[54] measures sustained attention, response speed, and visuomotor coordination. It involves filling in a blank space below a symbol with the appropriate symbol-paired number as quickly as possible for 90 seconds.

D4.g. Six-Month Follow-up: Participants will complete a six-month follow-up either in person or over the phone. They will complete a TLFB, CWS, HAM-A, HAM-D, and review DSM-5 CUD symptoms from the M.I.N.I. neuropsychiatric interview. Participants will also complete the MJPS, PSQI, SF36 self reports in the Survey Mode of Redcap. Participants who do not complete the visit in person will be given the option to complete the surveys though a RedCap Survey Link sent though MUSC email. Participants who complete the visit in person will provide a UDS.

D4.h. Participant compensation: Participants will be compensated for attendance using an escalating contingency management (CM) schedule, cash bonuses, and a chip pick to maximize retention. Participants will be paid $40 for the screening visit ($20 for the interview and $20 for the questionnaires/UDS). Participants will receive a cash incentive starting at $20 at week 1 and increasing by $5 each week; any missed session will reset the cash incentive to $20. Participants will receive cash bonuses for completing baseline/week 1 ($25) and week 4 ($50) Participants will be apid $50 at the one-month follow-up visit , and $20 at the 6-month follow-up visit if completed in person. Participants who come to their visit and produce a negative saliva drug screen will also draw from a bowl

containing 250 chips that are assigned a certain value. Two-hundred thirty chips denote a small amount ($1.00), 18 chips denote a moderate amount ($10.00), one chip denotes a large amount ($50.00), and one chip denotes a jumbo amount ($100.00). Participants will be allowed three draws at the screening visit if they provide a UDS and five draws at subsequent visits if their saliva drug screens are negative. Participants will be paid with a Greenphire ClinCard.

Total possible reimbursement is $295/participant plus the sum of what is gathered from the chip pick.

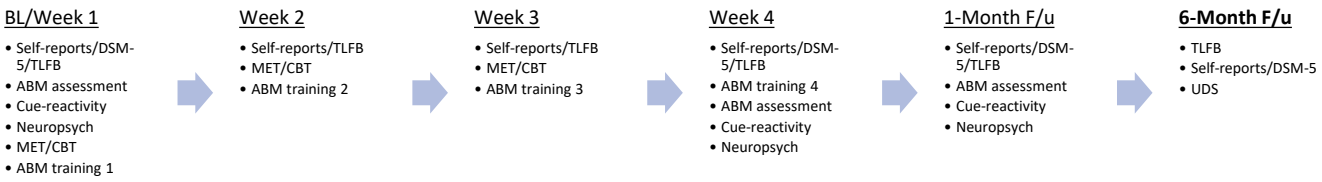
D4.i. Confidentiality: Confidentiality of all research data will be maintained by keeping all data in a locked file, limiting access to the computer database to only study personnel, and by using patient code numbers/initials as opposed to names on all paperwork. Any requests for the release of patient information will be referred to the candidate.

D4.i. Study Timeline

	Screen	BL/ Wk1	Wk 2	Wk 3	Wk 4	1 Month FU	6 Month FU
MINI	x						
DSM-5 CUD criteria		x			x	x	X
Urine pregnancy test	x	x			x		
Urine cannabinoid test, TLFB, CWS, PSQI, Menstrual History, HAM-A, HAM-D	x	x	x	x	x	x	x
MJ Summary Sheet, Self-reports	x	x			x	x	x
Neuropsych testing, Digit Span, SDMT		x			x	x	
Approach Bias assessment, Cue reactivity		x			x	x	
Integrated Treatment (MET/CBT + ABM)*		x	x	x	x		

*Participants will receive three sessions of MET/CBT over the four weeks.

D4.j. Study visit flow chart



D5. Statistical Considerations.

General Analysis: Baseline clinical and demographic characteristics will be collected and contrasts performed between treatment 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. In addition to baseline treatment group differences, preliminary analysis of baseline characteristics will examine significant correlates of outcomes. Characteristics found to be significantly associated with the primary outcome measures, will be included as covariates in the initial stages of adjusted model development. All analyses will be performed on the intent-to-treat sample consisting of all randomized subjects.

Study Aims: Aim 1 is to evaluate the efficacy of ABM in the reduction of cannabis cue reactivity outcomes between BL and EOT/FU, as well as the variance around each estimate. Generalized linear mixed (GLM) effects regression

models will be used to estimate each parameter and variance estimate of ABM or sham-ABM on cue reactivity measured at EOT and FU visit. Model based means and associated standard errors will be used to assess treatment group differences at EOT and FU. These methods are particularly well suited in instances where missing data is present. Aim 2 is to evaluate the efficacy of ABM on the reduction of cannabis use characteristics between BL and EOT/FU, as well as the variance around each estimate. Cannabis use data will be collected using the TLFB (proportion of use days, abstinence) and creatinine-adjusted cannabinoid levels (CN-THCCOOH) and will be compared between treatment groups using GLM models with appropriate distributional assumptions. Study data will be modeled as time invariant summary measures of the use at the end of the 4-week study period. Secondarily, we will also assess the efficacy of ABM on abstinence at FU (four-week abstinence). Study abstinence will be determined using UDS results (≤50 ng/ml) in concert with daily self-reported use. Exploratory Aim 1 will investigate the influence of gender on the treatment outcome and parameter estimates. Model interaction terms between study treatment assignment and gender will be added to each model developed for study aims 1 and 2 and tested for evidence of effect modification. When gender modification is present, pairwise comparisons within and across groups will be examined to assess the direction and magnitude of the modification. Additional analysis will assess neuropsychological data between groups over time using GLM models with appropriate distributions. Relative improvements over time associated with ABM will be assessed using between group comparisons taken at EOT and FU visits while controlling for baseline response data. Continuous outcome data will be assessed using a Gaussian distribution and count data will be assessed using a Poisson distribution. Second, neuropsychological data will be incorporated in the primary outcome models using interactions with treatment assignment to assess possible moderating effects on reported cannabis craving and use. Lastly, when ABM shows a significant relationship with changes in cannabis craving and use, neuropsychological measures will be assessed for mediating effects on the significant outcomes using bootstrap methods[45]. All analyses will be conducted using SAS v. 9.4.

Randomization: Participants will be randomized by study personnel to receive either active- or sham-ABM training using a stratified random block design. The randomization will be stratified on (1) gender and (2) baseline daily cannabis use intensity (less than 1 session or 1 and above). The purpose of stratification is to distribute these covariates equally across treatment groups. Study therapists and all personnel responsible for data analysis or interpretation will be blinded to group assignment. Only research personnel administering the ABM sessions will be unblinded.

Statistical Power and Sample Size: The proposed study is largely focused on obtaining preliminary data to inform and power a larger randomized controlled trial to assess ABM for CUD. However, the proposed sample size will allow for adequate power to assess the primary study aims. Primary AIM 1: Evaluate the efficacy of ABM combined with MET/CBT on cue-reactivity in adults with CUD**.** In a previous pilot study, we found evidence of greater reductions in cue induced cannabis craving at the end of treatment in those receiving active ABM as compared to sham ABM (MCQ: 43.2±1.0 vs. 39.5±1.0, Δ=3.7±1.4, d=0.58). We assume that the effect will be similar in the proposed study; however, we will measure use during the final treatment visit as well as at the FU visit. Under a correlated measures model assumption with a conservative within subjects correlation of rho=0.8, a sample size of 84 participants would be necessary to detect the noted treatment effect size with 80% power and a type 1 error rate of 5%. To account for an expected attrition of 20% based on our pilot study we have inflated our sample size to **106 participants (n=53 in each treatment assignment).** To achieve a randomized sample of 106 participants, we will need to enroll one hundred and thirty-six (136) participants. With a randomized sample of 106 participants, our 80% confidence interval around the sample estimated variance will be within 18% of the true population variance and the conservative upper estimate of the variance will be used to inform the power of the larger R01. Primary AIM 2: Evaluate the efficacy of ABM combined with MET/CBT on cannabis outcomes in adults with CUD**.** Cannabis use will be measured by a combination of self-reported use days and (CN-THCCOOH) levels measured following the 4th week of treatment. The sample size of 53 randomized participants (42 completers) in each treatment group necessary to provide adequate power in Aim 1 will provide 80% power with a type 1 error rate of 5% to detect a similar effect size to Aim 2 (d=0.58) in EOT (CN-THCCOOH) levels between study groups under similar model assumptions. The sample size of 42 completers per group will provide 80% power with a type 1 error rate of 5% to detect an 18% decrease in the proportion of use days in the ABM (39%) as compared to Sham (57%).Thus, a **total randomized sample size of n=106** participants will provide adequate power to address the clinically meaningful study aims in a statistically efficient manner.

Strategies to ensure a robust and unbiased approach: As detailed throughout this section, the proposed study will achieve robust and unbiased results via several design features including: explicit inclusion/exclusion criteria; randomization of treatment condition; sham control; blinding; use of validated measures and methods; explicit

hypotheses and corresponding planned statistical analyses; power estimates; and careful consideration of potential confounds.

D6. Design considerations: A four-session treatment protocol will be used based on the following considerations. First, building on pilot data from a non-treatment seeking sample, the proposed pilot treatment trial is the logical next step and is designed to *a)* assess the feasibility of conducting integrated ABM plus MET/CBT treatment for outpatients with CUD, and *b)* evaluate the efficacy of the intervention and variance around that estimate to help power a full RCT. Second, evidence suggests that while longer psychosocial interventions (9-12 weeks) produce greater abstinence rates, brief interventions (2-4 sessions) are effective in reducing frequency and quantity of cannabis use (MTPRG, 2004; Sherman et al., 2016; Stephens et al., 2000). Thus, we can reasonably expect to see a signal effect after three weeks of treatment. Third, the research team has experience with similar treatment designs (McRae-Clark et al., 2009; 2010; 2015; Sherman et al., 2017). Should this pilot trial be successful, a fully-powered nine-week RCT would follow.

D7. Future studies: Cognitive functioning is an important therapeutic target for cannabis and other substance use disorders. Successful completion of the proposed study and K23 training goals will provide the necessary experience for further investigation of both implicit (e.g. cognitive bias) and explicit (e.g. inhibitory control) cognitive processes in addiction. Future lines of research are at least threefold and will be pursued through additional funding mechanisms during the K23 period. Potential future studies could include 1) development of a mobile application of ABM for CUD (R21/R34), 2) a fully powered RCT of a 9-session course of ABM + MET/CBT (R01), and 3) integration of ABM with other cognitive processing interventions (e.g. inhibitory control or attentional bias training) (R01).

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a). Human Subjects Involvement and Characteristics

1. Involvement of Humans: Admission into the study is open to men and women and to all racial and ethnic groups, age 18-65. One-hundred and six subjects will be recruited primarily through internet and newspaper advertisements. Inclusion/exclusion criteria that apply to all subjects are listed below:

Inclusion criteria:

1. Be age 18-65 and must be able to provide informed consent.
2. Meet DSM-5 criteria for current moderate to severe CUD (past 60 days).
3. Identify cannabis as their primary substance of choice.
4. Express an interest in reducing marijuana use.
5. Consent to remain abstinent from alcohol and cannabis for 12 hours immediately prior to study visits and other drugs of abuse (except nicotine) for three days prior (see Additional Instrumentation below for methods); by restricting cannabis and other substance use as proposed, participants should not be under the acute effects of cannabis or other substances.

Exclusion Criteria:

1. Evidence of, or a history of serious medical or neurological disease that may affect cognitive processing.
2. History of, or current psychotic disorder, bipolar disorder, or current untreated major depressive disorder or attention-deficit hyperactivity disorder (ADHD) as these may interfere with subjective measurements.
3. Current use of psychotropic medications because these may affect subjective measurements (individuals taking antidepressants, or psychostimulants for ADHD will be allowed).
4. Current suicidal ideation. Individuals who endorse suicidal ideation will be seen by a psychologist or psychiatrist in the office and will be referred to treatment as necessary.
5. Women who are pregnant, nursing or of childbearing potential and not practicing an effective means of birth control.
6. Moderate to severe DSM-5 substance use disorder within the past 60 days (other than nicotine or cannabis).

2. Sample characteristics: We will recruit 106 adults age 18-65. We aim to recruit participants to approximate the cannabis treatment-seeking, racial, and ethnic composition of Charleston County, with the exception of gender, as we plan to enroll an equal number of males and females to address exploratory gender analyses (see Planned Enrollment Table).

b. Sources of Materials

1. Research material to be obtained: Structured diagnostic, psychosocial, substance use, and other cognitive questionnaires; behavioral tasks (i.e. MAAT computer task, cue-reactivity); breath and urine samples to detect recent substance use and pregnancy (in females); will be collected from participants. Every effort will be made to maintain participant confidentiality, in accordance with HIPAA.

2. Data that will be recorded: All forms of data described above will be recorded on computers or paper and pencil data forms that do not contain identifying information. Urine sample collection for toxicology analysis will be disposed by the federally certified lab; all samples will be code linked.

3. Linkages to subjects and access to identities: No personally identifying information will be recorded on the questionnaires, interviews, drug screen samples, behavioral data, or other scoring sheets assuring confidentiality. To ensure confidentiality, all subject data will be letter/number coded, and only the PI and HIPAA-trained research staff have access to the master code lists. All data will be stored in locked file cabinets in locked offices and on password-protected servers located behind secure and maintained firewalls.

4. How data are collected and whether data will be collected specifically for proposed research: Data are collected by the PI of the grant, co-investigators, or trained research associates. All staff will be required to complete on-line training in human subjects research, HIPAA, and clinical practices, PI-led in-lab training on research data management and confidentiality, and training to criterion on project protocol. Staff will also receive extensive training from Dr. Sherman on how to handle any adverse events. Data will be collected specifically for this proposed research project.

c. Potential Risks

1. Potential risks, likelihood, and seriousness: Questionnaires and interviews are non-invasive and therefore involve minimal risk to participants.

   a. Craving or discomfort: Exposure to cannabis cues may produce some craving for cannabis or other discomfort. However, this discomfort is usually brief and subjects will be in the cannabis-free safety of the human laboratory environment. In addition, exposure to cues will occur prior to psychosocial therapy sessions so any discomfort will be discussed by study therapists.

   b. Loss of confidentiality: Confidentiality issues are significant since this study collects a variety of sensitive data, in particular with respect to substance use. Procedures described above minimize the possible breach of confidentiality. Since personal information is gathered, there exists the risk of possible invasion of privacy. However, since informed consent is obtained, the likelihood of invasion of privacy is minimal. A Certificate of Confidentiality will be obtained prior to study initiation.

2. Alternative treatments and procedures: Subjects who wish to seek alternative treatment will be given referral resources. Subjects will be informed that their participation is voluntary, which includes study discontinuation to seek treatment. Subjects who discontinue cannabis use during the course of the study will be allowed to complete the protocol.

3. eSense Skin Response System (Mindfield Biofeedback)® GSR: Though minimal, there is an inherent risk due to design and manufacturing such that defects or improper use may lead to electrical shock and catastrophic overheating could lead to burns.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Patients will be recruited through the use of advertisements (internet, newspaper). Respondent driven sampling, where participants are offered cash incentives for referring others to the study, will also be used. Medical records will NOT be reviewed to identify potential study subjects. The study PI, a Co-I, or other qualified study staff will obtain informed consent. The informed consent form includes a detailed description of the study procedures, along with statements regarding participants' rights to withdraw from the procedure at any time without consequences. The informed consent form will be explained to subjects in easy-to-understand language, and subjects will be instructed to read the form carefully prior to signing it. Consent will be documented by the signature of the participant on the informed consent agreement, accompanied by the signature of the individual obtaining the consent.

b. Protection against Risk

All study participants will be closely monitored for psychiatric stability. All sessions will be conducted under the supervision of experienced personnel. The instrumentation used for physiological recordings meets all safety standards for non-invasive recordings, and participants are located out of reach of any AC-powered devices in the laboratory. If crisis intervention is necessary, licensed clinical staff will be available to evaluate the subject and provide an intervention or referral. If craving remains high for several hours after cue exposure, admission for an overnight stay can be arranged for which the subject will not be charged. If hospitalization is indicated, the patient will be hospitalized through the substance abuse treatment program at MUSC or an appropriate referral will be made.

All subjects will be fully informed that they may withdraw from the experiment at any time without penalty. All subject records will be kept in a locked filing cabinet, and confidentiality of all materials will be maintained. Offices also will be locked at times when not in use. To ensure confidentiality, all subject data will be coded by letters and/or numbers, and only the investigators will have access to the master lists of codes. All patient records will be kept in an office that will be locked at times when not in use. The research staff understands the importance of maintaining confidentiality. This method of maintaining confidentiality has been used for several years by our research group and has been effective. All co-investigators and study personnel have completed (or will complete upon hiring) training in Good Research Practices as mandated by the MUSC IRB.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Participation in this study involves minimal risk for participants. Benefits of participation include receipt of an evidenced based treatment for cannabis use, and referrals to treatment. The risks to subjects for this study are minimal, and given the minimal risks to participants, we believe the risk/benefit ratio is acceptable. Further, participants in the study may decrease their cannabis use which could positively affect other aspects of their lives.

4. DATA AND SAFETY MONITORING PLAN

Trial Management.

The study will be managed from the Addiction Sciences Division 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.

Data will be entered by research assistants directly into a computer using standard database software using REDCap. The data analysis plan is outlined in the Data Analysis Plan section.

Quality Assurance.

Quarterly data audits will be conducted. Confidentiality protections are outlined above.

Regulatory Issues.

Potential conflicts of interest will be reported using the upcoming NIH rules for disclosure. Adverse Events (AEs)/Serious Adverse Events (SAEs) occurring during the course of the project 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. A research assistant will identify any potential adverse events during the course of the study from participant self-report and administration of the visit assessments and procedures. The research assistant will provide information to a study physician, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness. Any significant actions taken by the local IRB and protocol changes will be relayed to ORWH/NIDA.

Definition of AE and SAE.

An Adverse Event (AE) is defined as any untoward medical occurrence in a study subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment (ICH GCP). Any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the trial is an adverse event. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes:

• Results in death,

• Is life-threatening,

• Requires inpatient hospitalization or prolongation of existing hospitalization,

• Results in persistent or significant disability/incapacity,

• Is a congenital anomaly/birth defect OR

• Requires intervention to prevent one of the above outcomes.

Documentation and Reporting.

AEs/SAEs are documented and reported as per protocol and IRB requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information if available should be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study as stated in the protocol. When a reportable SAE is identified, the research staff will notify the MUSC Institutional Review Board (IRB) within 24 hours and complete the AE report form in conjunction with the PI. The MUSC IRB meets monthly and is located at 165 Cannon Street, Rm. 501, Charleston, SC 29425. Communication with the IRB is through email, memos, official IRB forms, and online reporting. A report will also be sent to the NIH program officer assigned to the project.

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 NIH program officer as appropriate within 2 weeks of the initial SAE report. In addition, the PI will provide a signed, dated SAE summary report, which will be sent to the ORWH/NIDA Medical Safety Officer within two weeks of the initial SAE report.

We will report adverse events to the Medical University of South Carolina (MUSC) Institutional Review Board (IRB) 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.

Trial Safety.

The potential risks and benefits and methods to minimize these risks are outlined above. The research staff will report any unexpected AEs or any scores of “severe” on the side-effect symptom rating form or any FDA-defined serious AEs to the PI within 24 hrs so that the PI can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if treatment is needed. Study procedures will follow 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 Dr. Sherman.

Trial Efficacy.

An interim analysis is not planned at this time; however, an analysis will be performed if requested by ORWH/ NIDA or the DSMB.

DSM Plan Administration.

Dr. Sherman will be responsible for monitoring the study, and will participate in weekly study meetings. A DSM report will be filed with the IRB and ORWH/NIDA 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 outcomes at the end of the trial.

DSM Board.

A Data Safety and Monitoring Board will be formed to monitor both the rate and severity of adverse events. This panel will include 3 clinicians with expertise in substance use disorders and a statistician.

Risk Benefit Ratio.

The assessments and questionnaires are non-invasive and have inherently minimal risks. Potential risks of concern are loss of confidentiality and adverse events to progesterone and stress induction procedures. As discussed above, our research team will attempt to minimize these risks. Knowledge gained by the proposed study would help fill an important void in development of a potential gender-specific treatment for cannabis use disorders.

5. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study may provide important information concerning implicit cognition associated with cannabis cue- reactivity, as well as the potential efficacy of a novel treatment for individuals with cannabis and other substance use disorders. The minimal risks of the investigation are considered reasonable in relation to the expected knowledge to be gained.

6. CLINICALTRIALS.GOV REQUIREMENTS

In accordance with Public Law 110-85, this project will be registered at the ClinicalTrials.gov Protocol Registration System Information Website prior to study initiation.

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