RUTGERS
THE STATE UNIVERSITY
OF NEW JERSEY

INTERVENTIONAL
RESEARCH PROTOCOL TEMPLATE
(HRP-503a)

STUDY INFORMATION

Title of Project: Mindfulness Oriented Recovery Enhancement (MORE) Pilot

Principal Investigator:

Name: Nina Cooperman
RWJ-Department of Psychiatry, Division of Addiction Psychiatry
Contact Information: cooperna@rwjms.rutgers.edu; 732-235-4341

PROTOCOL VERSION AND DATE: Version 7, 5/15/19

NCT#: 2018001127

Table of Contents

RUTGERS
THE STATE UNIVERSITY OF NEW JERSEY

*Skip To Section: Hold **CTRL** + **Click (Below)** To Follow Link in **Blue***

1.0	**Research Introduction**
1.1	Purpose/Specific Aims
1.2	Research Significance
1.3	Research Design and Methods
1.4	Preliminary Data
1.5	Sample Size Justification
1.6	Study Variables
1.7	Drugs/Devices/Biologics
1.8	Primary Specimen Collection
1.9	Interviews, Focus Groups, or Surveys
1.10	Timetable/Schedule of Events
2.0	**Project Management**
2.1	Research Staff and Qualifications
2.2	Resources Available
2.3	Research Sites
3.0	**Multi-Site Research Communication & Coordination**
3.1	Outside Research
4.0	**Research Data Source/s**
4.1	Primary Data – Subjects and Specimens
4.2	Subject Selection and Enrollment Considerations
4.3	Subject Randomization
4.4	Secondary Subjects
4.5	Number of Subjects
4.6	Consent Procedures
4.7	Special Consent Populations
4.8	Economic Burden and/or Compensation For Subjects
4.9	Risks to Subjects
4.10	Secondary Data – Record/Chart Reviews, Databases, Tissue Banks, Etc.
4.11	Chart/Record Review Selection
4.12	Secondary Specimen Collection
5.0	**Special Considerations**
5.1	Health Insurance Portability and Accountability Act (HIPAA)
5.2	Family Educational Rights and Privacy Act (FERPA)
5.3	NJ Access to Medical Research Act
5.4	Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)
6.0	**Research Data Protection and Reporting**
6.1	Data Management and Confidentiality
6.2	Data Security
6.3	Data Safety And Monitoring
6.4	Reporting Results
6.5	Data Sharing
7.0	**Data and/or Specimen Banking**
8.0	**Other Approvals/Authorizations**
9.0	**Bibliography**

1.0 Research Introduction

1.1 Purpose/Specific Aims

This pilot study (R21), which is being funded by the National Center for Complementary and Integrative Health (NCCIH), aims to evaluate the impact of a novel intervention, Mindfulness Oriented Recovery Enhancement (MORE), on opioid use and chronic pain among individuals receiving methadone maintenance treatment (MMT). The main goal of this pilot study is to test the feasibility of our study methods before conducting a clinical trial to assess MORE with respect to a range of clinical outcomes. This study will involve a 2-arm individually randomized controlled trial design that compares MORE and treatment as usual (TAU).

A. Objectives

The main objective of this pilot study is to establish study feasibility in recruiting, retaining, and following up with MMT patients in the MORE and TAU interventions. Will track the following:

- When approached by study staff, the number of individuals who express interest in the study and the number who refuse (and reasons for refusal).
- The number of individuals who contact the staff with interest in the study.
- The number of individuals screened and eligible/ineligible.
- The number of individuals consented.
- The number of individuals who refuse participation after/during consent process.
- The number of sessions completed by study participants.
- The number of participants who drop out and reasons for drop out.
- Reasons for missed sessions.
- Tracking of all contact with participants for scheduling follow-up assessment sessions and completed/missed assessments.

In addition, the study will explore outcomes among participants in the MORE condition relative to treatment as usual (TAU) in regard to opioid use outcomes such as:

- Time until first opioid lapse
- Time until MMT dropout
- Total days of methadone treatment
- Total days of opioid or any drug use
- Trajectories of positive and negative affect
- Drug craving
- Pain severity and pain interference

B. Hypotheses / Research Question(s)

This is a pilot study designed to determine study feasibility and evaluate the impact of a novel intervention, MORE, on opioid use and chronic pain among individuals receiving methadone maintenance treatment. We will evaluate progression to a larger study based on the success of three key milestones. For the pilot study, we plan to evaluate our ability to recruit participants into the study, defining successful recruitment as 75% or more of our planned sample size by month 7. Retention will be considered successful if 50% of participants attend at least 4 MORE sessions, and will be assessed at month 9. We will evaluate our ability to collect 8-week and 16-week follow up data, defining success as a follow-up rate of 65% of participants at 8-weeks and 50% of participants at 16-weeks assessed at month 11. In addition to evaluating study feasibility through obtaining these milestones, we will obtain information about the efficacy of MORE on opioid use and chronic pain among MMT patients. It is hypothesized that: 1) Participants in MORE will have a longer duration of time to first opioid lapse than TAU participants; 2) Participants in MORE will have a longer duration of time to MMT dropout than TAU

participants; 3) At 8 and 16 –weeks post-enrollment, the MORE group will have fewer days of opioid use and fewer days of any drug use; 4) At 8 and 16 –weeks post-enrollment, the MORE group will have more days of methadone treatment than the TAU group; and 5) At 8 and 16 -weeks post-enrollment, the MORE group will have greater decreases in pain severity and pain interference than the TAU group.

1.2 Research Significance *(Briefly describe the following in 500 words or less):*

Despite the proven effectiveness of medication-assisted treatment (MAT) on opioid-use disorder (OUD), approximately 50% of people who begin methadone maintenance treatment (MMT) discontinue within twelve months, and 50% of people retained in MMT have an opioid relapse within six months.[1,2] Research also suggests that pain, which is highly prevalent in MMT patients (with 55%-61% of patients reporting current chronic pain and 80%-88% experiencing pain in the last week), may be an important contributor to MAT dropout, opioid relapse, and opioid overdose.[3] Unfortunately, effective pain management in MMT patients is challenging, as practitioners are reluctant to prescribe opioid pain medications to those with a history of substance use disorder.[4] Therefore, alternative interventions are critical to help people in treatment for OUD to cope with their pain and improve their quality of life.

Mindfulness Oriented Recovery Enhancement (MORE) is a novel intervention that addresses drug use and chronic pain, and is unique among current OUD interventions in that it helps break negative reinforcement cycles by modifying the associative learning mechanisms that process drug and non-drug related cues.[5,6] As a result, MORE promotes biobehavioral changes that strengthen responses to natural rewards while reducing responses to drug rewards, making the intervention more effective in helping people in MMT manage their pain and maintain long-term drug abstinence.[5,6] MORE, which integrates training in mindfulness, cognitive reappraisal skills, savoring of natural rewards and positive emotion regulation into an 8-week group therapy, is designed to target the attentional biases, affective dysregulation, and autonomic stress responses that underlie the feedback loop between chronic pain, craving, and opioid misuse[6,7] While MORE has shown positive outcomes in pain patients misusing, or at risk of misusing, opioids, it has not yet been tested in OUD patients with pain who are in recovery or receiving MAT. Therefore, we propose to test this promising intervention among individuals with pain who are receiving MMT for an OUD.

This study is significant because it could provide an additional and, as compared to existing behavioral interventions, a potentially more effective option for preventing relapse and managing chronic pain in people receiving MAT. Specifically, if found to be effective, MORE could help people on MAT cope with the stress and dysfunction associated with pain, reduce their risk of relapse, and enhance their overall quality of life.

1.3 Research Design and Methods

This pilot study is a 2-arm individually randomized controlled trial design in which outcomes of MMT patients randomized to MORE are compared to outcomes of those randomized to treatment as usual (TAU). In the pilot study (R21; N=31), we will randomize MMT patients with chronic pain to MORE (n=15) or TAU (n=16). This study phase will focus on establishing study feasibility in recruiting, retaining, and following up study participants before progressing to a larger Phase II clinical trial (R33, N=150). Participants with pain who are receiving MMT for an opioid use disorder (OUD) will be recruited from the New Brunswick Counseling Center (NBCC) and the Lennard Clinic.

A. *Describe, in order of occurrence, all research procedures being performed, when and where they are performed, and by whom (including procedures being performed to monitor subjects for safety or minimize risks).*

Participants will be recruited through flyers posted in the clinics, being approached by research assistants in the waiting room of their usual methadone clinic (New Brunswick Counseling Center or Lennard Clinic), and referral by clinic staff. The number of individuals who contact the study staff through the flyers or referral and who are approached by study staff in the clinics will be tracked. Number of individuals who refuse study participation and who consent to the study will also be tracked. If an individual is interested in study participation, a trained research assistant will lead the individual through the informed consent process in a private space.

Participants randomized to the MORE condition will participate in eight, weekly, two-hour group sessions led by a clinic or study counselor. Each session will contain 4-8 participants and take place in a private room at the New Brunswick Counseling Center (NBCC) or the Lennard Clinic. Attendance at each session and reasons for missing sessions will be recorded Participants randomized to the control condition will continue receiving treatment as usual at the NBCC.

All study participants will partake in a total of three interviews lasting up to 90 minutes and occurring at baseline, 8- and 16- weeks post-baseline in a private room at NBCC or the Lennard Clinic. Each participant will also have a urine or saliva sample collected during each assessment. This is required to verify self-report of drug use. Due to social desirability, it is common for people to not accurately report drug use; therefore, biochemical verification is the gold standard measure of drug use. All attempts to reach participants to schedule follow-up assessments will be tracked. Participants will also complete cognitive testing (for approx. 30-45 minutes) at baseline and 8-weeks and ecological momentary assessments (EMA) conducted via smartphones, which will be provided to each participant by study staff. EMA participation will require the participant to respond to twice-daily prompts in which they will be asked a series of brief questions regarding their current mood and exposure to opioid triggers. Additionally, subjects will be asked to initiate responses when they experience serious craving or relapse to opioid use. Each EMA assessment will last approximately 3-5 minutes.

B. *What data points will be collected including long-term follow-up?*

All study participants will participate in three face-to-face assessments at baseline, 8-weeks, and 16-weeks. If participants are unable or unwilling to attend a research appointment at their clinic, a research assistant will conduct a telephone interview. Information will be collected on demographic characteristics, substance use, methadone treatment, opioid craving and withdrawal, physical pain, non-reactivity, negative and positive affect, attentional bias, cognitive and mental health, physical health, and intervention implementation and attitudes. At the baseline and 8-week research visits, participants will complete three cognitive tasks on a computer that assess inhibitory control, implicit (automatic) associations, and the precedence of global features in visual perception. Urine and/or saliva samples will be requested at each assessment for confirmation of self-reported drug use. In addition, participants will partake in daily ecological momentary assessments (EMA) throughout the 16-weeks of study participation that include brief measures of pain intensity, mood, and substance use. Additionally, participants will be asked to initiate communication via smartphone when they either lapse to opioid use or experience serious craving. Self-initiated responses will include information about the circumstances surrounding their craving/lapse. A synopsis of all study instruments are included below (see 1.9B – Study instruments).

C. *Define the duration of the study and the length of time each subject will participate in the study.*

This pilot study is expected to take one year. Each subject will participate in the study for a total of 16-weeks.

Describe any primary and secondary study or safety endpoints

Feasibility will be assessed according to recruitment, retention and follow-up benchmarks. We will consider recruitment and retention efforts successful if we are able to enroll 75% of our target enrollment (31 participants) within a period of 4 months. Although we expect to recruit 100% of our planned sample by month 7, we set the criterion at 75% because we could adapt strategies for the next study to increase recruitment (including adding more MMT sites), if necessary. Retention will be considered successful if 50% of participants attend at least 4

MORE sessions. We will consider our ability to follow participants successful if we obtain 8-week assessments from at least 65% of participants and 16-week assessments from at least 50%. Although we are targeting a follow-up rate in both groups of at least 80% and 75% at 8 and 16 weeks, respectively, we set the benchmarks at 65% and 50% because, again, if necessary, we can adapt follow-up strategies for the next study, based on lessons learned in this study.

Preliminary outcome measures to be assessed during this pilot study will be time until opioid lapse and MMT dropout. Preliminary secondary outcomes will be: days of methadone medication use, days of opioid and other drug use, and changes in pain severity and intensity. Additional measures are described below.

1.4 Preliminary Data

Effects of MORE on cognitive, affective, and psychophysiological mechanisms implicated in addiction.

Dr. Garland conducted the first pilot randomized controlled trial (RCT; N=53) of MORE, and found that, relative to a support group (SG) control, MORE significantly decreased stress, modified addiction attentional bias, and increased heart rate variability recovery from substance cues during an affect-modulated cue-reactivity protocol. Two follow-up studies (N=58) found that trait mindfulness among substance dependent individuals in treatment was negatively associated with addiction attentional bias and positively associated with heart rate variability recovery from stress-primed cue-exposure.[8,9]

MORE as a treatment for opioid misuse and chronic pain – preliminary outcomes and processes.

Dr. Garland recently completed a pilot RCT of 8 sessions of MORE for chronic pain patients receiving long-term opioid analgesic therapy.[7] In the course of 1.5 years, 304 patients were recruited from community sources, 115 of whom met study criteria and were randomly assigned to treatment. Eighty-one percent of participants who began the study treatments completed treatment and were retained at the post-treatment assessment. Intent-to-treat analyses indicate that compared with a support group (SG; n=58) control, MORE (n=57) led to significant reductions in pain severity (p=.014, d=.63) and functional interference (p=.002; d= .84) that were maintained at 3-month follow-up and mediated by non-reactivity and reinterpretation of pain as innocuous sensory signals. Importantly, MORE improved addiction-related outcomes. Relative to SG, a greater proportion of opioid misusers treated with MORE no longer exceeded the validated threshold for opioid misuse following treatment, due to reductions in aberrant drug-related behavior, X^2=3.74, p=.05. MORE also significantly reduced opioid craving by post-treatment (p=.027, d=.50), and significantly decreased the correlation strength between craving and misuse.[7]

MORE and ecological momentary assessment of pain and affect.

In a sample of low SES individuals with OUD and comorbid psychiatric disorders, MORE (n=20) led to significantly greater reductions in opioid craving (p=.04, d=.63) and PTSD symptoms (p=.001, d=.84) compared to Cognitive Behavioral Therapy (CBT).[10]. In this trial, across 8 weeks of treatment, patients completed up to 224 EMA measures of pain and affect. Multilevel models and generalized estimating equations examined effects of treatment on momentary pain and positive affect, and generalized linear models examined associations between pain and affect and changes in opioid misuse by post-treatment. Patients in MORE reported significantly greater improvements in momentary pain (p=.01) and positive affect (p=.004) than patients in the SG. Further, over the entire course of treatment, patients in MORE were significantly more likely to exhibit positive affect regulation (OR=2.75) than patients in the SG. Finally, improvements in positive affect (but not pain) over the course of intervention were associated with reduced risk of misusing opioids by post-treatment (p=.02).[10]

1.5 Sample Size Justification

A total of 31 OUD patients with chronic pain who are receiving MAT will be recruited from New Brunswick Counseling Center (NBCC) and the Lennard Clinic. Patients will be randomized into either MORE (n=15) or TAU (n=16). Since this is a pilot study, a sample size of 31 is deemed sufficient to determine whether study methods are feasible for recruitment, retention, and follow-up for a larger, fully-powered randomized controlled trial. We will

make every effort to obtain a sample that represents the gender and minority composition of the methadone clinics.

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

Mindfulness Oriented Recovery Enhancement (MORE) structure (Intervention Condition). The MORE arm will participate in eight, weekly, two-hour group sessions led by a therapist. MORE sessions involve mindfulness training to prevent opioid relapse and reduce pain, cognitive reappraisal to decrease negative affect and regulate opioid craving, and savoring to augment natural reward processing and evoke positive emotion.[1] Each session begins with a mindful breathing or body scan meditation, followed by a debriefing session, in which the therapist provides reinforcement and troubleshooting to help guide successful implementation of mindfulness techniques. Following this debrief of the in-session mindfulness meditation, the therapist debriefs participants' homework practice of using mindfulness, reappraisal, and savoring skills to cope with pain and enhance well-being in everyday life. During this debrief of the homework practice, the therapist provides reinforcement and troubleshooting to help guide successful implementation of mindfulness, reappraisal, and savoring techniques. Next, new psychoeducational material is introduced according to the session topics outlined in Table 3. Sessions culminate with an experiential exercise, and close with a brief mindful breathing meditation. Participants are asked to practice 15 minutes of mindfulness/reappraisal/savoring skills each day (i.e. homework practice).

Table 3. MORE session content

Week	Theme
1	Introduction to mindfulness, and the relationship between nociception, pain and emotional suffering; mindful breathing and body scan
2	Automatic pain coping habits; awareness of automatic opioid use; instruction in mindfulness of automatic pilot; mindful breathing
3	Mindful reappraisal as means of coping with negative emotions; mindful breathing
4	Savoring natural rewards; positive emotion regulation; mindful savoring practice
5	Mindfulness of opioid craving; contemplation of negative consequences of opioid use; imaginal opioid cue-exposure; mindful breathing
6	The relationship of the stress response to pain and craving; imaginal stress exposure; mindful breathing; body scan
7	Concepts of thought suppression, aversion, and attachment; exercise in the futility of thought suppression; mindful breathing and acceptance
8	Discussion of how to maintain mindfulness practice; finding a sense of meaning and purpose of life; development of mindful recovery plan; imaginal rehearsal of skill learning; mindful breathing

Treatment as Usual (TAU). In the MMT programs, clients typically come to the clinic regularly (usually 6 days per week at the beginning of treatment) to get their methadone dose; as clients progress through the program and remain abstinent from drugs, they earn "take home doses" that they can take on days that they are not required to come to the clinic. Timing of the initiation of take-home doses and the scheduling of clinic days varies across clinics. Clients see their clinic substance abuse counselor for individual counseling, usually weekly at the beginning of treatment, with decreasing frequency if they remain abstinent and progress through treatment. Depending on clients' stage of MMT and success with remaining abstinent from drugs, they may be required to attend clinic treatment groups. Also, some clients may choose to go to voluntary counseling, educational, or support groups (none of these groups involve coping with pain oriented or are mindfulness-based). All individual treatment characteristics, including methadone dosage, take-home dosing, clinic attendance and attendance at clinic counseling sessions and groups, will be documented for all study participants and entered as covariates in the analyses.

B. Dependent Variables or Outcome Measures

The main objective of this pilot study is to establish study feasibility in recruiting, retaining, and following up with MMT patients in the MORE and TAU interventions. The primary feasibility outcome measures are:

- The number of individuals who express interest in the study and the number who refuse (and reasons for refusal).
- The number of individuals who contact the staff with interest in the study.
- The number of individuals screened and eligible/ineligible.
- The number of individuals consented.
- The number of individuals who refuse participation after/during consent process.
- The number of sessions completed by study participants.
- The number of participants who drop out and reasons for drop out.
- Reasons for missed sessions.
- The number of completed/missed assessments including questionnaire data, drug screens, cognitive tasks, and EMA assessments.

In addition, the study will explore outcomes among participants in the MORE condition relative to treatment as usual (TAU) in regard to opioid use outcomes such as:

- Time until first opioid lapse
- Time until MMT dropout
- Total days of methadone treatment
- Total days of opioid or any drug use
- Trajectories of positive and negative affect
- Drug craving
- Pain severity and pain interference
- Inhibitory control, implicit associations, and the precedence of global features in visual perception

1.7 Drugs/Devices/Biologics

- N/A

1.8 Primary Specimen Collection

A. *What types of specimen will be collected, where, and by whom?*

We will utilize a urine or saliva screen that tests for buprenorphine and methadone (to provide corroboration of MAT engagement and compliance) and additional substances (e.g., benzodiazepines, barbiturates, cocaine, marijuana, methamphetamine, morphine, oxycodone, phencyclidine and amphetamine). These specimens will be collected by study research assistants at baseline and each follow-up time point (8-weeks and 16-weeks). Biochemical verification of self-report opioid relapse and other drug use is the gold standard measurement of drug use and, without biochemical verification, self-reported drug use as an outcome variable will be questioned by the scientific community.

B. *How will the specimens be transported and by whom?*

The sample will be collected and results read at the time of sample collection. The sample will be disposed as soon as results are read (typically within 10 minutes of sample collection) and recorded. The sample will not be transported. Samples will be collected and read in a private area where others will not be able to see or hear the results.

C. *Who will process the specimens?*

Research assistants will process the sample.

D. *How long will the specimens be kept?*

The sample will be disposed of immediately after results are read and recorded.

E. *How will the specimens be destroyed upon study completion?*

Samples will be flushed down the toilet (urine test) or disposed of in the trash (saliva test).

F. *If specimens will be banked for future use, what will be the process for providing investigators with access to the bank and how will this be tracked?*
N/A

1.9 Interviews, Focus Groups, or Surveys

A. Administration

- **Timing and Frequency**

Research staff will collect interview data and drug screens from both intervention and control group subjects through face-to-face standardized measures conducted at baseline and either phone or face-to-face measures 8- and 16- weeks post baseline. Cognitive testing data will be collected at baseline and 8-weeks. If the research assessments are conducted over the phone, cognitive assessments and drug screen results will be considered missing data. Additionally, subjects will engage in twice-daily EMA assessments of approximately 3-5 minutes each. Subjects will also initiate EMA communications to report lapses or serious cravings, which will also last for under 5 minutes.

- **Location**

The assessments and drug screens will take place in private rooms at the New Brunswick Counseling Center (NBCC) and Lennard Clinic.

- **Procedures for Audio and Visual Recording**

Audio or video recordings will be made of the MORE therapy sessions and the recordings will be transcribed research staff. All recordings will be stored in password protected computers, in a locked office at 317 George St., New Brunswick, NJ, in password protected files, on the Rutgers network.

B. Study Instruments

Feasibility Outcomes:

- The number of individuals who express interest in the study and the number who refuse (and reasons for refusal) will be tracked in a log.
- The number of individuals who contact the staff with interest in the study will be tracked in a log.
- The number of individuals screened and eligible/ineligible will be tracked in a log.
- The number of individuals consented will be tracked in a log.
- The number of individuals who refuse participation after/during consent process will be tracked in a log.
- The number of sessions completed by study participants will be tracked in a log.
- The number of participants who drop out and reasons for drop out will be tracked in a log.
- Reasons for missed sessions will be tracked in a log.
- The number of completed/missed assessments will be tracked in a log.

Exploratory outcomes among participants in the MORE condition relative to treatment as usual (TAU) in regard to opioid use outcomes such as:

- Time until first opioid lapse assessed through ecological momentary assessment data and timeline follow-back.

- Time until MMT dropout assessed through clinic records (abstracted by the study counselor who will have access to the clinic records). Time until dropout will be calculated from enrollment until last dose of methadone.
- Total days of methadone treatment assessed through clinic records (abstracted by the study counselor who will have access to the clinic records). Number of days will be calculated from enrollment until each follow-up time-point.
- Total days of opioid or any drug use assessed through EMA data and timeline follow-back
- Trajectories of positive and negative affect assessed through Positive and Negative Affect Schedule.
- Drug craving assessed with an adapted version of the Penn Alcohol Rating Scale.
- Pain severity and pain interference assessed with the Brief Pain Inventory and the Graceley Box scale[8]

Additional secondary outcome and other relevant measures that could mediate or moderate outcomes will be piloted for feasibility of administration. Details of the measures to be piloted are described below.

Ecological Momentary Assessmenet (EMA) data collection (ongoing from baseline to 16 weeks). The EMA will be programmed as a REDCap survey delivered over a password-protected smart phone that will not store any EMA data. REDCap is a secure, HIPPA-compliant, web-based application for building and managing online surveys and databases. The EMA survey approach will involve 1) collecting event-contingent records of lapses when they occur as well as 2) regular random assessments , prompted by random text messages initiated by Twilio, twice daily via smartphones. For event-contingent records, participants will be asked to initiate an entry when an opioid lapse or opioid craving without use occurs, and note how they were feeling and the extent of craving. One random assessment probe will be scheduled between 9 am and 3 pm and one will be scheduled between 3 pm and 9 pm. The random probes will be generated by an algorithm in REDCap and linked to a Twilio phone number. For random assessments, participants will be asked to note how they are feeling, drug use, and whether they completed their homework (if in the intervention group). Research staff will demonstrate to study participants how to use the phones, respond to the prompts, and provide event contingent data. Research staff will observe participants using the phone and practice using the phone with participants until they are capable of using it.

Data will be received by the REDCAP system. Data access between the REDCap database and the web server is encrypted and restricted to a monitored port. All REDCap data, which is displayed or captured by the user interface, is encrypted for security. Within REDCap all data transactions including inserts, updates, deletions, import/export and reporting are logged. The EMA system in this study deployed via REDCap will reside in a HIPAA compliant protected space. The REDCap production and development servers use encrypted drives. Physical hardware will be secured in a locked facility.

The data will only be accessible to study investigators and staff. The data will be processed by an already developed REDCap program that formats the data as a "long file" with one row per time point per individual participant. The investigators will employ linear mixed models to test the effects of MORE vs. the control condition on substance use, craving, pain, and other study variables. The treatment X time interaction will be the main fixed effect of interest. Models will include a random intercept, as well as a random slope if warranted by model fit statistics. Auto-correlation between repeated measures will be modeled as a first-order autoregressive function. We will also compute within-group linear mixed models examining mindfulness practice duration as a predictor of clinical outcomes.

Substance use history (Baseline). We will use the PhenX Toolkit-Substance Abuse and Addictions Core Tier 1 Collection[2] to gather self-report information on lifetime use of opiates, alcohol, tobacco and substances, and past-30 day use of all substances.

Current substance use (Baseline, 8 weeks, and 16 weeks). We will utilize a urine screen that tests for buprenorphine and methadone (to provide corroboration of MAT engagement and compliance) and additional

substances (benzodiazepines, barbiturates, cocaine, marijuana, methamphetamine, morphine, oxycodone, phencyclidine and amphetamine). At each research visit we will conduct a timeline follow-back[3] with each participant to account for missing EMA drug use data. The timeline follow-back is a reliable and valid measure where participants are asked to recall and record events (e.g., drug use) within a specified time period on a calendar. We will combine self-report of opioid relapse and other drug use with biochemical measures because it is the gold standard, and without biochemical verification, self-reported drug use as an outcome variable will be questioned by the scientific community. If a biochemical measure is negative, but the participant reports drug use, the participant will be coded as using drugs since the biochemical measure will only capture a specific time point. However, if the participant self-reports drug abstinence, but the biochemical measure is positive for drug use (the more likely scenario) the participant will be coded as having used drugs.

Craving (Baseline, 8 weeks, and 16 weeks).Opioid and other drug craving will be assessed with an adapted version of the Penn Alcohol Craving Scale (PACS)[4] and the Craving Suppression Scale. The PACS is a valid, reliable, and internally consistent measure that consists of five self-report items that have been found to predict relapse. The items assess the intensity, frequency, ability to resist, and duration of craving. Originally developed to assess alcohol craving, it has been adapted and used to measure craving for various substances, including opioids,[5] and adapted versions have been used in trials of mindfulness-based interventions for substance use.[6] The Craving Suppression Scale is a 17 –item measure that assesses how individuals cope with craving

Pain (Baseline, 8 weeks, and 16 weeks). For study eligibility, pain intensity will be assessed at baseline only with Gracely Box Scale,[7] a visual analog scale that ranges from 0 (no pain) to 20 (extremely intense pain). At baseline and both follow-up points, pain severity will also be measured with the the Brief Pain Inventory[8] (BPI; α = .87) a well-validated measure that has been widely used to tap acute and chronic pain. Participants will be asked to report their worst pain during the past week, least pain during the past week, average pain, and current pain. Response options range from 0 (no pain) to 10 (pain as bad as I can imagine). An overall pain severity score will be computed by taking the mean of the four items. Pain will also be assessed with the Sensations Body Map.

Pain interference (Baseline, 8 weeks, and 16 weeks). Pain-related functional interference will be assessed with the pain interference subscale of the BPI[8] (α = .88). Subjects will be asked to rate on a 0 (does not interfere) to 10 (completely interferes) scale the extent to which pain interfered with each of seven domains of normal functioning in the past week, including: general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. An overall pain interference score will be computed by taking the mean of the seven items.

Coping with pain (Baseline, 8 weeks, and 16 weeks). Cognitive coping with pain by reinterpreting painful sensations as innocuous sensory experiences will be assessed via the reinterpreting pain sensations subscale of the Coping Strategies Questionnaire[9] (CSQ). This subscale has good internal consistency (α= 0.88), and is comprised of 6 items including “I don’t think of it as pain but rather as a dull or warm feeling,” and “I just think of it as another sensation such as numbness.” Participants will be asked to report how much they generally engaged in this form of coping when they felt pain. Responses are rated on a scale ranging from 0 (never) to 6 (always); a reinterpretation of pain sensations total score can be obtained by adding up the four items (range: from 0 to 36). Scores on this scale are meaningfully related to measures of pain and adjustment to pain,[9] and have been shown to mediate the therapeutic effects of mindfulness training on chronic pain.[10]

Nonreactivity (Baseline, 8 weeks, and 16 weeks). Nonreactivity to distressing thoughts and emotions will be measured with the Five Facet Mindfulness Questionnaire.[11] This scale is comprised of items such as “When I have distressing thoughts or images, I ‘step back’ and I am aware of the thought or image without getting taken over by it.” These skills appear to tap metacognitive decentering or disengagement from aversive experiences, and have been shown to mediate the effects of mindfulness training on decreased pain.[10]

Reappraisal (Baseline, 8 weeks, and 16 weeks). Reappraisal will be measured with the positive reappraisal subscale of the Cognitive Emotion Regulation Questionnaire (CERQ),[12] an internally-consistent subscale (α = .85) which asks the respondent how often they “think I can become a stronger person as a result of what has happened” or “look

for positive sides to the matter" to cope with stressful events. Responses are rated on a scale ranging from 1 (almost never) to 5 (almost always). In prior research, scores on this reappraisal scale were prospectively predictive of lower levels of future affective symptoms,[12] and changes in CERQ reappraisal scores mediated the stress-reductive effects of mindfulness.[13] Also reappraisal will be assessed with the 9-item Mindful Reappraisal Of Of Painful Sensations Scale. Responses are rated on a scale ranging from 0 (never do that) to 6 (always do that);

Positive and Negative Affect (Baseline, 8 weeks, and 16-weeks). We will assess positive and negative affect with the valid and reliable Positive and Negative Affect Schedule (PANAS).[14] The PANAS is a 20-item, self-report measure that consists of two scales (positive affect and negative affect) of 10-items each. Participants will rate factors related to positive or negative affect on a scale from 1 (not at all) to 5 (very much).

Cognitive impairment, psychosis, suicidality (screening). To determine study eligibility, cognitive impairment will be assessed with the Mini Mental Status Exam,[15] psychosis will be assessed with the Structured Clinical Interview for DSM-V (SCID) Psychotic screen,[16] and suicidality will be assessed with the Ask Suicide Screening Questions Tool. The MMSE is a widely used valid and reliable measure of cognitive functioning that assesses orientation to time and place, registration, attention and calculation, recall, language, Scores <24 indicate cognitive impairment. The SCID Psychotic Screen is a semi-structured clinical interview that assesses symptoms of psychotic disorders (e.g., delusions, hallucinations) based on the DSM-V criteria. The ASQ is a five item screening tool that is part of the NIMH toolkit.[17]

Mental health history (Baseline) and psychiatric symptoms and treatment (Baseline, 8 weeks, 16 weeks). At baseline, history of mental illness and psychiatric treatment will be assessed. At each subsequent research visit, participants will be asked if they took any psychotropic medications or received any mental health counseling since their last visit. At each research visit, symptoms of depression and anxiety will be evaluated with the Center for Epidemiologic Depress Scale and the Beck Anxiety Inventory.

Physical health history (Baseline) and symptoms (Baseline, 8 weeks, 16 weeks) and pain medication (baseline, 8 weeks, 16 weeks). At Baseline, history of illness such as HIV, cancer, heart disease, emphysema, asthma and other chronic conditions will be assessed. Daily health functioning will be evaluated at every research visit with the RAND 36-Item Health Survey 1.0 (SF-36).[20] The reliability and validity of this self-report scale that measures overall health and ability to complete daily activities has been shown. Current pain medication (prescribed and over the counter) will be assessed at each research visit.

Savoring (Baseline, 8 weeks, 16 weeks). Savoring will be measured by the Savoring Beliefs Inventory (SBI), The SBI is a reliable and valid scale that consists of 6 items that assess individuals' perceptions of their ability to derive pleasure through anticipating upcoming positive events, savoring positive moments, and reminiscing about past positive experiences

The following cognitive tasks will be completed on a laptop computer. The computer tasks will be administered online through the Inquisit platform. Pre-developed Inquisit scripts exist for each computer task, and participants' encrypted task data will be housed on a secure server "using Secure Sockets Layer (SSL)", the same technology used by online shopping and banking web sites to protect sensitive information transmitted over the web" (https://www.millisecond.com/support/docs/v5/Inquisit.pdf). Each task will be scored within the Inquisit platform according to validated scoring methods.

Inhibitory control, Go-No Go Task (Baseline, 8-weeks): To assess inhibitory control, participants are asked to press the Spacebar on a computer when they see, on the computer screen, a green rectangle (=go) but refrain from pressing the Spacebar when they see a blue rectangle (=nogo).[21] The blue and green rectangles can be vertical or

horizontal. The vertical rectangle has a high probability of being green (a go trial) and the horizontal rectangle has a high probability of being blue (a nogo trial). Participants get information about the orientation of the rectangle (=cue) shortly before the color of the rectangle is revealed. Mean reaction times will be derived from the Go/No-Go tasks.

Opioid/Natural Reward, Implicit Association Task (IAT; Baseline, 8-weeks): The IAT is a widely-used cognitive-behavioral paradigm that measures the strength of automatic (implicit) associations between concepts in people's minds relying on latency measures in a simple sorting task.[22] Participants are asked to, on a computer, categorize attributes (e.g. "pleasant"; "unpleasant") and and target items (e.g "friends" vs. "pills") into predetermined categories via keystroke presses. The basic task is to press a left key (E) if an item (e.g. "pleasant") belongs to the category presented on the left (e.g. "Good") and to press the right key (I) if the word (e.g. " unpleasant ") belongs to the category ("Bad") presented on the right. For practice, participants sort items into the target categories "Opioids vs. Natural Reward" and the attribute categories "Good vs. Bad". For the test, participants are asked to sort categories into the paired/combined categories (e.g. "Natural Reward OR Good" on the left vs. "Opioid OR Bad" on the right). Pairings are reversed for a second test (e.g. "Opioid OR Good" on the left vs. "Natural Rewards OR Bad" on the right). Block order is counterbalanced by group number. A d-score will be derived from the implicit association task.

Precedence of Global Features in Visual Perception, Global Local Task (Baseline, 8-weeks): On a computer, participants are briefly presented with letter shapes (e.g. H or S) that are made up of little letter shapes (e.g. H or S).[23] Some of these letters have the same global (overall shape) and local (individual building shapes) letters (e.g. an H that consists of Hs), and some have different global and local letters (e.g. an H that consists of Ss). In the global condition participants are asked to respond to the global shape of the letter (e.g. press key H if the global shape of the letter is an H regardless of individual building blocks); in the local condition participants are asked to respond to the local shapes of the letter (e.g. press H if the local building elements are Hs regardless of overall shape). The number of errors during the last block of the global/local task will provide a shifting attention score.

Intervention implementation (Week 8). Number of sessions completed and missed will be assessed for each participant in both conditions. Reasons provided for missed sessions will also be recorded.

1.10 Timetable/Schedule of Events

Table 1. R21 Timeline	Year 1											
Month	1	2	3	4	5	6	7	8	9	10	11	12
Protocol manual writing and staff training	■	■	■									
Recruitment				■	■	■	■					
Intervention period					■	■	■	■	■			
Follow-up data collection					■	■	■	■	■	■	■	
Pilot study data analyses										■	■	■
R33 protocol manual writing, institutional review board application and approval										■	■	■
Recruit and hire R33 staff										■	■	■

The project timeline proposes to spend three months conducting start-up activities, with study recruitment beginning in month 4 and continuing through month 7. The intervention will begin in month 4 and continue through month 9, 8-week follow-up assessments will begin in month 6 and continue through month 9, and 16-week follow-ups will begin in month 8 and continue through month 11. In month 11, we will finalize our assessment of study feasibility. At the end of

month 11, we will prepare a report summarizing our feasibility findings for NCCIH and seek approval for continuing to a larger, fully powered, randomized controlled trial. Data collection for this pilot study will be 8 months.

2.0 Project Management

2.1 Research Staff and Qualifications

Dr. Nina Cooperman, the Principle Investigator on this project, is a clinical psychologist and faculty member at Rutgers-RWJ Department of Psychiatry. Dr. Cooperman has more than 15 years' of clinical and research experience with substance abusing and mentally ill populations. Dr. Anna Kline, Co-Investigator, has more than 25 years' experience conducting research in the area of mental health and addictions in New Jersey, including epidemiological studies, qualitative research and clinical trials.

All research staff will have a minimum of a Bachelor's degree or experience working with substance users. All investigators and key personnel will have undergone mandatory education in human research participant protection, including completing the Human Research Curriculum of Collaborative Institutional Training (CITI), "HIPAA Security" training, and "HIPAA Privacy" training. Research staff will participate in ongoing team meetings with the study investigators to discuss any issues that arise.

2.2 Resources Available

Facilities

Rutgers Robert Wood Johnson Medical School, Addiction Psychiatry Research Offices at 317 George Street, Suite 105, New Brunswick, NJ 08901. The Division of Addiction Psychiatry is located in a clinical-research unit of 3000 sq. ft. which includes faculty and staff offices, sound proofing, and a conference room (where community advisory panel meeting will be held). In addition to several faculty members, Division office space is shared by administrative personnel, research assistants, and secretaries. Fax and copy machines are available in the Division offices.

New Brunswick Counseling Center (NBCC) at 320 Suydam St., New Brunswick, NJ 08901. Dr. Cooperman has conducted several research studies at NBCC, and the clinic is extremely enthusiastic about being a research site for this project (see attached letter). The New Brunswick Counseling Center (NBCC) provides comprehensive, evidence-based, individualized, substance abuse treatment services. NBCC's staff includes a multidisciplinary team of medical, psychological, social work, and substance abuse professionals. NBCC currently approximately 500 patients receiving methadone maintenance treatment, and, in the past year, almost 90% of admissions to the center reported current cigarette smoking. The clinic is in central New Brunswick, NJ, within walking distance from where the Division of Addiction Psychiatry offices are located, making this location ideal for patient recruitment and collaboration. Office and group counseling space is available at the NBCC for the research staff to see study participants.

The Lennard Clinic. The Lennard Clinic, with two offices in Newark and Elizabeth, New Jersey (61 Frelinghuysen Ave, Newark, NJ 07114 and 850 Woodruff Lane Elizabeth, NJ 07201), exists to enrich the quality of life of opioid dependent adults in Essex, Union and surrounding counties to reduce illicit drug use, decrease criminal activities, enhance health conditions and promote social/economic stabilities by providing superior treatment services. The Lennard Clinic provides: 1) medication Assisted Treatment (methadone, suboxone), 2) individual treatment, transition and discharge planning, 3) individual and group counseling, medical care for indigent clients, case management, and clinic based treatment on demand (CBTOD) free for eligible clients. The Newark site services approximately 700 clients on methadone maintenance treatment and the Elizabeth site serves approximately 300 clients on methadone maintenance treatment.

Medical Or Psychological Resources

Methadone clinic medical and psychological resources will be available to study participants. During assessment sessions, participants will be told that they do not need to discuss topics or disclose any information that makes them uncomfortable. The research assistant will be trained to deal with any distress related to the study interviews. Referrals for counseling or psychiatric evaluation will be made if necessary. If a participant expresses thoughts of harming himself or herself or others or discloses a child is at-risk, either verbally or on the study measures, a written protocol has been developed and confidentiality may be broken. A participant who endorses current thoughts of harming himself, herself, or others will be assessed by the methadone program clinical team to determine if the participant is safe to leave the clinic, if the individual is in the clinic or by Dr. Cooperman, if contact with the participant was over the phone, to determine if further action needs to be taken to ensure the safety of the participant or others. Dr. Williams will be available to assess and address any medical adverse events that occur during the course of the study.

Research Staff Training-

All research staff will have completed the online human subject's protection (CITI training). Staff will be trained and supervised by Dr. Cooperman and Dr. Kline on unbiased recruiting of study participants, data collection, and maintaining confidentiality. They will also be trained on assessing adverse events, tracking study participants, data entry, and procedures if a participant expresses intent to harm him/herself or others. A manual of procedures will be created for research staff and weekly research staff meetings will be held to assure protocol adherence and address any issues.

2.3 Research Sites

List the sites where research activities will be conducted.

Research will be conducted at Rutgers-RWJ Medical School, Department of Psychiatry, Division of Addiction Psychiatry at 317 George St, Suite 105, New Brunswick NJ 08901. In addition, subjects will be recruited from the New Brunswick Counseling Center (NBCC), 320 Suydam St., New Brunswick, NJ 08901and the Lennard Clinic, 61 Frelinghuysen Ave, Newark, NJ 07114 and 850 Woodruff Lane Elizabeth, NJ 07201.

3.0 Multi-Site Research Communication & Coordination

N/A

4.0 Research Data Source/s

4.1 Primary Data-Subjects and Specimens

4.2 Subject Selection and Enrollment Considerations

A. Recruitment Details

Thirty participants will be recruited from the New Brunswick Counseling Center (NBCC) or the Lennard Clinic. Participants will be recruited from flyers providing study information posted in the methadone clinic. In addition, clinic staff will refer potential participants to they study and research assistants will recruit on-site at the clinic. The research assistant will approach clinic clients in the waiting area at different times and on different days of the week to ensure adequate sampling. The research assistant will introduce him/herself to individuals waiting in clinic waiting areas, tell them they are conducting a study of an intervention for people with chronic pain and in methadone treatment, and ask them if they are interested in hearing more about the study. Patients expressing initial interest in the research will be given more detailed study information by the RA and screened for study eligibility.

B. Source of Subjects

Participants will be recruited from the New Brunswick Counseling Center (NBCC) and the Lennard Clinic.

C. Method to Identify Potential Subjects
Research assistants will screen individuals for eligibility after identifying interested individuals receiving services at NBCC or the Lennard Clinic.

D. Subject Screening

- **Inclusion Criteria**

Subjects must be age 18 or older, English-speaking, been in methadone treatment for at least 3 months, and experience a non-malignant pain with an intensity level of 8 or higher on the Gracely Box Scale[13] for a duration of 2 months or longer.

- **Exclusion Criteria**

Subjects will be excluded from participation if they do not meet the inclusion criteria above exhibit cognitive impairment (score <24 on the Mini Mental Status Exam[19]) or psychosis (positive SCID Psychotic Screen[20]), are at suicidal risk (positive score on ASQ Suicide Risk Screening Tool[23]), or unable to attend group sessions due to distance, work, commitments or other logistical problems, or are currently pregnant or breastfeeding or planning to be pregnant or breastfeeding the next 16 weeks.

E. Recruitment Materials
Flyers with study information and a phone number to reach research staff will be posted throughout the New Brunswick Counseling Center (NBCC) and the Lennard Clinic.

F. Lead Site Recruitment Methods
N/A

4.3 Subject Randomization
Since MORE is a closed group, we will randomize cohorts of 10-16 participants (depending on speed of recruitment) at each site to TAU or MORE with block randomization. Once we recruit at least 10 participants at a particular clinic, we will randomize participants to MORE or TAU, and the MORE group will begin. We estimate that we will recruit at least 10 participants per month.

4.4 Secondary Subjects
N/A

4.5 Number of Subjects

A. Total Number of Subjects
Total number of subjects to be accrued is 31.

B. Total Number of Subjects If Multicenter Study
N/A

C. Require Number of Subjects to Complete Research
N/A

D. Feasibility of Recruiting
Subjects will be recruited for up to four months. NBCC serves approximately 500 MMT clients and the Lennard Clinic serves approximately 1000 MMT clients at two sites.. Based on the prior research studies

conducted at these clinics and the high amount of clients served, there are no anticipated problems in recruiting ample subjects.

4.6 Consent Procedures

A. Consent

- **Documenting Consent**

If you will document consent in writing, provide a list of each document here and upload your consent document(s) in eIRB. For guidance see HRP-091.

Consent for Study Participation

- **Waiver of Documentation Of Consent**

N/A

- **Waiver or Alteration of Consent Process**

(i) Waiver or Alteration Details

N/A

(ii) Destruction of Identifiers

N/A

(iii) Use of Deception/Concealment

N/A

B. Consent Process

- **Location of Consent Process**

The informed consent process will take place at NBCC or the Lennard Clinic, in a private room reserved for the research study to take place.

- **Ongoing Consent**

N/A

- **Individual Roles for Researchers Involved in Consent**

The role of the individuals listed in the application as being involved in the consent process.

Study recruiters/research assistants, who have been trained in the study protocol and the process for obtaining consent, will consent subjects for the study.

- **Coercion or Undue Influence**

Those who choose to participate will complete a written, informed consent process before any study procedures are performed. A signed copy of the informed consent will be given to the study participants. Research staff will read the consent form out loud to any individuals who are unable to read the consent form on their own. Topics covered in the consent form will include a description of study procedures, the time involved, the right to withdraw at any time without penalty, procedures used to protect participant anonymity, information on the use of data, the potential benefits and risks of participating in the study, and limits of confidentiality regarding expressions of suicidal ideation, homicidal ideation, or a child at risk. Research staff will be trained to note signs that suggest that the individual is unable to consent and will: 1) ask permission from the individual before questioning him/her; 2) observe for signs of illness, intoxication, and other reasons causing individuals to be unable to consent; 3) assess orientation to person, place, time, and situation; and, 4) ask the potential participant to paraphrase the study requirements.

4.7 Special Consent/Populations

A. Minors-Subjects Who Are Not yet Adults

- **Criteria for Consent of Minors**

N/A

- **Wards of the State**

1. Research in NJ Involving Minors
N/A
2. Research Outside of NJ Involving Minors
N/A

- **Parental Permission**

N/A

- **Non-Parental Permission**

N/A

- **Assent Process**

N/A

- **Non-English Speaking Subjects**

N/A

B. Adults Unable to Consent / Cognitively Impaired Adults (*for interventional studies*)
N/A

4.8 Economic Burden and/or Compensation for Subjects

A. Expenses
Subjects will not incur any costs other than their time for participating in the study.

B. Compensation/Incentives
Participants will receive a $30 gift card for completing the baseline assessments and drug screen, $40 for the 8-week assessments and drug screen, and $50 for the 16-week visit. At each of the baseline and 8-week visits, participants will also receive a $20 gift card for completing the cognitive assessments. Also, participants will receive approximately 25¢ for completing each of two daily EMA assessments (e.g., $20 for 25%, $30 for 50%, $40 for completing 75%, and $50 for completing 100% of EMA assessments). In sum, participants who complete all study assessments will receive $210 total as well as a smartphone. Payments will be made in the form of a gift card. Participants randomized to the intervention condition will receive a $5 gift card for attending each intervention session (up to $40 total). These amounts are deemed fair compensation for the amount of time participants are asked to spend, without being large enough to be considered coercive.

C. Compensation Documentation
All participant incentive payments will be fully documented on incentive logs, which will record the date, amount, subject ID number, and name of the research staff distributing the payment for each incentive paid. Participants will also be asked to initial the log entry indicating that they have received their payment.

4.9 Risks to Subjects

A. Description of Subject Risk
This study involves accepted forms of treatment and assessment. Risks to subjects are minimal. The main risk associated with the study is discomfort related to talking about personal issues in study assessments and group sessions. However, participants do not have to talk about anything they do not want to. Loss of confidentiality is a risk. However, group participants will be informed about the importance of confidentiality and study staff will be trained to protect participant confidentiality. While we are not actively recruiting participants with an existing psychological disorder, it is possible we enroll individuals who we subsequently find to be suicidal or have other mental health problems. Personal information may be disclosed to a participant's clinic counselor, program director, or other public safety of healthcare personnel if study staff believes, based upon information reported during intervention sessions or

through research assessments, that a participant may harm himself or herself or others. Protocols have been developed to manage unexpected emergencies involving individuals with mental health problems, as well as to manage risks associated with participant discomfort and loss of confidentiality. If the study staff determine that the participant is a harm to him/herself or others to the extent that, based on the implementation of the protocol, it is a new or worsening symptom, it will be considered an adverse event. If the research staff determines that loss of confidentiality is required to protect the individual or others, the event will be reported to the IRB and NIH as a serious adverse event.

B. Procedures for Risks to Embryo, Fetus, and/or Pregnant Subjects

N/A

C. Risks to Non-Subjects

N/A

D. Assessment of Social Behavior Considerations

- **Reasonably Foreseeable Risks**

A risk associated with this study, among people who have substance use disorder and possibly a mental health disorder, is discomfort related to talking about personal or sensitive issues in study assessments and group sessions. However, participants do not have to talk about anything they do not want to. Loss of confidentiality, in general or about sensitive information like substance use, is a risk. While we are not actively recruiting participants with an existing psychological disorder, it is possible we enroll individuals who we subsequently find to be suicidal or have other mental health problems. Personal information may be disclosed to a participant's clinic counselor, program director, or other public safety of healthcare personnel if study staff believes, based upon information reported during intervention sessions or through research assessments, that a participant may harm himself or herself or others. Protocols have been developed to manage unexpected emergencies involving individuals with mental health problems, as well as to manage risks associated with participant discomfort.

- **Risk Of Imposing An Intervention On Subject With Existing Condition**.

All interventions will be voluntary and participants can discontinue at any time.

- **Other Foreseeable Risks**

N/A

- **Observation And Sensitive Information**

N/A

E. Minimizing Risks

During assessment sessions, participants will be told that they do not need to discuss topics or disclose any information that makes them uncomfortable. The study clinicians and research assistant will be trained to deal with any distress related to the study assessments or group sessions. Referrals for additional counseling or psychiatric evaluation will be made if necessary. If a client expresses thoughts of harming himself or herself or others either verbally or on the study measures, a written protocol has been developed and confidentiality may be broken. Participants will be made aware during the consent process that confidentiality may be broken if the study staff determine that he or she may be a risk to him or herself or others. As noted previously, assessments will occur in the methadone clinic where clinical staff will be present to assist in managing unexpected mental health emergencies. A participant who endorses current thoughts of harming himself, herself, or others will be assessed by study clinical staff and, if necessary, the participant's substance abuse counselor and/or the clinical director of the clinic to determine if the participant is safe to go home or if further action needs to be taken to ensure the safety of the participant or others. If a participant discloses information about harming him or herself or others

during a telephone interaction, Dr. Cooperman will be available to assess the participant and determine appropriate course of action. Written protocols have been established for these circumstances.

Group participants will be informed about the importance of confidentiality and study staff will be trained to protect participant confidentiality. Data will be collected in private areas to prevent disclosure of information. Also, to assure confidentiality, data and recordings will be secured in a database management system, password protected files, and in secure file cabinets. Data collection forms, databases and recording will not include identifiers other than a study ID code. The key to the code will be kept separately in a locked file. Informed consent forms will be kept separated in a locked file in the same office. Three levels of security are provided to prevent unauthorized persons from accessing data: password protection, computer or file cabinet locks, and a locked office. In addition, we will obtain a Certificate of Confidentiality from the National Institutes of Health that protects study data from forced disclosure.

F. Certificate of Confidentiality

Since all NIH studies are automatically issued a Certificate of Confidentiality (COC), the study is already covered by a COC. As of October 1, 2017, NIH funded researchers will no longer have to request a CoC, nor will they receive an actual certificate. The CoC will be issued automatically to NIH funded grants, cooperative agreements, contracts and intramural research projects research funded wholly or in part by the NIH that collects or uses identifiable, sensitive information.

G. Potential Benefits to Subjects

Participants in the MORE study group will receive the benefit of free group therapy sessions. Further, participants who do not use opioids or are better able to manage their chronic pain as a result of this study will gain important health and quality of life benefits. Because the risk of receiving free group treatment is very small, and the potential benefits for individual participants and society are quite large, the risk/benefit ratio is clearly weighted on the side of the benefit for those randomized to the intervention condition. Further, if MORE is ultimately found to be effective, in the future, it could help improve quality of life and prevent relapse for all individuals with chronic pain and in methadone treatment, including all of the participants. However, this study could also have no direct benefit to study participants.

H. Provisions to Protect the Privacy Interests of Subjects

Group participants will be informed about the importance of confidentiality and study staff will be trained to protect participant confidentiality. Data will be collected in private areas to prevent disclosure of information. Also, to assure confidentiality, data and recordings will be secured in a database management system, password protected files, and in secure file cabinets. Data collection forms, databases and recording will not include identifiers other than a study ID code. The key to the code will be kept separately in a locked file. Informed consent forms will be kept separated in a locked file in the same office. Three levels of security are provided to prevent unauthorized persons from accessing data: password protection, computer or file cabinet locks, and a locked office. Transmission of EMA data will be encrypted and data will not be stored on participants' mobile phones. The REDCap system, a HIPPA compliant, secure system will be utilized to collect and manage all EMA data and EMA data will not contain any identifying information. In addition, we will obtain a Certificate of Confidentiality (COC) from the National Institutes of Health (NIH) that protects study data from forced disclosure. NIH automatically issues a COC for all NIH funded research.

I. Research Team Access to Subject Data

Drs. Cooperman and Kline and the research staff will have access to all data stored on password protected files in Rutgers offices. All study data will be anonymous, and will contain no personal identifiers.

4.10 Secondary Data – Records/Chart Reviews/Databases/Tissue Banks/etc.
N/A

4.11 Chart/Record Review Selection
N/A

4.12 Secondary Specimen Collection
N/A

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

We will be obtaining individually identifiable health Information associated with a HIPAA-covered component or entity in the course of the research.

5.2 Family Educational Rights and Privacy Act (FERPA)
N/A

5.3 NJ Access to Medical Research Act
N/A

5.4 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

A. "Special" Classes Of Subjects

(1) *Pregnant Women: see guidance (HRP-412)*
(2) *Neonates: see guidance (HRP-413)*
(3) *Neonates of Uncertain Viability: see guidance (HRP-414)*
(4) *Prisoners: see guidance (HRP-415)*
(5) *Children: see guidance (HRP-416)*
(6) *Cognitively Impaired Adults: see guidance (HRP-417)*

N/A

6.0 Research Data Protection and Reporting

6.1 Data Management and Confidentiality

A. *Describe the data analysis plan, including any statistical procedures.*
Although this pilot study will not be powered to detect significant differences between the intervention and control group, we will conduct descriptive analyses (means, medians, and percentages) and examine group differences (e.g., chi-square, ANOVA, t-tests) to explore possible effects. Additionally, we will track and compare number of sessions completed and dropout using chi-square, Poisson regression, and t-tests.

B. *Provide a power analysis. (As applicable, e.g. quantitative research)*
Since this is a pilot study to determine feasibility and preliminary effect size, the study is not powered to detect significance, but to inform a larger study. A sample size of 31 is adequate for a pilot study.

C. *Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.*

All investigators and research staff will have undergone mandatory education in human research participant protection. To assure confidentiality, data will be secured in a database management system, password protected files, and in secure file cabinets. Data collection forms, databases, and recordings will not include identifiers other than a study ID code. The key to the code will be kept separately in a locked and/or password protected file for no longer than six years. Informed consent forms will be kept separately in a locked file in the same office. Three levels of security are provided to prevent unauthorized persons from accessing the data: password protection, computer or file cabinet locks, and a locked office. In addition we have a Certificate of Confidentiality from the National Institutes of Health that protects study data from subpoena. Access to data will be limited study investigators and staff. Research data will be kept no longer than 10 years.

D. *Describe any procedures that will be used for quality control of collected data.*

As we have done in prior studies, a manual of procedures will be developed during the initial start-up period that explicitly describes the specific procedures related to data collection, entry, storage, and quality assurance for both study conditions. Data will be collected by research staff in strict accordance with the study's protocols. All data collection forms will be independently reviewed for quality and consistency by a member of the research team who was not responsible for collecting the source data. The research staff will be trained to avoid omissions in data collection and data entry. Computer entry protocols will be programmed to avoid accidental skipping of question items. We will apply conditional formatting to datasheets to remove the possibility of out of range data. All data on written forms will be entered twice by two separate data entry personnel and compared via a macro we have experience using within Microsoft Excel datasheets other data will be entered directly into a secure Qualtircs databases. Once all data on paper forms is entered, paper forms will be housed at a facility that specializes in the storage of medical/research information. The destruction date of these files will be within 10 years from the termination of the study and will be authorized by the Principal Investigator. Under supervision from Dr. Kline, the Research Assistant will conduct monthly descriptive summaries on all data to ensure their accuracy. This will not involve completing any statistical comparisons. If problems are noted in data entry (e.g., out of range values, missing values), the Research Assistant and Dr. Kline will investigate the root cause, and solutions to rectify the problem will be generated and implemented.

6.2 Data Security

Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

As noted above, to assure confidentiality, anonymous data and recordings of therapy sessions will be secured in a database management system, password protected files, and in secure file cabinets. Data collection forms, databases, and recordings will not include identifiers other than a study ID code. We will include all three levels of security: password protection, computer or file cabinet locks, and a locked office. Participants' encrypted cognitive task data will be housed on a secure server "using Secure Sockets Layer (SSL), the same technology used by online shopping and banking web sites to protect sensitive information transmitted over the web"

6.3 Data and Safety Monitoring

A. Periodic Data Evaluation

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

The Data and Safety Monitoring Board (DSMB) will meet every 3 months to monitor and evaluate the safety of participants throughout the course of the research study. The DSMB will:

- Assess the performance of the study with respect to participant recruitment, retention and follow-up, protocol adherence, and data quality and completeness.
- Monitor interim data regarding the safety of the study regimes.
- Review and consider any protocol modifications or ancillary studies proposed by study investigators after the main trial begins to ensure that these do not negatively impact on the main trial.
- Advise the Institutional Review Board as to whether the protocol should continue as scheduled or undergo a modification due to a finding from the monitoring process.

B. Type of Data Evaluated

Include what data are reviewed, including safety data, untoward events, and efficacy data.

The study investigators and the DSMB will be responsible for data safety and monitoring. Quarterly, the DSMB and the investigators will monitor the cumulative safety data during the period when participants are in the study. They will: 1) assess the performance of the study with respect to participant recruitment, retention and follow-up, protocol adherence, and data quality and completeness, to help ensure the likelihood of successful and timely trial completion; 2) monitor interim data regarding the safety of the study regimens; 3) review and consider any protocol modifications by the study investigators after the trial begins to ensure that these do not negatively impact on the study; and 4) advise the Institutional Review Board and NIH as to whether the protocol should continue as scheduled or undergo a modification due to a finding from the monitoring process.

C. Collection of Safety Information

Explain how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Safety information will be collected during participant's assessments, telephone calls with participants, conversations with clinic staff, and MORE group sessions.

D. Frequency of Data Collection

The frequency of data collection, including when safety data collection starts.

Safety data collection will begin with collection of the first baseline assessment and continue through the end of the follow-up data collection period (12 months total). In addition to using assessment data to monitor safety, study clinicians will record any adverse events that they become aware of during MORE group sessions and study Investigators will ask NBCC and the Lennard Clinic personnel, with participant consent, to notify the research team should they become aware that any study participant has been hospitalized or experienced any other adverse event. Such notifications will be requested throughout the study period. All adverse events will be recorded on spreadsheets and will include details of the adverse event and whether or not it was study-related. Numbers and types of events and other quantifiable event details will be entered into a database for analysis.

E. Reviewer of Data

Who will review the data?

The DSMB will meet on a quarterly basis to monitor the cumulative safety data during the period when participants are in the study. The DSMB will monitor the study according to the guidelines specified in the study protocol and the operating procedures established at the initial DSMB meeting, unless the DSMB determines during the course of the trial that modification of the guidelines is in the best interest of the study and its participants. Such a decision may be based on new information that emerges during the course of the study (e.g., publication of the results of a similar study), realization of inappropriate initial study assumptions, or the occurrence of an unanticipated scenario.

F. Schedule of Review of Cumulative Data

The frequency or periodicity of review of cumulative data.

Under supervision of the investigators, the Research Assistant will conduct monthly descriptive summaries on all data to ensure their accuracy. This will not involve completing any statistical comparisons. If problems are noted in data entry (e.g., out of range values, missing values), the Research Assistant and the investigators will investigate the root cause, and solutions to rectify the problem.

G. Tests for Safety Data

The statistical tests for analyzing the safety data to determine whether harm is occurring.

Basic statistical tests, including frequency distributions, Anovas and t-tests, will be carried out to compare the control and intervention groups on numbers and types of adverse events within specific time frames in order to insure the safety of the intervention.

H. Suspension of Research

Any conditions that trigger an immediate suspension of the research.

Considering the minimal risk nature of the intervention, we do not anticipate any serious adverse events that could trigger the immediate suspension of the research.

6.4 Reporting Results

A. Sharing of Results with Subjects

Participants will be provided with the study PI's name and contact information along with an estimate of when the study results will be available. Participants my contact the PI should they be interested in obtaining results of the study.

B. Individual Results

N/A

C. Aggregate Results

As noted above, subjects will be given the PI's name and contact information and encouraged to follow-up with the PI should they be interested in obtaining results of the study.

D. Professional Reporting

Study results will be described in reports to the funding agency and published in peer-reviewed journals. Findings may also be presented at professional meetings.

6.5 Data Sharing

Analyses of data generated from this project will be shared with the scientific community through publications in peer-reviewed journals and presentations at scientific meetings. Because we will be following study participants, we will be collecting identifying information. Even though the final dataset will be stripped of identifiers prior to

release for sharing, we believe that there remains the possibility of deductive disclosure of participants with unusual characteristics. Thus, we will make the data and associated documentation available to research community scientists only under a data-sharing agreement that provides for: 1) a commitment to using the data only for research purposes and not to identify any individual participant; 2) a commitment to securing the data using appropriate computer technology; and 3) a commitment to destroying or returning the data after analyses are completed. The study will be registered with clinicaltrials.gov

7.0 Data and/or Specimen Banking

N/A

8.0 Other Approvals/Authorizations

Describe any approvals that will be obtained prior to commencing the research. (E.g., school site authorization, data use agreements, external site authorization, funding agency, Bio-Safety, Radiation -Safety etc.)

N/A

9.0 Bibliography

1. Garland EL. *Mindfulness-Oriented Recovery Enhancement for Addiction, Stress, and Pain.* NASW Press; 2013.
2. PhenX. Substance Abuse and Addiction Collection of the PhenX Toolkit http://www.phenxtoolkit.org. . Accessed January 13, 2018.
3. DeMarce JM, Burden JL, Lash SJ, Stephens RS, Grambow SC. Convergent validity of the Timeline Followback for persons with comorbid psychiatric disorders engaged in residential substance use treatment. *Addict Behav.* 2007;32(8):1582-1592.
4. Flannery BA, Volpicelli JR, Pettinati HM. Psychometric properties of the Penn Alcohol Craving Scale. *Alcohol Clin Exp Res.* 1999;23(8):1289-1295.
5. Tsui JI, Anderson BJ, Strong DR, Stein MD. Craving predicts opioid use in opioid-dependent patients initiating buprenorphine treatment: a longitudinal study. *Am J Drug Alcohol Abuse.* 2014;40(2):163-169.
6. Garland EL, Roberts-Lewis A, Tronnier CD, Graves R, Kelley K. Mindfulness-Oriented Recovery Enhancement versus CBT for co-occurring substance dependence, traumatic stress, and psychiatric disorders: proximal outcomes from a pragmatic randomized trial. *Behaviour research and therapy.* 2016;77:7-16.
7. Gracely RH, McGrath F, Dubner R. Ratio scales of sensory and affective verbal pain descriptors. *Pain.* 1978;5(1):5-18.
8. Cleeland C. *Brief Pain Inventory–Short Form (BPI–SF).* Houston, TX1994.
9. Rosenstiel AK, Keefe FJ. The use of coping strategies in chronic low back pain patients: relationship to patient characteristics and current adjustment. *Pain.* 1983;17(1):33-44.
10. Garland EL, Gaylord SA, Palsson O, Faurot K, Douglas Mann J, Whitehead WE. Therapeutic mechanisms of a mindfulness-based treatment for IBS: effects on visceral sensitivity, catastrophizing, and affective processing of pain sensations. *J Behav Med.* 2012;35(6):591-602.
11. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. *Assessment.* 2006;13(1):27-45.
12. Garnefski N, Rieffe C, Jellesma F, Terwogt MM, Kraaij V. Cognitive emotion regulation strategies and emotional problems in 9 - 11-year-old children: the development of an instrument. *Eur Child Adolesc Psychiatry.* 2007;16(1):1-9.

13. Garland EL, Gaylord SA, Fredrickson BL. Positive reappraisal mediates the stress-reductive effects of mindfulness: an upward spiral process. *Mindfulness.* 2011;2(59):59-67.
14. Crawford JR, Henry JD. The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. *Br J Clin Psychol.* 2004;43(Pt 3):245-265.
15. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.
16. First M, Williams J, Karg R, Spitzer R. *Structured Clinical Interview for DSM-5—Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV).* Arlington, VA: American Psychiatric Association; 2015.
17. Horowitz LM, Bridge JA, Teach SJ, et al. Ask Suicide-Screening Questions (ASQ): a brief instrument for the pediatric emergency department. *Arch Pediatr Adolesc Med.* 2012;166(12):1170-1176.
18. Radloff LS. The CES-D scale: A self report depression scale for research in the general population *Applied Psychological Measurements.* 1977;1:385-401.
19. Beck AT, Steer RA. *Beck Anxiety Inventory Manual.* San Antonio, TX: Psychological Corporation.; 1993.
20. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ.* 1992;305(6846):160-164.
21. Fillmore, M. T., Rush, C. R., & Hays, L. (2006). Acute effects of cocaine in two models of inhibitory control: implications of non-linear dose effects. Addiction, 101, 1323–1332.
22. Greenwald, A. G., McGhee, D. E., & Schwartz, J. K. L. (1998). Measuring individual differences in implicit cognition: The Implicit Association Test. Journal of Personality and Social Psychology, 74, 1464-1480.
23. Navon, D. (1977). Forest Before Trees: The Precedence of Global Features in Visual Perception. COGNITIVE PSYCHOLOGY, 9, 353-383.