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Mindfulness Oriented Recovery Enhancement for Chronic Pain and Opioid Relapse

NCT04491968

Version: 2/2/22

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INTERVENTIONAL RESEARCH PROTOCOL

(HRP-503a)

STUDY INFORMATION

Title of Project: Mindfulness Oriented Recovery Enhancement (MORE) as an Adjunct to Methadone Treatment for Chronic Pain and Opioid Relapse Prevention

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PROTOCOL VERSION AND DATE: Version 15, 2/2/2022

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1.0 Research Introduction

1.1 Purpose/Specific Aims

This study (R33), 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 study is conduct a clinical trial to assess online MORE, delivered remotely, through secure video or phone conferencing, 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

Aim 1. Determine MORE's efficacy for increasing opioid abstinence relative to TAU.

Aim 2. Determine MORE's efficacy for impacting secondary outcomes relative to TAU.

Aim 3. Evaluate the degree to which MORE's impact on opioid use and pain are mediated by changes in the three core therapeutic mechanisms of MORE.

Aim 4. Identify moderators of treatment response.

B. Hypotheses / Research Question(s)

As compared to the TAU group, the MORE group will 1) have a longer time until opioid relapse (primary outcome) and 2) have greater opioid abstinence, less other drug use, greater MMT adherence, and greater reductions in craving, pain symptoms, and emotional distress (secondary outcomes).

We hypothesize that the impact of MORE on opioid use and pain outcomes will be mediated by improvements in metacognitive awareness (mindfulness), negative emotion regulation (reappraisal), and amplification of natural reward processing (savoring).

Based on prior studies, we hypothesize that gender will moderate treatment response.[19-21] We will also explore other potential moderators like race, income, mental health, trauma, and MMT phase (i.e., stabilization/early recovery vs. maintenance/sustained abstinence).

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 MMT discontinue within 12 months,[1] and 50% of people retained in MMT have an opioid relapse within six months.[2] Research suggests that chronic physical pain, affecting 55%-61% of people receiving MMT,[3] could be contributing to opioid relapse and MMT dropout.[4,5] 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. 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 study is a 2-arm individually randomized controlled trial design in which outcomes of MMT patients randomized to MORE, delivered remotely, by secure phone or video conferencing, are compared to outcomes of those randomized to treatment as usual (TAU). In the study we will randomize MMT patients with chronic pain to MORE or TAU. This study phase will conduct a clinical trial to assess MORE efficacy and to explore factors impacting the efficacy of MORE on opioid use outcomes. Participants with pain who are receiving MMT for an opioid use disorder (OUD) will be recruited from the New Brunswick Counseling Center (NBCC), Burlington Comprehensive Counseling, the Lennard Clinic, and Jersey Shore Addiction Services (JSAS).

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, Burlington Comprehensive Counseling, Jersey Shore Addiction Services, or Lennard Clinic) if and when feasible, and referral by clinic staff. When a potential participant is referred by clinic staff, that means that the individual will be told about the study by staff and that it is up to the potential subject to volunteer by contacting the research staff on site or by phone. Alternatively, clinic staff will get permission from potentially eligible and interested individuals for the clinic to provide contact information to study staff for study staff to reach out to them for study recruitment by phone or in-person at their clinic or another safe and private location in the community (e.g., library, park, or coffee shop), if feasible. 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. Patients expressing interest in the research will be given detailed study information by the RA and initial screening for study eligibility will be conducted over the phone or in-person at their clinic. Once a patient is screened as likely eligible, the RA will email or standard mail an informed consent form or an electronic link to access the consent form to the individual. Alternatively, the patient can pick up a copy of the consent at their respective clinic. Also, clinic staff will hand out consents to potentially eligible and interested individuals. Once the individual has a copy of the informed consent, the research assistant will review the informed consent and further assess eligibility over the phone or by secure, HIPAA compliant, video meeting or

in-person. Participants will be asked to sign the electronic consent form on Qualtrics or REDCap, mail a signed paper version back to the research assistant, or drop off a signed paper version to their clinic for research staff to pick up. Alternatively, consenting maybe be done in-person. Participants will also keep a copy of the consent for their records.

Participants randomized to the MORE condition will participate in eight, weekly, two-hour online group sessions led by a clinic or study counselor. Each session will contain 5 to 9 participants and will be conducted online through secure video or phone conferencing. If a participant is unable to join the MORE session through video conference due to technical difficulties at the time of the session, the participant will be instructed to join the session by phone or the participant may go to their clinic and a research or clinic staff member can help them access the intervention through their tablet or a computer. 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 their clinic.

All study participants will partake in a total of three interviews lasting up to 120 minutes occurring at baseline, 8-, and 16-weeks (week 1 will be considered the week of the first MORE group session) by video or phone conferencing or in-person. If more than 3 months since baseline survey was administered from start of group (study intervention), clients will be asked to do another baseline survey. 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. Participants will be mailed a urine or saliva test prior to the interview. Alternatively, the patient can pick up urine or saliva test at their respective clinic. At the time of the interview, participants will be instructed on how to administer the test and will be instructed to show the research assistant the results on the video conference. The research assistant will then record the results. If a participant is unable or unwilling to attend a video meeting, a research assistant will conduct a telephone or in-person interview. If the interview is conducted by telephone, the participant will self-report their drug test results, and the fact that it was self-reported will be noted. Alternatively, when feasible, drug screen will be done in-person at their clinic. When drug tests cannot be completed, the reasons will be noted. Results from the most recent drug tests administered by the participants' clinics may also be obtained with participant consent.

All attempts to reach participants to schedule 8 and 16 week follow-up assessments will be tracked. If participant is not able to be reached by phone/email or in-person at clinic, follow-up letter for respective week will be mailed. Participants will also complete cognitive testing (for approx. 30-45 minutes) at baseline and 8-weeks and ecological momentary assessments (EMA) conducted during the entire study period via their own smartphone or computer, or tablet, which will be provided to each participant by study staff. Tablets from T-Mobile will be ordered on an as needed basis and based on t-mobiles availability. EMA participation will require the participant to respond to 3x-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. For those who do not complete their EMA, our research staff will do a timeline follow-back over the phone, video conferencing, or in-person to collect missing drug use data. Weekly EMA completion reports will be reviewed and a phone or in-person TLFB completed, as needed.

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

All study participants will participate in three video, phone conferencing, or in-person visits at baseline, 8-, and 16-weeks. 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 or tablet 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 or recent drug test results will be obtained from the participants' clinic chart. 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. Participants will also be asked to initiate communication via smartphone, computer, or tablet 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 study is expected to take two years. Each subject will participate in the study for a total of 16-weeks.

D. *Describe any primary and secondary study or safety endpoints*

- Primary Outcome: time until opioid relapse
- Secondary Outcomes: opioid abstinence, days of drug use, MMT adherence, craving, pain symptoms, and emotional distress

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

With 1.5 years of subject accrual and an additional follow-up of 16 weeks after the accrual interval, our study needs 47 subjects per group to test a hazard ratio of 0.55 when comparing MORE to TAU, with 80% power and alpha=5% (two-sided). To account for attrition, we will recruit up to 92 subjects per group (a total of 184 subjects at a 1:1 ratio for MORE vs. TAU).

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 on video or phone conference. 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.[6] 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; during periods of social distancing or as clients progress through the program and remain abstinent from drugs, they can "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. During periods of social distancing, these individual or group sessions may be remote, through video conference or phone. 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 (whether in-person or remotely), will be documented for all study participants and entered as covariates in the analyses.

B. Dependent Variables or Outcome Measures

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 (primary outcome)
- Opioid abstinence
- 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

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 at baseline and each follow-up time point (8- 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. Participants will be mailed a urine or saliva test prior to the interview. Alternatively, the patient can pick up urine or saliva test at their respective clinic. If feasible, drug screen may be done in-person. At the time of the interview, participants will be instructed on how to administer the test and will be instructed to show the research assistant the results on the video conference. The research assistant will then record the results. If participants are unable or unwilling to attend a video research appointment, a research assistant will conduct an interview over the phone and participant will self-report the drug screen results. The fact that drug screen results are self-reported will be noted. Alternatively, if feasible, the drug screen may be done in-person. All results (positive or negative) be will be recorded in the research database that will only be identified with participant's study ID and not the participant's name. Drug test results will not be shared with anyone, including the participant's clinic, without written consent from the participant. With participant consent, the results of the most recent drug tests conducted by the patients' clinics may be obtained from the patients' charts.

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

The sample will be collected by the participant and results read by research staff 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.

C. *Who will process the specimens?*
Participants will be mailed a urine or saliva test prior to the interview. Alternatively, the patient can pick up urine or saliva test at their respective clinic. At the time of the interview, participants will be instructed on how to administer the test and will be instructed to show the research assistant the results on the video conference. The research assistant will then record the results. If participants are unable or unwilling to attend a video research appointment, a research assistant will conduct an interview over the phone and participant will self-report the drug screen results. Alternatively a drug screen can be done in-person. In this case, the participant will collect the specimen and the research staff will read the results directly, in person.

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 video, phone interview, or in-person using standardized measures conducted at baseline and 8- and 16-weeks. Cognitive testing data will be collected at baseline and 8-weeks. If the research assessments are conducted over the phone, drug screen results will be recorded as self-reported. Additionally, subjects will engage in twice-daily EMA assessments of approximately 3-5 minutes each for 16-weeks. For 16-weeks, subjects will also initiate EMA communications to report lapses or serious cravings, which will also last for under 5 minutes. For those who do not complete their EMA, our research staff will do a timeline follow-back over the phone or video conferencing to collect missing EMA drug use data. EMA completion reports will be reviewed, weekly, and participants will be contacted, as needed, to collect missing daily drug use data.

- **Location**

The assessments and drug screens will take place via video/online, phone interview, at their clinic, or at another safe and private location in the community (e.g., library, park, or coffee shop).

- **Procedures for Audio and Visual Recording**

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

B. Study Instruments

- 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 Gracely Pain scale[7]

Assessment of additional secondary outcome and other relevant measures that could mediate or moderate outcomes are described below:

Ecological Momentary Assessmenet (EMA) data collection (ongoing from baseline to 16 weeks). The EMA and other survey data will be programmed as a REDCap or Qualtrics survey delivered over a password-protected smart phone, computer, or tablet that will not store any data. REDCap and Qualtrics are 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, 3x 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 early in the day and one will be scheduled in the evening. The random probes will be generated by an algorithm in REDCap or Qualtrics 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/tablets, respond to the prompts, and provide event contingent data. Research staff will provide instructions about how to use the phone/tablet and practice using the phone/tablet with participants until they are capable of using it.

Data will be received by the REDCAP or Qualtrics system. Data access between the REDCap and Qualtrics databases and the web servers aew encrypted and restricted to a monitored port. All REDCap and Qualtrics data, which is displayed or captured by the user interface, is encrypted for security. Within REDCap and Qualtircis all data transactions including inserts, updates, deletions, import/export and reporting are logged. The EMA system in this study deployed via REDCap and Qualtrics will reside in a HIPAA compliant protected space. The REDCap and Qualtrics 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 or Qualtrics 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.

EMA completion reports will be reviewed, weekly, and, as needed (at a maximum weekly), we will conduct a timeline follow-back[9] 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.

Substance use history (Baseline). We will use the PhenX Toolkit-Substance Abuse and Addictions Core Tier 1 Collection[8] 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- and 16-- weeks). 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). Participants will also be asked about overall number of days of use in the past 30 with questions based on PhenX Toolkit-Substance Abuse and Addictions Core Tier 1 Collection. For those prescribed opioids for pain, misuse will be assessed with the Current Opioid Misuse Measure. Drug test results conducted by the clinic during the study period will be obtained from participants' clinic charts. We will combine self-reports 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- and 16-- weeks). Opioid and other drug craving will be assessed with an adapted version of the Penn Alcohol Craving Scale (PACS)[10] 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,[11] and adapted versions have been used in trials of mindfulness-based interventions for substance use.[12] The Craving Suppression Scale is a 17 –item measure that assesses how individuals cope with craving

Pain (Baseline, 8- and 16-- weeks). For study eligibility, pain intensity will be assessed at baseline only with Gracely Box Scale,[13] 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[7] (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- and 16-- weeks). Pain-related functional interference will be assessed with the pain interference subscale of the BPI[7] (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- 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[14] (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,[14] and have been shown to mediate the therapeutic effects of mindfulness training on chronic pain.[15]

Nonreactivity (Baseline, 8- and 16-- weeks). Nonreactivity to distressing thoughts and emotions will be measured with the Five Facet Mindfulness Questionnaire.[16] 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.[15]

Reappraisal (Baseline, 8- and 16-- weeks). Reappraisal will be measured with the positive reappraisal subscale of the Cognitive Emotion Regulation Questionnaire (CERQ),[17] an internally-consistent subscale ($\alpha = .85$) 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,[17] and changes in CERQ reappraisal scores mediated the stress-reductive effects of mindfulness.[18] 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- and 16-- weeks). We will assess positive and negative affect with the valid and reliable Positive and Negative Affect Schedule (PANAS).[19] 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). If cognitive functioning, current psychosis, and suicidality is questionable based on information provided by clinic staff, patient history, or research staff observation, to determine study eligibility, cognitive impairment will be assessed with the Mini Mental Status Exam (MMSE),[20] psychosis will be assessed with the Structured Clinical Interview for DSM-V (SCID) Psychotic screen,[21] and suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS). The Mini-Mental Status Exam, 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 C-SSRS is a five-item reliably and valid measure that assesses suicidal ideation, plans, and intent.

Mental health history (Baseline), trauma (baseline, 8-weeks, and 16-weeks) 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. Trauma history will be assessed with the Brief Trauma Questionnaire (BTQ).[23,24] The BTQ is a 10-item self-report questionnaire that assesses traumatic experiences. At each research visit, symptoms of depression and anxiety will be evaluated with the Center for Epidemiologic Depress Scale and the Beck Anxiety Inventory.[25]

Physical health history (Baseline) and symptoms (Baseline, 8- and 16-- weeks) and medication (Baseline, 8- and 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).[26] The reliability and validity of this self-report scale that measures overall health and ability to complete daily activities has been shown. Current pain and other medication (prescribed and over the counter) will be assessed at each research visit.

Savoring (Baseline, 8- and 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 or the Momentary Savoring Scale,[27] which assesses the propensity to focus on the moment as a means of intensifying positive experience from naturally rewarding events.

Mindfulness practice. In addition to collecting EMA data we will assess mindfulness practice with the timeline follow-back. The timeline follow-back is a reliable and valid measure where participants are asked to recall and record events within a specified time period on a calendar.

MMT dose, MMT days of treatment, MMT services. This information will be abstracted from participants' clinic charts, with participants' consent.

The following cognitive tasks will be completed on a laptop computer or tablet. The online tasks will be administered 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 (=no go).[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/tablet, 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. Timeline	Year 1				Year 2			
Quarter	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Protocol finalizing and staff training								
Recruitment								
Intervention period								
Follow-up data collection								
Data analyses, manuscript preparation								

2.0 Project Management

2.1 Research Staff and Qualifications

Dr. Nina Cooperman, the Principal 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.

University of Utah, Center on Mindfulness and Integrative Health Intervention Development. The Center has four 12' X 10' laboratory/clinical interview-observation suites with one-way mirrors, "bug in the ear" wireless audio technology, and audio/video recording capacity for behavioral observation/coding at the College of Social Work.

This laboratory space houses BIOPAC MP150 psychophysiology data acquisition units, actiCHAMP EEG systems, Eyelink eye trackers, computers with stimulus presentation software, and additional computers for offline data processing of psychophysiological and cognitive-task data.The center offices have two desktop computers (with videoconferencing capability), three laptop computers, two printers, desks, chairs, and locking file cabinets, is located at the Center on Mindfulness and Integrative Health Intervention Development at the College of Social Work. Two high performance computers are dedicated for psychophysiological and cognitive-task data processing. Computers are loaded with Acqknowledge 4.1 and Kubios 2.0 psychophysiological data processing software. Copy machines, fax machines, and telephones with conference calling capabilities are also available at the CSW. The Center on Mindfulness and Integrative Health Intervention Development has two 32-channel actiCHAMP EEG systems, two Eyelink eye trackers, and a BIOPAC MP150 psychophysiology data acquisition unit, with the following amplifiers and corresponding electrodes/signal transducers: electrocardiogram, galvanic skin response, electromyogram (X 3), respiration, and skin temperature.

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, if necessary.

Burlington Comprehensive Counseling (under the same leadership as NBCC) 75 Washington Street, Mount Holly, NJ 08060. Burlington Comprehensive Counseling provides comprehensive, evidence-based, integrated mental health and substance abuse treatment services. Services are individualized and provided in an outpatient setting for prevention, early intervention, and treatment of people with mental health, substance use and/or co-occurring disorders. Program provides access to substance abuse and mental health services addressing the bio-psycho-social consequences associated with substance use and dependence.

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.

Jersey Shore Addiction Services (JSAS) Healthcare, Inc. JSAS HealthCare, Inc. is a private, non-profit agency that provides comprehensive outpatient substance abuse treatment. Additional services provided to patients include: perinatal and neonatal services; HIV counseling and testing, HIV Early Intervention and medical treatment, and case management. JSAS HealthCare, Inc. currently occupies 12,400 square feet of professional space in Neptune, New Jersey. They have a total census of approximately 700 patients in their methadone maintenance treatment

program, and enroll approximately 500 patients per year. Group counseling and office space is available at JSAS for MORE intervention groups and research interviews, if necessary. JSAS receives State Targeted Response funds to expand their medication assisted treatment (MAT) services.

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. Procedure guides (e.g.,interview checklists) 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, and the University of Utah, 201 Presidents Cir, Salt Lake City, UT 84112 (for data analyses only). In addition, subjects will be recruited from the New Brunswick Counseling Center (NBCC), 320 Suydam St., New Brunswick, NJ 08901, NBCC 2nd site Burlington Comprehensive Counseling, 75 Washington St, Mt. Holly, NJ 08060, the Lennard Clinic, 61 Frelinghuysen Ave, Newark, NJ 07114 and 850 Woodruff Lane Elizabeth, NJ 07201, and Jersey Shore Addiction Services, 685 Neptune Blvd, Neptune City, NJ 07753.

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

Up to 184 participants will be recruited from the New Brunswick Counseling Center (NBCC), Burlington Comprehensive Counseling, the Lennard Clinic, Jersey Shore Addiction Services (JSAS). MMT clinic staff will be asked to refer appropriate patients to the study. Clinic patients who are interested and potentially

eligible for the study will be provided with the study phone number to reach the research staff. Alternatively, clinic staff will get permission from potentially eligible and interested individuals for the clinic to provide contact information to study staff for study staff to reach out to them for study recruitment by phone. Clinic staff will be informed of the eligibility criteria for the study and will be asked to not refer patients that they know are actively suicidal or psychotic. Also, flyers will be posted in dosing areas and the waiting rooms of all participating clinics. Research assistants (RAs) may recruit patients in clinic waiting areas, if and when feasible. Patients expressing interest in the research will be given detailed study information by the RA and initial screening for study eligibility will be conducted over the phone, through video conference, or in-person.

B. Source of Subjects

Participants will be recruited from the New Brunswick Counseling Center (NBCC), Burlington Comprehensive Counseling, the Lennard Clinic, and Jersey Shore Addiction Services.

C. Method to Identify Potential Subjects

Clinic staff will be informed of the eligibility criteria for the study and will be asked to not refer patients that they know are actively suicidal or psychotic. Patients expressing interest in the research will be given detailed study information by the RA and initial screening for study eligibility will be conducted over the phone, through video conference, or in-person. Also, flyers will be posted in dosing areas and the waiting rooms of all participating clinics.

D. Subject Screening

An initial eligibility screen will be conducted over the phone. Based on the initial screening, if further screening measures are needed, they will be done after the patient consent.

- **Inclusion Criteria**

Only individuals meeting all of the inclusion criteria at baseline will be able to participate in the study. Subjects must be age 18 or older, English-speaking, currently on methadone, and have been experiencing non-malignant pain with an intensity level of 8 or higher on the Gracely Box Scale[13] or pain ≥3 out of 10 on the BPI average pain severity item for 3 months or longer.

- **Exclusion Criteria**

Subjects will be excluded from participation if they do not meet the inclusion criteria above exhibit cognitive impairment (based on observation, history, clinician feedback, or score <24 on the Mini Mental Status Exam[19]) or psychosis (based on observation, history, clinician feedback, or positive SCID Psychotic Screen[20]), are at suicidal risk (based on observation, history, clinician feedback, or positive score on C-SSRS), unable to attend group sessions for any reason, or participated in formal mindfulness training within the past 5 years.

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), Burlington Comprehensive Counseling, JSAS, 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 10-18 participants (depending on speed of recruitment) at each site to TAU or MORE with block randomization. Once we recruit at least 10 to 18 participants at a particular clinic, we will randomize participants to MORE or TAU, and the MORE group will begin.

4.4 Secondary Subjects

N/A

4.5 Number of Subjects

A. Total Number of Subjects

Total number of subjects to be accrued is up to 184.

B. Total Number of Subjects If Multicenter Study

N/A

C. Require Number of Subjects to Complete Research

N/A

E. Feasibility of Recruiting

NBCC serves approximately 500 MMT clients per year, the Lennard Clinic serves approximately 1000 MMT clients at two sites, and JSAS serves about 700. 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. Additional sites will be added to the study if necessary if recruitment targets are not being met.

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**

Once a patient is screened as likely eligible, the RA will email or standard mail an informed consent form or send an electronic link to access the consent form to the individual. Alternatively, the patient can pick up a copy of the consent at their respective clinic. Once the individual has a copy of the informed consent, the research assistant will review the informed consent and further assess eligibility over the phone, by secure, HIPAA compliant, video meeting, or in-person. Along with the informed study consent, the participant will be asked to sign two releases of

information--one for the clinic to release information to the RWJMS study team and one for the RWJMS study team to release information relevant to their care at the clinic.

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. Participants will be asked to sign the consent form and mail it back to the research assistant to be kept filed or sign electronically through Qualtrics or REDCap. Alternatively, the patient can drop their consent at their respective clinic. Participants will also keep a copy of the consent for their records. 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 assessment and drug screen. At each of the baseline and 8-week assessments, participants will also receive a $20 gift card for completing the cognitive assessments. If more than 3 months since baseline survey was administered from start of group (study intervention), clients will be asked to do another baseline survey and will be provided an additional $30 gift card. Also, participants will receive approximately 25¢ for completing each of 3x daily EMA assessments (e.g., $20 for 10-25%, $30 for 26-50%, $40 for completing 51-85%, and $50 for completing 86-100% of EMA assessments). 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 online 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. Gift cards will be standard mailed or emailed to participants.

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. If an incentive is sent via mail, a copy of the envelope with patient address on it, the mail tracking number, and photocopy of the gift card sent will be kept in the patient file.

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. 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 (through a video conference, phone meeting, or in-person) to determine if the participant is safe 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 or video interaction, Dr. Cooperman or Dr. Williams will be available by phone or in-person to contact the participant for assessment or help the research staff 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 or password protected 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

have 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 online 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 or a HIPAA compliant video/phone meeting 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

Study investigators and the research staff will have access to all data stored on stored in Qualtrics, REDCap, and Box. All of these programs are HIPAA compliant and secure programs that allow storage and management of data that will be accessible only to study investigators and research staff at Rutgers and Utah. All study data will be anonymous and will contain no personal identifiers. Audio or video files will not have participants' names on them and will be shared only among Utah and Rutgers research investigators and staff using Office 365 OneDrive or Box, HIPAA compliant, secure systems.

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.*

Data Analyses. Analyses will be conducted on an intent-to-treat basis. Adjustment for multiple comparisons using Bonferroni-Holm procedure[28] will be applied in outcome analyses. We will first examine baseline between-group differences on demographic and other key variables - those that show a difference of p<.10 will be entered as covariates in the analyses below. Given that this RCT occurs within a naturalistic treatment context (i.e. MMT programs in which study participants will also be receiving usual care), significant group differences in usual treatment (e.g., methadone dose or number of TAU psychotherapy sessions) will be treated as covariates. For all analyses specified below, we will perform sensitivity analyses to test response differences or clustering by site, group cohort, and therapist either as fixed or random effects and assess the robustness of results when accounting for these site and therapist effects. To handle **missing data**, we will conduct a series of sensitivity analyses using pattern-mixture (PM) approaches,[29-31] assuming missing-at-random (MAR),[32] not-missing-at-random (nMAR) and/or a mix of nMAR and MAR, to assess plausible treatment effects in the presence of missing data. Other PM approaches such as control-based pattern imputation approach or the tipping-point approach will also be considered.[33] The missing data handling strategy will be carefully selected depending on the distributions, type, and mechanism of missing data (informative vs. non-informative).

AIM 1 Analyses.

Hypothesis 1.1. (**Primary Outcome**) MORE will result in longer duration of time to first opioid lapse and MMT dropout than TAU. We will use survival analysis (Kaplan Meier curves and marginal model analysis for multivariate survival data)[34] to test effects of MORE vs. TAU on time until first opioid lapse and MMT dropout– evidenced either on EMA, Timeline Follow-Back, urinalysis or medical records (whichever is first). Survival analysis will be run once, at 16 weeks post-baseline. Clustering within cohort will be adjusted in the multivariate marginal model analysis.[34] We will estimate the hazard ratios of opioid lapse and MMT dropout when comparing MORE with TAU, controlling for covariates.

Hypotheses 1.2 and 1.3 (**Secondary Outcomes**). MORE will result in more days of opioid abstinence (or less days of use) and a higher rate of biochemically-verified abstinence over time than TAU. Generalized linear mixed model (GLMM)[35] repeated measures analysis will be used. Specifically, identity link will be used for "number of abstinent days" as the dependent variable, and logit link will be used for "opioid abstinence (yes/no via urinalysis)" as the dependent variable. Days of use/abstinence will be assessed via EMA, number of drug use days since last visit and past 30 days, and the Timeline Follow-Back. In cases of conflicting findings across data sources, we will assume the highest number of days of use or lowest number of abstinent days recorded for that period. Analyses will include group (MORE vs. TAU), time, and group by time interactions as the fixed effects independent variables. Correlations among repeated measures and among subjects within cohorts will be modeled using nested random effects. Potential confounders that meet the $p<0.10$ criterion stated above will be entered as covariates. Linear contrasts will be constructed to test between-group differences in "days of use" or "days of abstinence" separately at each timepoint. In comparing days of use, if a substantial proportion of subjects do not use opioids, resulting in excessive zero days of use, we will use a two-part logistic/linear analysis model.[36,37]

Hypotheses 1.4 (**Secondary Outcomes**). MORE will result in more days of MMT and greater decreases in pain severity, pain interference, days of non-opioid drug use, and emotional distress over time than TAU. We will use GLMM to compare days of MMT, pain severity and interference scores, days of non-opioid drug use, and emotional distress among the treatment groups, using the same analytic strategy described above.[35]

AIM 2 Analyses. Mediational analysis. To test whether the three mediators specified in Aim 2 statistically mediate the effect of treatment on changes in days of opioid use over time, we will conduct a multivariate path analysis via a latent growth curve framework conducted in structural equation modeling software (i.e., MPlus) according to established guidelines[38] evaluating 3 regression paths for each mediator: A) *'a'* path between treatment indicator and pre-post treatment change in the mediator (e.g., savoring); B) the *'b'* path between pre-post treatment change in the mediator (e.g., savoring) and the latent slope (change) of the outcome (e.g., opioid use); and C) the *'c'* path between treatment indicator and the latent slope of the outcome (e.g., opioid use). We will emulate similar multivariate analyses from published studies of meditation interventions[39,40] by testing treatment effects on the latent slope of changes in days of drug use over time as mediated by changes in proposed mechanisms. We will test mediation by evaluating the significance of the joint product of the *a* and *b* paths, with bootstrapping used to test the significance of the indirect effect. A similar model will be estimated for changes in pain severity. Path models will be corrected for multiple comparisons. Simultaneous estimation of mediational effects from all three mediators to days of drug use and pain will allow us to determine unique effects of the core therapeutic mechanisms of MORE (mindfulness, reappraisal, savoring) – representing one of the most comprehensive mediation modeling attempts of the MORE intervention research program to date.

Exploratory, temporally-dynamic analysis of the effects of mindfulness practice on EMA measures of craving, affect, and pain. Growth curve analyses and multivariate autoregressive latent trajectory analyses (m-ALT) of EMA data will examine antecedents and consequences of drug use as well as the impact of skill practice on craving and drug use. EMA data will yield granular analyses of process variables (mindfulness, reappraisal, and savoring practice) and quantify how skill use dynamically co-varies with pain, craving, and drug use during and after treatment. Lagged growth curve analyses[41] will examine treatment and practice effects on: A) trajectories of positive/negative affect, craving, and pain; B) relationships among these variables over time; and C) how trajectories in affect, craving, and pain predict drug use in separate m-ALT models.[42] m-ALT models, like ones published by Dr. Garland,[43] will estimate cross-lagged and auto-regressive effects, as well as latent intercept and growth factors, among EMA variables, conditioned on a treatment group variable and measures of mindfulness, reappraisal, and savoring practice. EMA models will be corrected for multiple comparisons.

AIM 3 Analyses. To test gender as a moderator of treatment response, we will include all main effects and all two-way, and three-way interactions of gender, treatment, and time in GLMM analysis models, and all main effects and the two-way interaction of gender and treatment in the marginal multivariate survival analysis models. A significant gender x treatment x time interaction in GLMM models, tested by F test, indicates that treatment effect on changes in outcomes over time differ by gender. A significant gender x treatment interaction in survival models, tested by Wald test, indicates that treatment effect on time to event differs by gender. In GLMM analysis, gender differences on outcomes at 8, 16, 24, and 52 weeks will be estimated and tested using linear contrasts. Other potential moderators (e.g., race, income, mental health, trauma, and MMT phase) will be explored using similar approaches as exploratory analyses.

C11. Outcomes and Future Directions. We expect to establish the efficacy of an innovative intervention that can enhance MAT by supporting chronic pain management and MMT adherence while preventing drug use and opioid relapse. Results from this study will inform the development of services in New Jersey and other states seeking efficacious strategies to combat the opioid epidemic. If this study demonstrates MORE's efficacy as an adjunct to MMT, we will follow this study with a Stage IV implementation/dissemination study to enhance the rapidity and fidelity of uptake of the intervention into standard of care for persons with OUD.

B. *Provide a power analysis. (As applicable, e.g. quantitative research)*

We powered the R33 study based on data from prior research. We used a study of an MBI for substance users,[4] which showed that the hazard ratio of relapse to drug use for the intervention compared to TAU was 0.46. We thus assumed a similar, but more conservative hazard ratio of relapse to opioid use of MORE compared to TAU at about 0.55. (We are using a slightly more conservative hazard ratio than in the original application due to the increased power obtained by reducing the number of treatment conditions from three to two.) We also assumed that the median relapse time to opioid use is 99 days, based on a prior study of relapse to drug use in a general MMT population.[5] With 1.5 years of subject accrual and an additional follow-up of 16 weeks after the accrual interval, our study needs 47 subjects per group to test a hazard ratio of 0.55 when comparing MORE to TAU, with 80% power and alpha=5% (two-sided). To account for attrition, we will recruit 85 subjects per group (a total of 184 subjects at a 1:1 ratio for MORE vs. TAU).

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, protocols 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 collected 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. Data will be entered directly into a secure Qualtircs or REDCap databases. 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 6 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. 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 (about 2-years 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, JSAS, 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 every six months 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. 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. However, the Investigators and the DSMB will monitor and evaluate the safety of participants throughout the course of the research study. The Independent Monitors will advise the Investigators and IRB as to whether the protocol should continue as scheduled, undergo a modification, or halt study activities due to a finding from the monitoring process. An interim analysis of the data may be conducted when 50% of the sample is accrued. If the results show statistically overwhelming significant differences between groups, the DSMB will consider the clinical meaning of the results and determine whether the study should be stopped.

F. Schedule of Review of Cumulative Data

The frequency or periodicity of review of cumulative data.

Under supervision of the investigators, a Research Assistant or the Study Coordinator 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, if necessary, 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

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