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Protocol Cover Page

Official Title: CoMBAT Opioid Use Disorder: A Pilot RCT of a Combined Medication and Behavioral Activation Treatment for People Living with Opioid Use Disorder.

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CoMBAT OUD: Protocol

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BACKGROUND

Opioid use disorder is a chronic, relapsing disease and a major source of morbidity and mortality in the U.S.[1-8] Medications for Opioid Use Disorder (MOUD), such as methadone and buprenorphine, has been shown to reduce opioid use across diverse subpopulations of individuals living with opioid use disorder.[9,10] Despite the benefits of MOUD initiation for individuals living with opioid use disorder, research finds that MOUD maintenance is often suboptimal.[11]

One risk factor for MOUD discontinuation and opioid use relapse is depression. The prevalence of diagnosed depression among individuals with opioid use disorder ranged from 20% to 61% across studies.[12-15] Depression can occur due to changes in brain chemistry from long-term opioid use and withdrawal.[16] Depressed people may also use opioids to alleviate their psychiatric symptoms.[17,18] Depression can also arise from the stress of coping with the stigma of opioid use as well as the stress of navigating the economic instability, poor health, and relationship difficulties (e.g., estrangement from family, lack of reliable friends, death of friends, social isolation).[19] Further, people with comorbid depression and opioid use disorder are significantly more likely to drop out of treatment and relapse than those who are not depressed.[20-22] An intervention that integrates MOUD with an evidence-based behavioral therapy to improve mood and navigate life challenges could lead to greater MOUD retention and boost the effects of MOUD in preventing opioid use relapse.

Behavioral activation (BA) is an evidence-based behavioral treatment[23-26] that has been shown to be effective in treating comorbid depression and substance use for diverse samples with smoking, alcohol, stimulant, and poly-substance abuse.[27-32] The conceptual model underlying BA posits that self-defeating behaviors, such as substance use and the behavioral avoidance of health-promoting resources, serve the function of coping with negative feelings and make individuals feel better in the short-run, but ultimately exacerbate depression through a process of negative reinforcement. BA utilizes therapeutic techniques that help patients gradually increase goal-directed, potentially rewarding and pleasurable activities while decreasing the intensity and frequency of adverse events and consequences in order to improve mood. Despite the success of BA in other populations, to the best of our knowledge, no published studies have examined the combined efficacy of BA and MOUD to improve retention in care and reduce opioid use for individuals living with opioid use disorder in the U.S. Given that BA utilizes strategies that can support individuals in coping with stigma and addressing life challenges—skills that are greatly needed for populations living with opioid use disorder—pairing BA and MOUD could help to ensure continued engagement in care and long term reductions in opioid use for this population.

The ultimate goal of this research is to develop a fully efficacious intervention that combines BA and MOUD to improve depressed mood and enhance behavioral skills to navigate life challenges in order to maintain

engagement in MOUD care and decrease opioid use. In order to accomplish this goal, we will enroll up to 50 individuals currently being treated with MOUD for opioid use disorder in a pilot randomized controlled trial (RCT) testing the CoMBAT (Combined Medication and Behavioral Activation Treatment) intervention against Treatment-As-Usual. This study will provide the requisite data to inform future efficacy testing of the intervention in a large-scale efficacy trial, with the ultimate goal of developing an efficacious intervention to address the opioid epidemic.

SPECIFIC AIMS AND STUDY OBJECTIVES

This study is a junior investigator project funded through a larger parent COBRE award focused on providing training to junior investigators and supporting innovative research to better understand and ameliorate the opioid epidemic. Following the NIH Stage Model of psychosocial treatment development and testing,[33] this study seeks to determine the feasibility of study procedures, enhance participant acceptability, and provide preliminary efficacy data to support the submission of a full-scale, NIH R01 efficacy trial. Our central hypothesis is that BA will improve depressed mood by helping individuals re-learn how to engage in pleasurable non-drug using aspects of their life, and develop the behavioral skills to cope with stigma and better navigate life challenges, which will facilitate sustained engagement in MOUD care and long-term reductions in opioid use.

Thus, we will enroll up to 50 individuals currently being treated with MOUD for opioid use disorder in a pilot randomized controlled trial (RCT) of the CoMBAT (Combined Medication and Behavioral Activation Treatment) intervention. Prior to randomization, participants will receive two sessions of health navigation with standard substance abuse counseling. Participants will then be equally randomized to either: 1) the 8-session CoMBAT intervention; or 2) MOUD alone (treatment-as-usual; TAU).

The Specific Aims are as follows:

> **AIM 1.** To evaluate, in a two-arm pilot RCT, the preliminary efficacy of CoMBAT vs. TAU for individuals receiving MOUD for opioid use disorder on the primary outcome: days of MOUD use (including care drop-out) assessed via self-report and secondary outcomes: self-reported days of opioid use; opioid-negative urine-over follow up; and self-reported intervention feasibility and acceptability at follow-up (assessed via qualitative exit interview).
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> **AIM 2.** To examine the degree to which treatment outcomes are: 2a) mediated by decreases in depressed mood and increases in pleasurable activities, stigma coping skills, other-substance use, and mental health conditions; physical health (e.g., HIV, Hepatitis C, and other infectious disease and related behaviors) and psychosocial factors (e.g., trauma, social support, criminal justice system involvement).

CONTENT OF THE COMBAT INTERVENTION

The study involves the delivery of 2 health navigation with standard substance abuse counseling sessions (all participants) and the 8-session CoMBAT intervention (those randomized to the intervention only) together with the MOUD participants are already receiving in the community. To facilitate ready dissemination and application by community substance abuse counselors, we will utilize a manualized protocol that incorporates evidence-based strategies to decrease depressive symptoms, cope with stigma, and navigate life challenges in order to facilitate retention in MOUD care and reductions in opioid use for individuals receiving MOUD for opioid use disorder. All sessions take ~50 minutes and will be delivered by a master's-level therapist, as this is the most common background for community substance abuse counselors. The therapist will be trained and supervised by Drs. Pantalone and Nelson.

MOUD Treatment (All participants). Participants will receive standard MOUD care delivered by community providers. Only those who are currently on MOUD will be eligible for the study (see *Eligibility Criteria*).

Health Navigation & Substance Abuse Counseling (All Participants). Prior to randomization, all participants will receive 2 health navigation sessions with standard substance abuse counseling that uses motivational interviewing[58] to facilitate engagement in MOUD care and prevent opioid use.

> ***Substance abuse counseling & MOUD navigation 1.*** This session will largely rely on standard substance abuse counseling strategies used by community treatment centers. The session will act as an intake to lay the groundwork for the future sessions. To encourage a Q&A discussion, participants will receive a fact sheet on the immediate and long-term harms of opioid use. Substance abuse history and plans for relapse prevention (e.g., motivation or skills) will be discussed. During this visit, the therapist will help the participant to identify and navigate barriers to remaining engaged in MOUD and provide support to overcome challenges. Throughout the visit, motivational interviewing, a standard counseling approach,[58] will be used to assist in formalizing an individualized behavioral skills plan.
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> ***Substance abuse counseling & MOUD navigation 2.*** This session will build on the information and behavioral skills for opioid use prevention discussed in the first navigation session. Substance abuse history and barriers to relapse prevention and MOUD engagement will be discussed. Motivational interviewing will be used to encourage engagement in the individualized behavioral skills plan developed in the prior session.

CoMBAT: Combined Medication and Behavioral Activation Therapy (Intervention Arm Only). The following intervention sessions are only provided to participants randomized to the experimental condition. Participants in this arm receive 8 sessions (detailed below) that integrate behavioral activation therapy and substance abuse counseling together with the standard MOUD care they are receiving in the community.

The sessions focus on behavioral activation: re-learning how to enjoy previously enjoyed activities without the use of opioids and the continued integration of substance abuse counseling to encourage sustained reductions in opioid use and retention in MOUD care. Each of the sessions begins with an evaluation and discussion of opioid use and medication taking, a review of the skills learned in the previous sessions that target the behavioral skill aspects of opioid use reduction, and an assessment of mood over the past week.

> ***Introduction to behavioral activation with psychoeducation & motivational interviewing (1 session).*** A major focus of this session is to lay the groundwork for the aspects of the intervention that target re-activating one's self in activities that do not involve opioid use. This involves gathering and presenting information in a way that promotes credibility and confidence in the treatment, which is associated with better treatment outcomes for mental health problems.[59] The therapist will use motivational interviewing to examine the impact of opioid use on the patient's life including changes in mood and decreased feelings of enjoyment and mastery that are associated with opioid use and the relationship between these constructs. The therapist provides an introduction to behavioral activation as a means to interrupt the cycle of use. Lastly, pros and cons of non-use are discussed and motivational interviewing is used to help participants move to a higher level of readiness to change. This process is tailored to each participant using BA-specific intervention techniques.
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> ***Behavioral activation (8 sessions).*** Our conceptual model suggests that disengagement in MOUD care and opioid use are driven by depressive symptoms which derive from stigma, life challenges, and the inability to find pleasure from previously enjoyed activities. The core component of these sessions is behavioral activation, which entails helping participants to become re-engaged in their lives as a means to elevate mood. By elevating mood, participants are theorized to be better able to stay engaged in care and abstain from opioid use. In these BA sessions, participants learn to identify times and situations when they are more and less likely to feel enjoyment from activities that do and do not involve opioid use. With the use of a positive events checklist, participants identify activities that involve pleasure or mastery that they used to participate in before using opioids. Through weekly sessions, participants are encouraged to re-try positive events that they previously enjoyed, and problem-solve with the therapist ways to re-

engage in such activities. Participants are then set up with mood and activity monitoring procedures to track re-engagement in such events. These sessions provide ongoing monitoring of engagement in pleasurable activities, problem-solving the continued integration of activities, review of potential additional activities, and reducing barriers to behavioral activation.

Throughout the behavioral activation sessions, participants receive problem-solving training[60] that involves teaching participants how to cope with barriers to MOUD engagement and opioid use triggers by breaking down overwhelming tasks into manageable steps. The goal of these strategies is to reduce behavioral avoidance of care and other health-promoting resources (e.g., social support) and build the self-efficacy to navigate life challenges such as securing and/or maintaining employment and housing, and navigating relationships. Problem-solving training also helps participants to manage the challenges of continued engagement in MOUD care including getting to scheduled appointments in order to receive treatment. Additional problem-solving techniques include training in how to define and approach problems, generate alternative solutions, make effective decisions, and implement optimal solutions. These tactics are commonly used for the treatment of depression[61] and have specific application to MOUD maintenance and the treatment of opioid use disorder. Specifically, these strategies may be particularly helpful in breaking the maladaptive and self-perpetuating cycle of opioid use in response to wanting to improve one's mood.

Relapse prevention (1 session). In the final session, the therapist reviews the previous sessions and skills with the participant and develops a plan for MOUD maintenance and sustained engagement in enjoyable life activities that do not involve the use of opioids as a means to encourage long-term reductions in opioid use. This session involves differentiating a lapse from a relapse, anticipating difficult or stressful situations that may triggers lapses, and encouraging ways to utilize learned skills to maintain gains. In general, the focus of the final session is to transition participants to be their own therapist.

Fidelity monitoring. Fidelity monitoring of the intervention will take into account therapist adherence.[63] A rating checklist for therapist adherence will be used to ensure that specific components of the modules of treatment are delivered. At least 10% of the sessions and at least one session per week will be reviewed for clinical supervision and will have the rating checklist applied.

STUDY VISITS

Participant will be followed for a period of 6 months. During this time, they will complete the following study visits:

Baseline. After providing written informed consent, participants will complete a survey that includes an evaluation of MOUD treatment history, opioid use, and potential psychosocial mediators and moderators of the intervention. Participants will also provide a urine sample for rapid toxicology screening. The 5-panel urine drug test cup will screen for the presence of methadone, buprenorphine and 12 other drugs (opiates, fentanyl, oxycodone, cocaine, amphetamines, methamphetamines, ecstasy, barbiturates, benzodiazepines, propoxyphene, marijuana, and phencyclidine).

Health Navigation + Substance Abuse Counseling Sessions. All participants will receive 2 sessions that include MOUD navigation with standard substance abuse counseling to identify and navigate common barriers to MOUD engagement and relapse prevention/ongoing use. At each session, participants will also complete a brief assessment of their MOUD and drug use at each session as well as provide urine for testing the presence of MOUD and 12 other drugs (same test as baseline).

Randomization. After the second health navigation session, participants will be randomized (using a computerized random number generator) to the CoMBAT intervention or the MOUD Treatment-As-Usual (TAU) control arm.

Intervention Arm. In addition to the 2 health navigation and substance abuse counseling sessions, participants randomized to the intervention will receive 8 weekly BA sessions, plus standard MOUD treatment as delivered by their community healthcare provider. Each week, participants will also complete a brief assessment of their MOUD and drug use as well as provide urine for testing the presence of methadone, buprenorphine and 12 other drugs.

Control Arm. Participants randomized to the control will only receive the 2 health navigation and substance abuse counseling sessions and MOUD TAU as delivered by their community healthcare provider. Participants in the control arm will be asked to complete 8 additional weekly assessment visits during which time they will complete a brief assessment of their MOUD and drug use as well as provide urine for testing the presence of MOUD and 12 other drugs. After randomization, participants in the control arm will not receive additional counseling as part of the study.

Follow-up Assessments. Assessments and urine toxicology screening will be conducted at 3- and 6-months post-randomization. A brief qualitative exit interview will also be conducted at the 6-month visit to assess intervention feasibility and acceptability.

Retention. The Research Assistant (RA) will track participant retention. As has been successful in our previous trials with marginalized populations,[28,29] we will collect extensive locator information such as information regarding at least 2 people with whom participants are in regular contact with. We will maintain contact with individuals who discontinue the intervention or who move outside of the study area but are still willing to complete follow-up assessments. We will also use patient health records (see below) to monitor whether participants have discontinued MOUD care in the community. To facilitate retention, we have also budgeted for appropriate financial incentives for participants.

Remote Participation. Individuals who are unable to travel to the study site can complete any visit remotely. Staff members will administer the consent remotely by phone.

> ***Baseline and Follow-Up Visits.*** Following consent, the research staff person will administer the interviewer portion of the survey over the phone. Participants will receive a web-based link for the REDCap, self-administered portion of the survey or they have the option of completing the whole survey over the phone. Urine toxicology kits will be given to participants in-person or sent via mail. Participants will be asked to connect with a study team member via Zoom to show study staff the results of the urine test.
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> ***Weekly Sessions***. Regardless of intervention arm, participants are asked to take a brief weekly survey and provide urine for toxicology screening. Participants completing these study procedures remotely have the option of completing the survey online (via a REDCap link that is sent to them) or over the phone with a study team member. Participants who consent will then complete the weekly assessment over the phone or via a web-based link to the REDCap survey. Urine toxicology kits will be given to participants in-person or sent via mail. Participants will be asked to connect with a study team member via Zoom to show study staff the results of the urine test. Those in the intervention arm, will also be asked to complete their 50 minute counseling session with the therapist over the Zoom platform or by phone if they do not have access to the internet.

STUDY POPULATION AND SETTING

Number of Participants: We aim to enroll up to 50 individuals (25 per arm) who are currently receiving MOUD for opioid use in Massachusetts or Rhode Island and randomize a minimum of 32 participants (16 per arm).

Inclusion/Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
• Age 18 years or older • Initiated MOUD for opioid use >= 30 day prior to screening • Current depressive symptoms • Plans to Rhode Island or Massachusetts for at least 6-months • Able to read, speak, and understand English • Willing and able to provide informed consent	• Does not plan to continue taking MOUD • Unable to provide informed consent due to severe mental or physical illness, or substance intoxication at the time of interview • Discovery of active suicidal ideation at the time of interview • Pregnant and in second or third trimester • Enrolled or due to begin an intensive outpatient treatment program at the time of screening or enrollment

Inclusion/Exclusion Criteria Justification. The criteria were chosen to preserve methodological rigor and internal validity, while being attentive to the need for interventions that generalize to clinical populations. Included are individuals 18 years of age or older. We will include these individuals as opioid dependence is widespread across adult populations. We are studying individuals who initiated MOUD prior to enrollment for the purpose of treating opioid use disorder. While opioid use disorder will be evaluated, it is not an eligibility criterion as a diagnosis of opioid use disorder is a pre-requisite for initiating MOUD. Additionally, we included the 30 days MOUD criterion as treatment guidelines suggest that patients stabilized on these medications can also engage more readily in counseling and other behavioral interventions.[62] Individuals not on MOUD for at least 30 days prior to enrollment will be excluded. All participants must demonstrate symptoms of depression at screening given that depression is a key mediator of the intervention. Notably, participants who are actively seeking or receiving other behavioral substance use treatment services will not be excluded and may continue receiving behavioral treatment throughout the course of their participation in the study (we will track other services participants are receiving and control for these services in analyses). We are currently only including individuals who plan to stay in Rhode Island or Massachusetts for at least 6 months in order to ensure that they can access the behavioral health intervention (if randomized) and participate in at least one follow-up visit. Participation is limited to individuals who read, speak, and understand English since the study assessments and interventions are currently only available in English. Excluded patients are those that are unable to provide informed consent, including those with severe mental illness that require immediate treatment (e.g., active psychotic episode) or with disorders that would limit their ability to participate (e.g., dementia). We will also exclude any individual with active suicidality or any other mental health condition that would prevent them from complying with, or attaining benefit from, the study procedures. These individuals will be referred to other, more intensive mental health treatment options. Since retention could be a concern for women post-pregnancy, we will restrict enrollment to women who report being in the first trimester of their pregnancy, to maximize the potential for the participant to complete the required study procedures before delivery. Finally, intensive outpatients programs (IOP) are a form of intensive treatment that involves multiple days a week of counseling. Since co-enrollment in an IOP could serve as a barrier to retention and limit our ability to detect intervention effects, we will exclude anyone who is currently participating or about to participate in an IOP program.

SCREENING AND CONSENT

Screening.

Cross-Study Pre-Screener: This study will collaborate with the FRESH research team at Brown to recruit participants. Specifically, interested individuals who see the study ads, have an option of calling the study line

or completing the cross-study pre-screener. Interested individuals who are preliminary eligible for the study via the cross-study screener will be contacted by study staff at which time the full screening process will begin.

Study Screener: All screening activities will be conducted by study staff over the phone or in person. Potential participants will be provided with a brief explanation of the study and initial eligibility will be assessed. Participants will be clearly informed that they are under no obligation to participate in the study and that the decision to participate in the study or not will have no effect on their relationship with Brown University or the clinic where they are receiving care. If eligible and interested, participants will be scheduled for a baseline visit during which time, staff will explain the research study in detail, answer any questions, and obtain informed consent. We will maintain detailed eligibility and tracking logs for each stage of the study. All eligibility information will be maintained for the length of the study and destroyed upon completion of the study.

Consent.

Screening Consent. As noted above, participants will partake in a prescreening process. Screening will be conducted over the phone or in person by study staff. Potential participants will be provided with a brief explanation of the study and initial eligibility will be assessed. Participants will be clearly informed that they are under no obligation to participate in the study and that the decision to participate in the study or not will have no effect on their relationship with Brown University or the clinic where they are receiving care. Participants will also be told that the information that they provide during the screening process will maintained as part of the study and destroyed upon completion of the study.

Study Consent. All potential participants will undergo a detailed informed consent process in person, in a private research room. The consent process will be conducted by research staff (i.e., Principal Investigator, Project Director, Therapist, or Research Assistant) who have been fully trained in best practices for conducting informed consent. The PI will provide one-on-one training for all study staff. The informed consent documents are written according to Federal OHRP standards with eighth grade or below reading levels. Study staff (e.g., Principal Investigator, Project Director, and/or Research Assistant) explain all study procedures and answer questions concerning the study and consent process. Study staff will give the participant as much time as needed and will address any questions or concerns they may have. Study staff will ask the participant questions to gauge comprehension. The consent form describes all study procedures, including confidentiality and privacy, information about potential risks, discomforts, benefits of participation, and information regarding who they can contact with further questions.

The form also states that participation is voluntary, that participants may decide not to take part without penalty or loss of any benefit to which they might otherwise be entitled, and that study participation is in no way related to being able to access or continue getting care or services at any participating study site. Participants can refuse to answer any question and can withdraw from the study at any time. If participant choses to withdraw from the study, any medical release forms on file will be destroyed and will not be utilized for future record requests. The PIs, Co-Is, or designee will review all informed consents.

Facilitate Understanding

Once the study is thoroughly explained, the consent form is read and understood, research staff will review the informed consent document to make a formal assessment of participants' decisional capacity and ability to provide consent prior to signing, using a 2-step process. First, the staff member will determine if the person understands the study goals by asking "Can you tell me what this study is about?" In step 2, potential participants will be asked questions designed to assess their capacity to understand, appreciate, reason with, and express a choice about participation in our specific protocol. Potential participants will be enrolled only if they are able to provide clear and correct answers to these items, without prompting or correction. If the staff member feels there is a question about the need for a more formal assessment of the decisional capacity of a potential participant s/he will contact the PI or other senior staff members, who may refer the participant to medical or psychosocial services for evaluation.

Should any study procedures change that impact future participation in the study, currently enrolled participants will be reconsented.

Documentation
Once all study related questions have been answered, and the participant agrees to voluntarily join the study, the participant will be asked to sign (via REDCap) the detailed consent form. Participants will be offered a paper copy of the consent form for their records. All informed consent forms will be reviewed for accuracy as part of the quality control and assurance procedures.

COMPENSATION / REIMBURSEMENT

All participants will receive $40 USD for the baseline visit and $50 USD for each follow-up visit. Participants will receive $10 USD for each the weekly assessment visits they complete. Compensation will be provided at the end of each study visit which will occur at baseline, weekly for 10 weeks, and 3 and 6 months post-randomization for follow-up visits. If a participant chooses to end any visit early, they will still be compensated for the visit. These compensation amount are aligned with behavioral health treatment studies conducted by our team and others and do not place undue influence on study subjects.

POTENTIAL RESEARCH RISKS / DISCOMFORTS TO PARTICIPANTS

There is some risk of participants feeling embarrassed or uncomfortable during this study, such as talking about personal issues, or about behavior related to drugs and alcohol. Participants can refuse to answer any question and can leave a study session early at any time. Participants can request that the researcher refer them to a counselor or other means of psychosocial support.

Questions relating to substance use, depression, and anxiety can be upsetting. Participants may also feel uncomfortable providing urine for drug testing. If they feel unconformable with any study procedures, we ask that they please share their feelings with study staff. As part of the study, participants will have access to qualified counselors who can help them deal with any feelings they may have. Participants are also free to stop participation in this study at any time.

We will take several steps to protect personal information. Although the risk is low, it is possible that personal information may be given to someone who should not have it. If that happens participants could face discrimination, stress and embarrassment. We will ensure participants will be told how we will protect your personal information.

Information risks (e.g., loss of privacy and/or breach of confidentiality). As in any form of human subjects research, there is a risk of breach of confidentiality on the part of study staff or another research participant.

> Likelihood: The likelihood that any additional breaches of confidentiality would occur is minimal, as steps will be taken to guard against this risk (see below).
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> Magnitude. A breach of confidentiality may result in psychological harm to individuals (embarrassment, guilt, stress, etc.) or in social harm, which is considered low magnitude relative to other risks.
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> Protection against information risks. All contact with participants will be made by research staff under explicit guidelines to preserve confidentiality when telephoning, emailing, or mailing information to participants. All staff will undergo rigorous training in maintaining participants' privacy and confidentiality and will be in possession of valid Collaborative Institutional Training Initiative (CITI) certificates.
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> All audio files (intervention sessions and exit interviews) will be kept confidential and stored in a locked/limited access folder on the secured servers at Brown University, which are only accessible to study staff. The intervention audio files will focus on the therapist and will only be used for the purpose

of intervention fidelity monitoring. In the event that exit interviews are transcribed for the purposes of evaluating the intervention, any identifying information that may have been verbalized during the course of the discussion, will be excluded from the transcription. Audio files will be destroyed upon completion of the study.

Additionally, immediately upon providing consent, all participants will be assigned a participant identification number. The file linking participant name to their ID will only be kept on an electronic database that will be password protected and only accessible to study staff. This information will not be stored with any other data and no other identifying information will appear on any form.

Psychological or emotional risks. Participants may find some of the questions asked in the survey or discussed during the counseling sessions to be upsetting. Receiving toxicology tests results may also be distressing. Additionally, participants who receive the intervention but do not find it to be useful may find this upsetting, or those who are randomized into the control condition may be disappointed or upset to not receive the intervention.

Likelihood: It is likely that during the trial some participants will experience these feelings.

Magnitude: Most psychological risks are minimal or transitory. Based on previous experience conducting similar research with individuals with substance use disorder, we do not expect psychological harms to result in any serious adverse events (e.g., suicide attempts).

Protections: Participants are free to refuse to answer any survey questions and may terminate participation in the study at any time in order to minimize psychological risk. Participants with mental health concerns beyond the scope of the experimental treatment (e.g., active suicidality), or other acute health conditions (e.g., HIV infection, Hepatitis C and other health conditions), will be referred to appropriate treatment programs/services, and linkages will be made with the participants' consent to do so. Study staff will be trained to make appropriate referrals for clinical care in consultation with the PIs or designee to help participants cope with any emotional discomfort and/or issues that may arise over the course of the study. All participants will be provided with a resource page alerting them to local services.

Social risks. Inadvertent disclosure of a participant's involvement in the study may cause social harm (e.g., discrimination, false assumptions, rumors).

Likelihood: Such social harms are possible, but likely to be rare.

Magnitude: While these social harms may cause emotional discomfort, the magnitude of this risk is minimal.

Protections: To ensure protections against this risk, we will warn participants of this possibility and suggest that they do not disclose their involvement in the study to people who are unaware that they have opioid use disorder.

Legal risks (e.g., risk of prosecution, mandatory reporting). Individuals will be asked about illicit substance use and criminal history. If data were to become known to others outside the study, participants could be at risk for prosecution. Similarly, if a participant reports any indication of current, ongoing abuse or neglect of children or elders and/or of imminent danger to self or a specified individual these indications will be considered for clinical intervention and mandated reporting to the appropriate authorities.

Likelihood: Although the possibility of passive suicidal ideation (i.e., without a plan or intent) is moderate, the likelihood of thoughts of harm to self or others with a plan and/or intent or current, ongoing abuse, or neglect are low. Thus, the likelihood of mandatory reporting is low.

Magnitude: If the authorities were contacted in relation to a threat oneself and others, this would constitute a serious adverse event.

Protections: To ensure protections against this risk, participants will be informed of the confidentiality of their responses as well as the limits of that confidentiality, which include, most notably, the disclosure of imminent suicidal or homicidal risk, and/or abuse/neglect reported by a participant. Consistent with state-mandated abuse and/or neglect reporting requirements, should a report to the authorities be required, the information provided will be from the PI. No mention of the study site or the participation in this particular research protocol will be disclosed.

Intervention Risks. The behavioral intervention provided as part of this study confers no additional risk beyond what is already provided for the standard of care condition (e.g., emotional discomfort).

Additional Protections.

Research Staff Training. All research staff will be trained in how to conduct human subjects research. All research staff will learn to recognize signs of distress from those participating in the study and will be trained on the appropriate procedures. There will be continued monitoring of adverse events such as any untoward medical occurrence (study related or not), an exacerbation of pre-existing conditions, a recurrence of an intermittent illness, or sigs related to symptoms, disease or fatality.

Data Safety and Monitoring. Data and safety monitoring during the trial will be supervised by the PI in cooperation with the Brown University IRB. Due to the brief time period and the pilot nature of the intervention (6 months), a Data and Safety Monitoring Board (DSMB) will not be formed. The PI, however, will monitor data safety and report any safety events to the IRB and funders in accordance with their guidance and timeline for reporting.

From our experiences, these methods have proven to be effective to protect against risks.

POTENTIAL BENEFITS OF THE RESEARCH

Participants may not directly benefit from being in this research study. Each participant will be provided with information on local substance use treatment mental health services, and other local resources. They will also have a minimum of 2 counseling sessions that have been shown to help others cope with life challenges, improve mood, and reduce opioid use. Participation in this study will also further opioid use disorder treatment research, which may help other members of the general population to manage opioid use disorder in the future.