PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL

PRINCIPAL/OVERALL INVESTIGATOR
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PROTOCOL TITLE
Randomized Controlled Trial of Cognitive Behavioral Therapy for Anxiety and Opioid Dependence

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I. BACKGROUND AND SIGNIFICANCE

Opioid dependence and anxiety disorders frequently co-occur, with over 60% of opioid-dependent individuals meeting criteria for a lifetime anxiety disorder (Conway et al., 2006). Individuals with anxiety disorders are more likely to use opioids (Sareen et al., 2006) and have higher incident risk for opioid dependence (Martins et al., 2009). Anxiety symptoms often precede opioid use (Ouimette et al., 2010), with anxiety reduction among the most commonly reported motives for opioid use (Rigg et al., 2010). The co-occurrence of opioid dependence and anxiety disorders is associated with lower quality of life (Carpentier et al., 2009) as well as poor treatment retention (Lejuez et al., 2008) and worse drug use and anxiety outcomes (e.g., Compton et al., 2003; Lavie et al., 2009). However, there has been a paucity of research on treatment for co-occurring opioid dependence and anxiety disorders. Clinical trials testing behavioral treatments for anxiety disorders have consistently excluded participants with substance dependence (e.g., Barlow et al., 2000), and there are no published large-scale pharmacotherapy trials for this population. Few studies have examined integrated behavioral treatments for co-occurring substance dependence and anxiety disorders, with most focused specifically on posttraumatic stress disorder (PTSD; Hien et al., 2009; Mills et al., 2012), and one study of obsessive-compulsive disorder (OCD; Fals-Stewart et al., 1992). For other anxiety disorders, which are present in 60% of opioid-dependent individuals and are the focus of the current application, published research has focused on alcohol dependence (Hesse, 2009), with no published studies to date for opioid dependence. Thus, research on optimal treatment approaches is needed to improve outcomes for this population.

In recent years, treatment research in the anxiety disorders has begun to shift from a disorder-specific approach (e.g., treating panic disorder one way and social phobia another way) to a transdiagnostic approach that can be applied to any of the anxiety disorders or their combination (McHugh et al., 2009). Several lines of evidence have supported this development, including: (1) the recognition that efficacious behavioral treatments for individual anxiety disorders are highly similar (Chorpita et al., 2009); (2) the high lifetime co-occurrence of anxiety disorders with each other (>75%; Brown et al., 2001); (3) symptom and pathophysiological overlap among anxiety disorders (Brown et al., 1998; Etkin et al., 2007); and, (4) the improvement of co-occurring anxiety disorders when treating the principal anxiety disorder (Craske et al., 2007). Studies have

supported the efficacy of transdiagnostic treatments for anxiety disorders (e.g., Craske et al., 2011; Wilamowska et al., 2010).

In attempting to address the treatment needs of populations with co-occurring substance dependence and other psychiatric disorders, one approach has been to integrate disorder-specific behavioral treatments based on similar disorder features and overlapping treatment elements, treating co-occurring disorders as if they were a "single disorder" (Weiss et al., 2011). Such integrated behavioral treatments have demonstrated evidence of superior outcomes for both disorders (e.g., Lydecker et al., 2010; Mueser et al., 2013; Weiss et al., 2009). Using this model to integrate transdiagnostic treatment for anxiety disorders with behavioral therapy for opioid dependence has potential to increase the efficiency of treatment and to improve outcomes for both disorders. Specifically, anxiety disorders and opioid dependence: (1) share a number of overlapping features, such as elevated distress intolerance (McHugh et al., 2011); (2) are treated using similar core elements (e.g., functional analysis, skills for coping with emotion- or craving-driven urges); and, (3) are characterized by symptoms that interact (e.g., the use of opioids to manage anxiety; Rigg et al., 2010). The integration of behavioral treatments for anxiety disorders and opioid dependence could capitalize on these overlapping and interacting features. For example, stress reactivity (the emotional and physiological response to a stressor) is implicated as a risk factor for the development of anxiety disorders (McLaughlin et al., 2010) and substance dependence (Koob, 2009), and elevated stress reactivity is associated with worse treatment outcome for both disorder types (e.g., Abelson et al., 1996; Sinha et al., 2006). Thus, understanding this shared vulnerability may be critical to the treatment of co-occurring opioid dependence and anxiety disorders. Studies indicate that elevated stress reactivity predicts poorer treatment response in substance-dependent patients (Sinha et al., 2006, 2011); however, this has yet to be examined in those with co-occurring anxiety disorders. Given the potential link between stress reactivity and outcome for both disorders independently, examination of whether a treatment for their co-occurrence reduces stress reactivity may provide insight into a mechanism of treatment change.

This study seeks to extend and adapt transdiagnostic treatment for anxiety disorders into a novel integrated cognitive behavioral treatment (ICBT) for co-occurring opioid dependence and anxiety disorders. Given the absence of treatment research in this population, this study has the potential to advance the field by providing information on the efficacy of a standard versus a novel behavioral treatment approach. From a public health perspective, the development of treatments that target multiple disorders has the potential to enhance efforts to increase access to evidence-based treatments by substantially reducing the training and implementation burden on treatment settings (McHugh et al., 2009). An integrated treatment extending this transdiagnostic approach to include both anxiety disorders and co-occurring opioid dependence would have wide applicability, even if more than one anxiety disorder or substance dependence diagnosis is present.

II. SPECIFIC AIMS

Anxiety disorders are highly prevalent in opioid-dependent individuals and confer risk for poor response to treatment. Opioid dependence and anxiety disorders share a number of overlapping and interacting features that may contribute to the maintenance of both chronic anxiety and opioid use. For example, anxiety is among the most commonly reported motives for opioid use, and both disorders are characterized by elevated intolerance of distressing internal states (distress intolerance). However, despite the high prevalence and poor prognostic impact of anxiety disorders on opioid dependence, little is known about treating these co-occurring conditions.

Given the overlapping and interacting nature of symptoms, this population may be best served by integrated treatment approaches targeting both conditions simultaneously. To address this notable need, the overarching aim of the proposed study is to test an integrated cognitive behavioral treatment for co-occurring opioid dependence and anxiety disorders.

Specific Aim 1. To examine the feasibility and acceptability of an integrated cognitive behavioral treatment manual for opioid dependence and anxiety disorders (ICBT). We hypothesize that ICBT will be a feasible and acceptable treatment as assessed by the ability to recruit and retain the target population and participant self-report of treatment satisfaction.

Specific Aim 2. To examine the efficacy of ICBT for the improvement of opioid dependence and anxiety symptoms relative to Individual Drug Counseling (IDC). We hypothesize that patients will report greater pre-post reductions in interviewer-rated anxiety symptoms and less opioid use in ICBT relative to IDC.

Specific Aim 3. To examine the association between stress reactivity and treatment outcome in opioid-dependent patients. We hypothesize that: (a) higher levels of stress reactivity at baseline will be associated with more days of opioid use following treatment, and (b) reductions in stress reactivity from baseline to post-treatment will be greater in the ICBT group relative to the IDC group.

Specific Aim 4. To examine the association between ovarian sex hormones, negative reinforcement bias, and treatment outcome in opioid-dependent patients. We hypothesize that: (a) greater negative reinforcement bias will be associated with poor treatment outcomes, and that this association will be stronger in women than men, and (b) within women, high progesterone will be associated with lower negative reinforcement bias and less severe opioid symptoms (e.g., opioid craving, anxiety severity).

III. SUBJECT SELECTION

Participants will be recruited for a randomized controlled trial of the efficacy, feasibility, and acceptability of ICBT. We aim to enroll 54 participants in this trial, and anticipate that up to 110 participants will need to complete informed consent and screening in order to initiate treatment. Participants will be recruited via either: (1) invitation to participate by a member of the study staff, or (2) self-selection in response to posted advertisements.

III.1. Inclusion/Exclusion Criteria

Subjects will be **included** if they: (1) are age 18 or older, (2) meet *DSM-5* diagnostic criteria for opioid use disorder, (3) are currently receiving pharmacotherapy for opioid dependence (e.g., buprenorphine, buprenorphine-naloxone, naltrexone, Vivitrol), (4) have used opioids illicitly within the previous 90 days, (5) exhibit clinically-significant anxiety defined as a score of 14 or higher on a clinician-rated anxiety symptom severity scale (the Hamilton Anxiety Rating Scale), (6) meet *DSM-5* diagnostic criteria for a current diagnosis of an anxiety disorder, (7) are able to read and provide informed consent, and (8) intend to remain in the geographical area for the duration of the study period.

Subjects will be **excluded** if they: (1) meet criteria for a current substance use or psychiatric disorder requiring a level of care higher than outpatient, (2) are currently receiving cognitive behavioral therapy, (3) report recent initiation of a psychiatric medication indicated for anxiety (defined as less than 4 weeks on a stable dose; not including PRN medications for sleep), (4) are

receiving and taking an as-needed (PRN) prescription for benzodiazepines (taking a stable, prescribed dose or misusing/abusing a benzodiazepine prescription is acceptable), (5) exhibit presence of a psychiatric or medical condition that would interfere with participation or that requires additional care (e.g., psychosis, acute suicidality), or (6) were admitted to McLean Hospital for their current treatment episode on an involuntary status.

III.2. Source of Participants and Recruitment Methods

The Principal Investigator (PI) will supervise the identification and recruitment of subjects. Subjects will be recruited from patients who are being treated at McLean Hospital's Alcohol and Drug Abuse Treatment Program (ADATP) continuum of inpatient, residential, partial hospital, or outpatient programs; subjects must be deemed appropriate by the PI for an outpatient level of care at the time of enrollment. The PI will determine if a patient is appropriate for an outpatient level of care based on either: (1) consultation with the treating clinician, or (2) referring to the patient's level of care based on the current treatment plan with their primary treatment provider. Although some subjects will initially be recruited from inpatient or residential settings, they will begin the study treatment only after discharge to outpatient status. In order to identify potential participants on the inpatient detoxification unit, the research assistant will check Epic for patients currently on the unit that meet eligibility criteria. The research assistant will then check with the patient's case manager, or other staff member on the inpatient unit, to confirm eligibility and introduce the patient to the research assistant. To recruit from outpatient, partial hospital, and residential programs, the study research assistant will check with clinical staff as well as the electronic medical record daily for potentially eligible subjects, who will be approached by their clinician to see if they are interested in meeting with the research assistant. Following initial identification and introduction to potential participants, regardless of level of care, the research assistant will meet with those who agree, and will ask if they are interested in completing a screening assessment. If a patient wants to participate, he or she will be invited to complete the Informed Consent process.

In addition to recruiting potential subjects from the ADATP at McLean Hospital, we will also use direct notices by which patients can self-refer into the study, such as posting Institutional Review Board (IRB) approved recruitment fliers where potential subjects are likely to read them (e.g., McLean Hospital, waiting rooms at other local area hospitals) and other media advertising on the Internet, newspaper, and local radio. Potential subjects responding to these notices and advertisements will contact the research assistant by telephone for a brief description of the study and to be screened for initial eligibility.

Subjects will not be recruited from among the Investigators own patients. However, because the PI does provide limited group therapy services in the ADATP, it is possible that the PI will know someone in this capacity. Under these circumstances, the study will be presented by another member of the study staff that is not involved in the patient's treatment.

Participants expressing interest in the study will be provided with additional information by a member of the study staff and will be offered the opportunity to ask questions. An initial screening will be conducted to provide an initial determination of study eligibility (see attached Screening Form). Participants who appear to be eligible at this stage and who express interest in participating will be scheduled for an informed consent meeting with a member of the study staff.

IV. SUBJECT ENROLLMENT

Potentially eligible subjects will be asked to complete the Informed Consent process, at which point the subjects will read through the IRB-approved consent form, and will meet with a research staff member who will answer any questions, explain the schedule of study procedures, and review the risks and benefits of the study. Subjects will be informed about the experimental nature, purpose, risks, and benefits of the study in accordance with procedures of the Partners IRB. There will be no time-limit placed on the consenting process. Research staff members understand that the consent is a process and not simply a matter of signing and dating the consent form. Either the PI or one of the Co-Investigators (serving as designees of the PI) will be available to help explain the study and answer questions. Once the subject consents to participate in the study, the subject will sign and date the consent form along with a member of the research staff. The subject will be provided with a copy of the consent form and the original will be stored in a secure location by a member of the study staff.

Participants will be randomly assigned to receive either ICBT or IDC. This randomization will be stratified by the following variables: (1) presence of a medication for anxiety, (2) gender, (3) type of opioid medication (agonist/partial agonist vs. antagonist), and (4) severity (defined by presence vs. absence of opioid use since initiating pharmacotherapy for opioid use).

V. STUDY PROCEDURES

All participants will receive 12 individual weekly sessions of ICBT or IDC and will complete assessments at baseline, week 12, and 1- and 3-month post-treatment follow-up visits. Breath alcohol screens will be conducted at each session and assessment visit to confirm absence of acute alcohol use. Procedures for response to a positive breathalyzer screen are specified below in Section VII. Qualitative exit interviews will be conducted at the completion of treatment. These interviews will focus on issues related to feasibility and acceptability, such as identifying the most and least helpful sessions and areas for improvement. Details of the procedures are included below.

V.1. Eligibility and Baseline Assessment

Following provision of informed consent, participants will complete a baseline assessment to further assess study eligibility and to evaluate substance use, anxiety, and related variables of interest. This baseline visit will begin with the administration of the Anxiety Disorders Interview Schedule for *DSM-5* and the Hamilton Anxiety Rating Scale to evaluate diagnostic and clinical inclusion/exclusion criteria. Any participants deemed ineligible at this time will be compensated $10 for their time and effort and will be discontinued.

Participants who are eligible will then complete the remainder of the baseline assessment. This will include a battery of self-report and interviewer-administered measures (see below), and a urine drug screen.

V.2. Study Treatment

Participants will then schedule the first treatment session with the study clinician. All participants in this open pilot trial will receive ICBT or IDC, both consisting of weekly, individual, 45-60 minute psychotherapy sessions. At each study session, participants will be asked to provide a urine drug screen and will complete weekly self-report measures (see below). ICBT treatment will target behaviors and cognitive patterns that are purported to maintain anxiety and harmful substance behaviors, with a focus on common maintaining processes across

both disorders. IDC treatment will target opiate dependence and will focus on addiction and recovery education. See Appendix for a session by session overview of ICBT and IDC.

For this trial, Dr. McHugh and other trained clinicians will administer the study treatment. All clinicians will be supervised by Dr. McHugh in the provision of treatment. All treatment sessions will be audiotaped (see Audiotape Informed Consent Form) and a selection of these will be evaluated for fidelity.

V.3. Retention and Compensation

The following procedures will be implemented to maximize study retention: (1) collection of locator information (see attached Locator Form), including multiple methods of contact for the participant (e.g., phone, email, text messaging) and at least one person who will be able to reach the participant if study staff are unable to; (2) use of mailed reminder postcards for appointments, bi-weekly check-in calls during the follow-up period, and mailed thank you notes for completed assessments; (3) use of text messaging to make contact with participants throughout the study; and, (4) provision of reimbursement for completion of study assessments (see below). These procedures are consistent with those of other longitudinal clinical trials to maximize retention (Zweben, Fucito, & O'Malley, 2009), including trials conducted within the ADATP (e.g., Weiss et al., 2009). Participants will be informed of these procedures in the consent form, including the nature of the collection of locator contacts. In the event that study staff need to contact participants' locator (e.g. if a participant's phone number changes), study staff will not disclose any information about the nature of the research study or the participant's health. If participants indicate that they are comfortable communicating via text (see attached Screening Form and Locator Form), study staff will not reference the nature of the study or clinical information, and will only use text messaging as a scheduling tool for participants for whom contact by phone has not been successful, or for those who indicate that texting is their preferred method of contact. In order to maintain confidentiality, all text messages to participants will be sent through email. These strategies have yielded exceptional data completion in previous studies of integrated behavioral therapy conducted in the ADATP (e.g., > 95% main outcomes completion; Weiss et al., 2009).

In line with the recent Partners system-wide policy update, "Procedure: Requests to Receive Unencrypted Email" (original approval date 7/18/2017), study staff will follow procedures/proper documentation regarding sending encrypted and/or unencrypted emails to participants to protect PHI. The study staff will use the following research template as provided by the policy update before initiating/responding to unencrypted email messages, either by obtaining written/verbal approval at the time of recruitment or during the study period regarding preferred method of email communication: *The Partners HealthCare standard is to send email securely. This requires you to initially set up and activate an account with a password. You can then use the password to access secure emails sent to you from Partners HealthCare. If you prefer, we can send you "unencrypted" email that is not secure and could result in the unauthorized use or disclosure of your information. If you want to receive communications by unencrypted email despite these risks, Partners HealthCare will not be held responsible. Your preference to receive unencrypted email will apply to emails sent to you from research staff in this study. If you wish to communicate with other research staff at Partners regarding additional studies, your preference will have to be documented with <u>each</u> research group.*

Participants will be asked to complete research assessments at four time points, each approximately 2-2.5 hours in duration. These visits will be compensated on an escalating schedule accounting for length of the session as follows: baseline = $25 (stress reactivity = additional $20), post-treatment = $40 (stress reactivity = additional $30), 1-month follow-up = $40, and 3-month follow-up = $50. Participants who are determined to be ineligible following the screening with be compensated $10. Participants who complete the exit interview will be paid $10. Research staff will work closely with the participants to attempt to schedule all research assessments in person, and will provide flexible scheduling as needed to maximize data completion. However, if after repeated attempts to schedule an in-person assessment are unsuccessful, participants will be given the opportunity to complete assessments by phone. Because phone assessment will preclude collection of several data points, the compensation for these visits will be reduced. The compensation for phone assessments will be: post-treatment = $10, 1-month follow-up = $10, 3-month follow-up = $15 (the baseline assessment must be conducted in person for enrollment in the trial). The stress reactivity assessments are listed separately to allow for the collection of the primary outcome measures first, and additional compensation for completing the full baseline and post-treatment assessments (including stress reactivity).

V.4. Measures

A battery of interviewer-administered, behavioral, biological, and self-report measures will be administered at 4 major assessment points: baseline, end of treatment, 1 month follow-up, and 3 month follow-up. In addition, weekly measures will be administered at each session, including a slightly larger assessment battery at week 6 (mid-treatment). Self-report questionnaires will be completed either by paper or electronically. Electronic completion will be done via RedCap. The proposed research use the RedCap Database, an encrypted, electronic database that is both HIPPA compliant (Health Insurance Portability and Accountability Act) and approved by Partners IRB for the administration and storage of human subject information (for addition information on the RedCap Database feature see http://rc.partners.org). Epic will be used for data collection to supplement participant self-report when necessary. Examples include: 1) using Epic to confirm a participant's address before sending payment, or 2) confirming a participant's current medications and treatment provides for the Concomitant Treatment Questionnaire (see below). For schedule of assessments see Table 1. Descriptions of measures are included below.

V.4.1. Self-Report and Interviewer-Administered Measures

Demographics. Participants will self-report sociodemographic variables. Demographic questions were drawn from the Tier 1 Core measures of the PhenX Toolkit (http://www.phenxtoolkit.org, 9/2014, Ver 5.8), and adapted as indicated for this particular study.

Addiction Severity Index, 5th Edition (ASI-V). The ASI-V (McLellan, Kushner, Metzger, & Peters, 1992) is a semi-structured interview that provides information on functioning across seven life domains and is used extensively in the study of substance dependence. The domains have demonstrated high internal consistency (alpha ranges from .65-.89; Leonhard, Mulvey, Gastfriend, & Schwartz, 2000). For this study, the sections on drug and alcohol use will be administered in order to identify level of functioning relative to substance use as an index of disorder severity in the SD group.

Anxiety Disorders Interview Schedule for DSM-5 (ADIS-5). The ADIS-5 (Brown & Barlow, 2014) is a semi-structured diagnostic interview that assesses DSM-5 psychiatric disorders. In addition to providing categorical diagnoses, the ADIS-5 also provides dimensional ratings of

symptom and disorder severity. The previous version of the ADIS for DSM-IV demonstrated good to excellent reliability for most DSM-IV categories (Brown et al., 2001). The shorter current diagnosis version of the ADIS (Mini-ADIS) will be administered at all assessments.

Anxiety Sensitivity Index (ASI). The ASI (Peterson & Reiss, 1992) is a self-report instrument designed to assess one's tendency to respond fearfully to anxiety-related symptoms. For each statement, respondents rate each item on a Likert scale ranging from very little (0) to very much (4). The ASI total score is computed by summing responses across the 18 items. Data on the reliability and validity of the ASI scales have been favorable (e.g. Reiss et al., 1986). An updated and validated version of the ASI will be used in this study (Taylor et al., 2007).

Brief Pain Inventory - Short Form (BPI). The BPI (Cleeland, 1989) is a 9-item self-report measure of pain and pain-related functional interference. The BPI is a widely used measure of pain that has demonstrated strong internal consistency reliability and construct validity in diverse patient samples for both the long (e.g., Gjeilo et al., 2007; Tan et al., 2004) and short forms (Mendoza et al., 2006). This measure will be used to examine pain and pain interference. The BPI will be administered at baseline, post-treatment, and 3-month follow-up.

Client Satisfaction Questionnaire (CSQ). The CSQ (Larsen et al., 1979), an 8-item self-report measure of treatment satisfaction, will be administered at post-treatment.

Concomitant Treatment Questionnaire (CTQ). Participants will be asked to report on any current treatment in addition to the study treatment for substance use or psychiatric problems.

Credibility and Expectancy Scale (CES). The CES (Borkovec & Nau, 1972) is a measure of the degree to which participants anticipate a therapy will be helpful for their symptoms and the degree to which it is credible. This measure will be administered at sessions 3 and 7 as a measure of feasibility.

Distress Intolerance Index. The Distress Intolerance Index (DII; McHugh & Otto, 2011) is a 10-item self-report measure of the intolerance of distressing states that was derived from a study of distress intolerance measures. The DII has demonstrated strong internal consistency reliability in clinical and unselected samples (McHugh & Otto, 2011) as well as strong concurrent and discriminant validity and distinguishes clinical from non-clinical groups (McHugh & Otto, 2012).

Drug Use Motives Questionnaire (DUMQ). The DUMQ (Mueser, Nishith, Tracy, DeGirolamo, & Molinaro, 1995) is a 15-item self report inventory designed to provide an assessment of coping, social and enhancement motives for alcohol use (Cooper, Russell, Skinner, & Windle, 1992). We will use a modified DMQ to assess non-alcohol drug use motives (as utilized by Mueser et al., 1995) with the addition of 5 items to assess for use of opioid for pain coping.

Exit Interview. Participants will be asked to complete an exit interview with a study investigator after the completion of the treatment. Participants will be given the opportunity to share feedback on their experience with the treatment and will be asked how well the treatment addressed their needs. This will be audiotaped and transcribed for analysis.

Fagerstrom Test for Nicotine Dependence (FTND). The FTND (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) will be used as a continuous measure of nicotine dependence. The FTND has shown good internal consistency, a single dimension factor structure, and positive relationships with degree of nicotine intake as assessed by saliva cotinine. FTND items are combined with other smoking history items in this study.

Hamilton Anxiety Rating Scale (HARS). The HARS (Hamilton, 1959) is an interviewer-administered measure of anxiety symptoms. The Structured Interview Guide for the HARS (Shear et al., 2001) was developed to improve the reliability of the HARS and will be used in this study. This will be the primary outcome measure for the study.

Homework Compliance. Both participants and clinicians will separately rate compliance with homework/skills practice on a weekly basis with a form adapted from an assessment of homework compliance developed by Primakoff, Epstein, & Covi (1986).

Insomnia Severity Index (ISI). The ISI (Bastien et al., 2001) is a 7 item self-report measure of sleep difficulty. This will be administered to assess whether sleep difficulty is associated with the achievement and maintenance of gains in treatment.

Key Concepts Questionnaire (KCQ). The KCQ is a brief self-report assessing beliefs about the nature of anxiety and opioid use as well as their interaction. This measure was developed by the study investigators for the purpose of this study in order to investigate beliefs about anxiety and substance use as a potential mechanism of treatment effectiveness.

Menstrual Cycle Information. The Menstrual Cycle Information form is a measure tracking patient menstrual cycle history, current phase of menstrual cycle, hormonal contraceptive use, and hormonal contraception compliance. The first part of this measure (Baseline Menstrual Cycle Information) will be administered during the baseline assessment. The second part of the form (Menstrual Cycle and Compliance Calendar), will be filled out during baseline and weekly assessments to characterize menstrual phase and ovarian sex hormones throughout the trial.

Opioid Craving Scale (OCS). The OCS is an adaptation of the Cocaine Craving Scale that has been used widely as a brief measure of craving for both drugs and alcohol (Weiss et al., 2003). This 3-item scale has demonstrated validity across a number of substances of abuse and will be used in this study as a marker of opioid craving over the previous 24 hours.

Opioid Use Questionnaire. Participants will self-report several variables related to the nature of their opioid use, including use of heroin and prescription opioids, duration of use, and primary opioid for which they are seeking treatment.

Overall Anxiety Severity and Impairment Scale (OASIS). The OASIS (Norman et al., 2006) is a very brief (5-item) measure of anxiety. The OASIS is a transdiagnostic measure of anxiety designed to capture both syndromal and sub-syndromal symptoms. A cut-off score of 5 for the OASIS reflects a clinical level of anxiety symptoms (Campbell-Sills et al., 2009).

Perceived Stress Scale (PSS). The Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983) is a 4-item measure that evaluates the extent to which individuals perceive the events in their life as stressful. The PSS has demonstrated adequate test-retest reliability, external validity, and predictive validity (for severity of symptoms, health service utilization, and smoking cessation outcome). The PSS will be administered at both baseline and post-treatment assessments and will be used to evaluate individual differences in perceived stress in order to appropriately analyze stress reactivity data.

Perseverative Thinking Questionnaire. The Perseverative Thinking Questionnaire (PTQ; Ehring et al., 2011) is a 15-item self-report measure of repetitive negative thinking. It has demonstrated excellent internal consistency reliability and satisfactory re-test reliability, in addition to strong convergent and predictive validity. As the PTQ was developed to measure repetitive negative thinking as a transdiagnostic process, it has been studied in various clinical populations (Ehring et al., 2011).

Positive and Negative Affectivity Scale (PANAS). The PANAS (Watson, Clark, & Tellegen, 1988) was developed as a brief measure of affect and yields the factors of Positive Affectivity (PA) and Negative Affectivity (NA). Internal consistency for both scales is high. The PA subscale will be administered at baseline, mid-, and post-treatment.

Primary Anxiety Symptom Measure. Participants will also be asked to complete a measure of anxiety symptoms for the primary anxiety disorder diagnosis identified at baseline. This will include the following measures: Penn State Worry Questionnaire (Meyer et al., 1990) for generalized anxiety disorder, Social Interaction Anxiety Scale (Mattick & Clarke, 1998) for

social anxiety disorder, Panic Disorder Severity Scale-Self Report (Houck et al., 2002) for panic disorder, Body Sensations Questionnaire (Chambless, Caputo, Bright, & Gallagher, 1984) for agoraphobia, and Fear Questionnaire (Marks & Matthews, 1979) for specific phobias.

Quick Inventory of Depressive Symptoms (QIDS). The QIDS (Rush et al., 2003) is a 16-item self-report measure of depressive symptoms. The QIDS has been validated for measurement in clinical trials to assess change and will be used as a measure of depressive symptoms during the trial.

Risk Assessment Battery (RAB). The RAB (Metzger et al., 2001) is a self-report questionnaire of HIV/infectious disease risk behaviors. This measure has been extensively validated, including in both substance abusing and dual diagnosis populations and will be administered to assess risk behaviors in 3-month increments at baseline, post-treatment, and 3-month follow-up.

Timeline Follow-Back. Self-report of alcohol and other substance use will be collected weekly from participants using the Timeline Follow-back (TLFB) method, which has demonstrated good reliability and validity with adult alcoholics (Sobell & Sobell, 1996) and illicit drug users (Robinson et al., 2014).

Saliva Sample Activity Documentation. The Saliva Sample Activity Documentation is a brief interviewer-administered questionnaire designed to assess recent use of medication, alcohol, caffeine, or nicotine in the past 12 hours, as well as physical activity or oral disease/injury that may affect saliva sample collection.

Short Grit Scale (SGS). The SGS is an 8-item measure of grit, which is an individual's tendency to persevere towards long-term goals. The SGS has demonstrated strong psychometric properties (internal consistency reliability, test-retest reliability, predictive validity for educational attainment and career stability) across various populations (Duckworth & Quinn, 2009). This measure will be used in the present study to assess if grit is related to treatment outcome, and will be administered at baseline and post-treatment.

Substance Abuse Stigma Scale – Self-Devaluation subscale (SASS). The Self-Devaluation subscale of the SASS is an 8-item measure assessing internalized or self-stigma among individuals abusing substances (Luoma et al., 2013). The SASS has shown strong psychometric properties among individuals receiving treatment for substance use disorders. The SASS will be administered at baseline and post-treatment, and will be used to evaluate the impact of self-stigma on treatment outcome.

WHO Quality of Life (WHOQOL). The WHOQOL (Murphy et al., 2000) is a 26-item measure of self-reported quality of life that has been validated cross-culturally and will be used as a secondary outcome measure in this study.

V.4.2. Behavioral Computer Task

The Escape Go/NoGo Learning Task is a novel task of negative reinforcement sensitivity and learning. This task is a modified version of a previously validated measure of reward and punishment sensitivity and learning (Guitart-Masip et al., 2012). In this task, participants are required to learn contingencies between cues, responses and outcomes. A trial starts with the presentation of the cue (a picture of a fractal) for 2 seconds. During the cue, the words "Choose: Press or Not Press" are displayed and the participant makes a choice to press the spacebar (Go) or withhold a response (NoGo). Pressing the spacebar does not terminate the cue. Following the cue, feedback consists of either an aversive sound being played, accompanied by a pink sound wave, or silence accompanied by a straight blue line. Feedback also contains participants' choice on the prior cue (e.g. "You chose to PRESS") and is presented for 2 seconds. The aversive sound is an unpleasant sound of a fork scraping on slate presented over headphones no louder than 85

dB. In pilot studies, these sound and volume levels induced sufficient distress (average subjective distress rating of 7.1/10) without causing lasting effects on participants (i.e. ringing ears, etc.) and are below the Occupational Safety and Health Administration levels for permissible occupational noise. Feedback is followed by a 1 second inter-trial stimulus. There are 4 cues within 2 conditions. For the two cues in the "Escape" condition, the onset of the aversive sound coincides with the presentation of the cue. The two cues in the "Avoid" condition are presented in silence. Participants' goal in the task is to select the option (i.e., Go or NoGo) which tends to produce silence during the feedback. Within each condition, one cue will produce silence 80% of the time following a Go and the other cue will do the same following NoGo responses. Each cue is presented during 40 trials, for a total of 160 trials. Cumulative outcome measures for the Escape Go/NoGo Learning Task include: accuracy percentage, a global measure of learning/performance, and win-stay, lose-shift, to examine the effect of immediate reinforcers on choice. In addition, a computational model of behavior will help determine the extent to which automatic processes interfere with instrumental control.

V.4.3. Stress Reactivity Assessment

The stress reactivity paradigm includes two imagery conditions (neutral-relaxing, stress related) and a laboratory session. This paradigm will be completed at pre- and post-treatment assessments. During a visit prior to laboratory sessions, participants will complete two Scene Development Questionnaires (Sinha & Tuit, 2012) that are designed to collect information about each imagery condition (a non-drug-related stressful event in their life, and a neutral-relaxing event); scripts for the imagery conditions will be developed using the information collected. Each script will be written, recorded, and edited by trained research staff in order to ensure that scripts are standardized in terms of length and content. During laboratory sessions, participants will listen to each script. The order of the scripts will be randomized. Psychophysiological measures (skin conductance) will be collected before, during, and after each imagery script. Skin conductance response will be collected using a Biopac MP150 system running AcqKnowledge 4.4 software (Biopac Systems Inc., USA) and the Biopac electrodermal activity amplifier (EDA100c). Skin conductance response is used as an index of physiological arousal, and therefore stress reactivity. Subjective measures that will be administered prior to and following each imagery condition include the Positive and Negative Affect Scale (Watson, Clark, & Tellegen, 1988), and the Opioid Craving Scale (Weiss et al., 2003) that has been adapted to assess craving in the present moment (i.e., "right now"). Following each imagery script participants will also be asked to rate how "clearly and vividly" they were able to imagine the scenario on a 10-point visual analog scale.

V.4.4. Urine Toxicology

Participants will provide weekly urine samples to screen for drug use. Although opioid use is the primary outcome for this trial, the presence of other substances of abuse will be used as secondary outcome. We will use the Alere Toxicology iCup 13 panel drug test screening cup, which tests for the presence of the following substances: cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidines, benzodiazepines, barbiturates, methadone, tricyclic antidepressants, oxycodone, propoxyphene, and buprenorphine. We will also use a Drug Screen Test Dip Card to test for fentanyl in the urine sample.

V.4.5. Measurement of Sex Hormones and Menstrual Cycle Phase

Female participants will provide saliva samples and will report descriptive data on menstrual cycle phase in order to measure fluctuations in estradiol and progesterone throughout the study period. Salivary assays of estradiol and progesterone will be performed in duplicate and in

accordance with manufacturer specifications at the Laboratory for Biological Health Psychology at Brandeis University. Saliva samples will be collected using the passive drool method and according to recommended collection procedures. Samples will be collected at baseline (immediately prior to the Escape Go/NoGo Task) and at each weekly session. In addition to measurement of salivary estradiol and progesterone, we will also collect descriptive data on menstrual cycle phase (with the Menstrual Cycle Information form), following recommendations for optimizing measurement of menstrual phase (Allen et al., 2016). Specifically, we will utilize both self-reported onset of menses and weekly hormone data to characterize menstrual cycle phase throughout the trial. We will also assess for presence, type, dose, and compliance with birth control at each time point. Furthermore, using the interviewer-administered Saliva Sample Activity Documentation form, we will collect information on participant activity in the past 12 hours that may affect saliva collection.

VI. BIOSTATISTICAL ANALYSIS

Data from this randomized controlled trial will be analyzed using descriptive and qualitative analytic methods as well as traditional significance tests. Measures of patient satisfaction will be considered along with qualitative exit interviews to determine the acceptability of the treatment. Randomized groups will be compared with respect to baseline demographic and clinical variables using t-tests and chi-square tests; if significant group differences are identified in any variables known to be highly predictive of outcome, these variables will be adjusted for via their inclusion as covariates. These covariates will also be summarized with descriptive statistics and graphical methods to determine the most appropriate way to incorporate them in the analyses (e.g., continuous or categorical representation). All outcome analyses will utilize an intent-to-treat approach, complemented by exploratory completer analyses.

The hypothesis that I-CBT will yield greater reduction in opioid use and anxiety symptoms will be tested using separate linear mixed effects models for opioid use (weeks of use in the previous 4 weeks) and anxiety (HARS score) examining the main effect of treatment condition and its interaction with time on each outcome. The correlation among the repeated measures of the dependent variable will be appropriately accounted for via the inclusion of random subject effects (e.g., random intercepts and slopes for time). Covariates will include pre-treatment values of the dependent variable and any baseline demographic or clinical variables identified as necessary covariates in preliminary analyses.

To test the hypothesis that baseline stress reactivity is associated with treatment outcome at post-treatment (week 12), linear regressions will be utilized with primary opioid and anxiety outcomes at week 12 as the dependent variables and post-stress task anxiety, craving, and heart rate variability as independent variables, co-varying for baseline severity and any other covariates identified in preliminary analyses. In addition, to test the hypothesis that reduction in stress reactivity over time will be greater in the I-CBT condition, a linear mixed effects model will be conducted examining whether stress reactivity decreased from pre- to post-treatment and whether groups differed with respect to this change; this analysis will include the main effects of time and group and the time x group interaction. The correlation among repeated measures of the dependent variable will be accounted for via the inclusion of random subject effects.

With repeated assessments over 7 months of study participation, some amount of missing data is inevitable. Extensive efforts will be made throughout all stages of follow-up to minimize missing data by vigorous outreach, including to any participants who elect to dropout of treatment prior to completion. For all of the proposed analyses, we will use statistical methods (e.g., linear

mixed effects models) that incorporate partially observed data on participants who are lost to follow-up.

We do not expect more than a 10% loss to follow-up (see C.4); nonetheless, the sample size of 54 participants was selected to provide adequate degrees of freedom to estimate the treatment effect size and its reliability, even when allowing for up to 20% loss to follow-up. In this Stage 1 trial, we will focus on the estimation of effect sizes and clinically-significant change (as defined by Jacobson & Truax, 1991). If promising results (i.e., presence of clinically-significant change) are detected, these data will provide an estimate of the reliability of the effect to inform power calculations for a larger Stage 2 clinical trial. Although the focus of this trial is the estimate of an effect size and its reliability, we have conducted a power analysis for the proposed sample size; effect sizes are expressed as standardized differences in means for ease of interpretation. For Aim 2, based on unpublished data from previous clinical trials, we anticipate a small correlation between repeated measures of the opioid use outcome ($r < .20$) and a small to medium correlation ($r = 0.42$) for the HARS. Thus, the proposed sample size would provide adequate power (power of at least 0.80) to detect a minimum between-group difference from baseline to end of treatment in the magnitude of a large effect size ($d = .70$-$.75$). For Aim 3, based on previous studies examining stress reactivity and alcohol and cocaine use following treatment, which have consistently reported medium to large effect sizes (Sinha et al., 2009; 2011), the proposed sample size would provide adequate degrees of freedom to detect an effect size in the range of high medium to large.

VII. RISKS AND DISCOMFORTS

The anticipated risks associated with the proposed study are minimal. As in any study involving assessment of psychiatric symptoms, there is some risk of emotional discomfort from discussing emotional topics (e.g., symptoms of anxiety, substance use). However, this discomfort is expected to be transient. In addition, the stress reactivity tests are designed to elicit mild to moderate, transient distress. Accordingly, evidence suggests that completion of laboratory stress-reactivity paradigms is not associated with increased risk of subsequent substance use (DeSantis et al., 2009). Participants will be monitored by study staff. If a participant reports experiencing, (or study staff observes) distress at a higher level or longer duration than the mild to moderate, transient distress anticipated in study procedures, the PI will be contacted to determine whether intervention or withdrawal is indicated.

Presence of any of the following criteria throughout the study will trigger a review of the participant's appropriateness for the study by the study PI in consultation with at least one other clinical provider (either a clinician on the research team, or another member of the patient's treatment team, if a release of information has been provided): (1) any serious adverse event, (2) evidence for a significant worsening of clinical status as indicated by (a) 2 consecutive weeks of a positive urine toxicology screen (not including prescribed medications or marijuana), or (b) 2 consecutive weeks of no-showing study treatment sessions.

A core component of cognitive behavioral approaches to anxiety disorders is exposure to feared stimuli (e.g., social interactions, heights). This approach is intended to elicit moderate levels of anxiety in order for extinction of fear responding (the purported mechanism of change) to occur. Accordingly, this procedure has consistently demonstrated efficacy across the range of anxiety disorders for symptom reduction and disorder remission (e.g., Barlow et al., 2000). These

procedures are expected to elicit moderate levels of anxiety, which are similar to the anxiety experienced by individuals with elevated anxiety symptoms in daily life. Evidence from numerous large-scale clinical trials supports the safety and tolerability of these procedures, as indicated by high retention rates (see Hembree et al., 2003) and high levels of patient satisfaction (e.g., Stein et al., 2011), including in substance-dependent samples (e.g., Mills et al., 2012; Otto et al., 2010). Nonetheless, subjects will be closely monitored for evidence of excessive or enduring distress following these procedures and precautions to protect against this risk will be taken.

Another potential risk includes the possibility that subjects may experience dangerous or suicidal behavior. These are possible because of the nature of the dually diagnosed population studied in this research. We do not anticipate that our study procedures will increase this particular risk, but there is a risk that this could occur during the study period. If a subject becomes very upset, is intoxicated, or is suicidal during the study, he or she will be seen by one of the study clinical staff members. An assessment will be conducted, and the appropriate clinical recommendation will be made; this could involve treatment either at McLean Hospital or elsewhere. If a patient provides a positive breath alcohol screen, a member of the study clinical staff will meet with the patient to determine whether he/she is able to complete the clinical or research session and to determine the participant's safety level and appropriate next steps (e.g., send to emergency room, refer to detox, send home in taxi, send home with a friend, etc.).

Accidental opioid overdose, including fatal overdose, is a possible outcome of opioid use disorder. We do not believe study procedures will increase this particular risk, because treatment enrollment has been found to be protective against overdose-related mortality among opioid-dependent individuals (Degenhardt et al., 2011). In addition, all participants are required to be on pharmacotherapy for opioid dependence which is robustly associated with a decreased risk of overdose in this population (Volkow et al., 2014). As noted above, all participants will be closely monitored and appropriate level of care will be re-evaluated if there is evidence of a worsening of clinical status.

Another potential risk is a breach of confidentiality. However, as with the other risks mentioned above, we will take precautions to protect against this risk. Participants will receive a copy of the informed consent form explaining their privacy and confidentiality. All data will be coded with a unique identifier and will be stored separately from any identifying information (i.e., informed consent forms, clinical charts). Given the longitudinal nature of this clinical trial, a key linking the unique subject identifier to the participant's name will be maintained. This will be stored on password protected computer and a locked cabinet separate from other data. Informed consent forms and data will be stored separately in locked files and only research staff will have access to this information. Electronic questionnaires will be stored in the Redcap Database. As noted above, Redcap is an encrypted, electronic database that is both HIPPA compliant (Health Insurance Portability and Accountability Act) and approved by Partners IRB for the administration and storage of human subject information (for addition information on the RedCap Database feature see http://rc.partners.org). Only research staff affiliated with this proposal will have access to any identifying information. Data being analyzed will not include identifying information. The identity of the participants will not be revealed in the presentation or publication of any result from the project. To provide additional privacy protection given the sensitive nature of the data collected (e.g., substance use data), a certificate of confidentiality will be requested from the National Institute on Drug Abuse. This will be requested following IRB approval, consistent with NIDA procedures.

Participants will be fully informed of the nature of the risks involved during the informed consent process and will have the ability to discontinue and withdraw consent at any time. All study personnel will be trained in the appropriate care of human participants, and will have completed the National Cancer Institute (NCI) course, Human Participants Protections Education for Research Teams, and research assistants will be closely supervised by the study PI. As part of the informed consent process, participants will be informed that if they feel uncomfortable responding to any question that they are free to choose not to respond or to express their discomfort. Each participant will be made aware that participation is completely voluntary and that he or she may withdraw participation at any time without penalty.

VIII. POTENTIAL BENEFITS

The major potential benefit to participants is the receipt of treatment that might help them to achieve their goals of maintaining abstinence from opioids and reducing anxiety. Participants will receive free cognitive behavioral treatment as part of this study from providers experienced in treating substance dependence. Participants also will receive the potential benefit of participating in a study that may contribute to establishing more effective treatment for patients with co-occurring opioid dependence and anxiety disorders. Given the minimal risks associated with the proposed investigation, we believe that this is a very acceptable risk-benefit ratio.

IX. MONITORING AND QUALITY ASSURANCE

The PI will have responsibility for continuous monitoring of the data and safety of subjects in the study. Further consultation will be obtained if necessary from the McLean Hospital Office of Research Administration.

Continuous, close monitoring of safety issues by the PI will take place throughout the study's duration with prompt reporting of adverse events to the Partners IRB. At the time of annual, continuing review we will provide the Partners IRB with a summary of any unexpected and related adverse events as well as any other unanticipated problems that occurred since the last continuing review. We will also follow the Partners IRB policies for expedited reporting of Adverse Events and Serious Adverse Events.

IX.1. Reporting Unanticipated Problems Including Adverse Events (AEs) and Serious Adverse Events (SAEs)

Tracking of Unanticipated Problems including AEs will begin at the time of consent. Unanticipated Problems including AEs will be assessed at every research assessment and treatment session (i.e., baseline, weeks 1-12, post-treatment, 1-month follow-up, and 3-month follow-up). At every study appointment, research staff will ask about any emergency room visits, inpatient admissions, etc. (see Unanticipated Event Form). In addition, participants will be closely monitored during study assessment and treatment for any psychological distress or adverse reactions to any treatment procedures and study clinicians will assess for suicidal behavior or increased severity of psychological distress. Study staff will follow the guidelines below to determine how to report and categorize Unanticipated Problems. Any AE that results in hospitalization or death will be reported to the IRB within 24 hours and will be categorized as an SAE. We will consult the IRB for guidance on any event not outlined in the protocol that are possibly related to study participation. Events that are unrelated to the disorder or study participation will not be collected in the present study given that it is a psychotherapy trial (e.g., common medical illness, such as cold or flu).

	Reporting Procedure	Data Collection Form(s)
Unanticipated problems possibly related to study participation: • Unanticipated psychological stress following treatment procedures • Adverse Reactions to Physiological equipment	Report to the PHRC IRB	Unanticipated Event Form, note as Adverse Event
Other Unanticipated Problems that are possibly related to study participation: • Breaches of confidentiality	Report to the PHRC IRB	Research progress note
Unanticipated problems related to the course of the clinical disorder being treated not related to study participation, including such examples as: • Drug overdose • Suicidal ideation/suicide attempt • Increase severity of psychological distress requiring medical/psychiatric attention • Participation incarceration	Report to PHRC IRB	Unanticipated Event Form, consult with IRB to determine whether Adverse Event or Unanticipated Problem
Hospitalization	Report to PHRC IRB	Unanticipated Event Form, consult with IRB to determine whether Adverse Event or Unanticipated Problem
Death	Report to PHRC IRB	Unanticipated Event Form, consult with IRB to determine whether Adverse Event or Unanticipated Problem

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Table 1. Schedule of Assessments

Measure	Time Point						
	Screening	Baseline	Weekly	Mid-Tx	Post-Tx	1MFU	3MFU
Diagnostic/Screening							
Screening Questionnaire	X						
Anxiety Disorders Interview Schedule	X				X		X
Locator Form	X						
Descriptives & Predictors							
Demographics		X					
Brief Pain Inventory		X			X		X
Fagerstrom Test for Nicotine Dependence		X					
Addiction Severity Index Lite		X			X	X	X
Opioid History Questionnaire		X					
Drug Use Motives Questionnaire		X			X		X
Quick Inventory of Depressive Symptoms		X		X	X	X	X
Concomitant Treatment Questionnaire		X		X	X	X	X
Short Grit Scale		X			X		
Substance Abuse Stigma Scale		X			X		
Primary Outcomes							
Hamilton Anxiety Rating Scale	X				X	X	X
Timeline Follow-Back		X	X	X	X	X	X
Urine Drug Screen		X	X	X	X	X	X
Secondary & Instrumental Outcomes							
WHO Quality of Life		X			X		X
Primary AD Symptom Measure[a]		X			X		X
Risk Assessment Battery		X			X		X
Moderators & Mediators							
Anxiety Sensitivity Index		X	X	X	X	X	X
Opioid Craving Scale		X	X	X	X	X	X
Overall Anxiety Symptom and Impairment Scale		X	X		X		X
Insomnia Severity Index		X			X		X
PANAS-Positive Affect		X		X	X		
Perseverative Thinking Questionnaire		X			X		X

Perceived Stress Scale		X			X		
Distress Intolerance Index		X		X	X	X	X
Process							
Client Satisfaction Questionnaire				X	X		
Credibility and Expectancy Scale			3 & 7				
HW Completion			X				
Key Concepts Questionnaire		X			X		X
Qualitative							
Exit Interview					X		
Behavioral							
Go/NoGo Task		X					
Psychophysiological/Biomarkers							
Saliva Samples[b]		X	X	X			
Menstrual Cycle Information[b]		X	X	X			
Stress Reactivity Paradigm		X			X		

Note. [a]Based on the primary presenting anxiety disorder, participants will complete a self-report measures specific to that diagnosis.
[b]Only female participants will be asked to provide saliva samples given that we are examining fluctuations in ovarian hormones.