HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: Computer Based Treatment for Cognitive Behavioral Therapy and Cooperative Pain Education and Self-Management --CBT4CBT-COPES

Working Title: CBT4CBT-IMPACT

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(*If applicable*) Clinicaltrials.gov Registration #: NCT 05204576

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
   The specific aims are as follows:
   - To develop the integrated CBT4CBT-COPES program as adapted from our existing CBT4CBT program
   - To conduct a 12-week randomized trial to evaluate the efficacy of CBT4CBT-COPES versus standard care (treatment as usual) at 3 months (primary endpoint). The primary adherence outcome will be retention in OAT (defined as continuous and verified enrollment in OAT at the 3-month point). The primary pain outcome will be PROMIS 6-item Pain Interference Short Form.
   - Conduct a 6-month follow-up to evaluate the durability of effects on OAT adherence and pain interference.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   Five years

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Current challenges for OUD Treatment

The statistics associated with the current opioid crisis are staggering: overdose has become the leading cause of accidental death in the US, and approximately 70 individuals die from overdose each day[1]. There is compelling evidence that access to, and retention, in medicated-assisted treatment (MAT) is protective against mortality in individuals with OUD[2-5]. There are currently three approved medications to treat OUD with demonstrated efficacy: opioid agonist treatment (the full agonist methadone and the partial agonist buprenorphine), and the antagonist naltrexone (in its extended release form). The most commonly used form of MAT is OAT as naltrexone has yet to find widespread use for OUD. Retention in OAT is associated with reductions in all-cause and overdose mortality [6], reducing mortality by a factor of three. However, despite demonstrated efficacy in reducing opioid use and mortality and improving health consequences, access remains limited, with less than half of treated individuals with OUD receiving any form of MAT[7]. Of those initiating MAT, adherence is a major challenge, as only about half are retained for at least 6 months[8, 9]. Multiple long-term follow-up studies indicate that it requires extended periods, often years, for MAT to confer its full benefits [10-14], primarily by stabilizing individuals so that they may return to work, regain their health, terminate illegal activities and establish supportive networks of non-drug using individuals[15].

The role of pain in the development of OUD

A sometimes overlooked aspect of the OUD crisis is that four out of five individuals who use heroin report their initial exposure to opioids was via a prescription for pain relief[16]. The CDC estimates that 11% of adults in the US experience chronic pain[17]. Prescription of long-acting opioids with longer durations for the treatment of chronic non-cancer pain has been shown to contribute to development of OUD[18]. Although only about 3% of individuals initially prescribed opioids for pain eventually develop OUD[19], over 62 million individuals in the U.S. are prescribed opioids per year[20]. Prescription opioids have greatly contributed to the current opioid crisis[1, 21]. Unfortunately, opioids

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are ineffective for the treatment of chronic pain and carries multiple risks including risk of addiction[17, 22] and overdose[23]. Long-term exposure to opioids is associated with tolerance and reduced pain threshold, which may represent one of the key neuroadaptations that may contribute to ongoing opioid use[24, 25].

Comorbidity among individuals on agonist treatment with chronic pain

Among individuals enrolled in methadone or buprenorphine treatment, estimates of chronic pain range from 40-80%[26-29]. Among individuals on OAT for OUD, those who have chronic pain, compared to those who do not, have higher rates of psychiatric and medical comorbidities including sleep disturbances, psychiatric disorders and symptoms (especially depression and anxiety); medical problems and higher rate of utilization of health services; and higher levels of functional impairment [28, 30-33]. Comprehensive treatment for individuals with comorbid chronic pain and OUD may require interventions that address mood, anxiety, sleep and functional difficulties to maximize both adherence and treatment outcome.

Chronic pain with OUD does not simply indicate a more severe OUD; rather, it represents a comorbid disorder that may have a different clinical course and treatment response than OUD alone[34]. This point is well-illustrated in a study in which Hser et al examined medical record data of 5307 individuals with OUD in a large health system [35]. They found that 36% indicated no pain, 10% indicated OUD occurred first, 15% had OUD and pain start at the same time, and for 40% of the cases, chronic pain preceded the development of OUD. In comparison to the other 3 groups, the "OUD first" group had higher rates of other substance use disorders and HIV/HCV. The "pain first" group had the highest rates of mental disorder (82%), heart disease (72%), respiratory disease (68%), and sleep disorder (42%). Thus, comorbidity of sleep, psychiatric, and other problems in this population may be related to the relative onset of the chronic pain versus OUD.
Finally, long-term exposure to opioids may produce increased pain sensitivity in some individuals[36,37 38, 39], further complicating treatment of this group[37, 40, 41].

Chronic pain complicates and worsens OAT outcomes

Not only is there ample evidence that chronic pain is common among individuals on OAT for OUD, but also that presence of chronic pain may undermine the effectiveness of OAT. Pain, especially volatility or variability of pain for individuals taking OAT, is associated with enhanced craving and higher rates of drug use including illicit opioids, benzodiazepines, and cannabis[5, 42-44]. For example, the CTN POATs study, a randomized, controlled multisite trial of buprenorphine in prescription OUD patients, found greater pain severity significantly increased the odds of opioid use in the following week[45]. Among individuals in OAT for OUD, variability or volatility in pain intensity have been associated with relapse and poorer outcomes[5, 45], but these relationships are not well understood. Finally, few people in OAT receive adequate evidence-based care for their pain; this has been recognized as an important gap in treatment of comorbid OUD and chronic pain[27, 30, 34, 44, 46, 47].

In summary, a substantial proportion of individuals on agonist treatment (even the majority in some settings) experience chronic pain. Chronic pain and pain fluctuations may interact to undermine treatment and precede relapse to opioid use in patients on OAT, who also experience a range of other problems, particularly sleep disturbances, psychiatric comorbidities, and limited function. Integrated approaches are needed for this complex comorbid and rapidly growing population[43]. Approaches that are evidence based, easily disseminable (especially to rural areas where the opioid crisis has been particularly devastating), and affordable are particularly needed, given the pressing nature of the crisis.

Strong evidence base for cognitive behavioral therapy for both chronic pain and substance use

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Cognitive-behavioral treatment has a strong evidence base for the treatment of chronic pain (reviewed in [48]). Broadly speaking, CBT has been found to produce small to moderate effects on pain, disability, catastrophizing and mood among people with non-headache pain[49] (of note, though, is that individuals with SUDs were typically excluded in these studies). The goal of CBT for chronic pain (CBT-CP) is to "reduce pain and psychological distress and to improve physical and role function by helping decrease maladaptive behaviors, increase adaptive functioning, identify and correct maladaptive thoughts and beliefs, increase self-efficacy for pain management"[48]. CBT-CP appears particularly effective at reducing catastrophizing (defined as "magnification of threat, rumination about, and perceived inability to cope with pain"), which in turn is related to more physical and psychological dysfunction. CBT-CP has been recommended by the CDC and NIH as a first line treatment to reduce pain and improve function[17 50].

Our group has extensive experience developing and testing CBT-CP interventions and particularly on improving access to CBT-CP through technology. Though CBT-CP has been shown to be effective for improving pain-relevant outcomes, numerous barriers exist to in-person treatment, including patient travel limitations, the need for frequent in-person sessions, and the scarcity of trained therapists. Using technology-based interventions, like interactive voice response (IVR) which allow patients to engage in treatment from their home, may improve access. We have been conducting a series of studies examining the effectiveness and implementation of technology-based interventions for chronic pain (see Previous Work). Although most of our trials have focused on interactive voice response (IVR) based interventions, we have also developed and tested web- and mobile application-based chronic pain interventions. Technology-based interventions for chronic pain have been shown to be effective[51-53] and because they often can be completed at home, are less burdensome to patients than multisession in-person treatments[54].

CBT is also widely recognized as an empirically supported treatment for substance use disorders[55-58]. Dr. Carroll developed the widely used CBT manual published by NIDA[59] and has conducted a series of trials evaluating its efficacy, durability, and mechanisms in range of substance-using populations alone[60-65] and in the case of trials targeting OUD, in conjunction with OAT[66, 67]. However, as in the treatment of chronic pain, there have been multiple barriers to the dissemination of CBT in many clinical settings[67, 68]. Thus, and as described in Previous Studies below, Dr. Carroll and her group were one of the earliest to develop and evaluate web-based versions of CBT (computer-based training for cognitive behavioral therapy, or CBT4CBT), with particular emphasis on making it highly user-friendly and engaging, while retaining essential core features of CBT (e.g., emphasis on focused skills development and practice). We have conducted a rigorous series of studies evaluating CBT4CBT for a range of substance use disorders[69-72], including two trials indicating its effectiveness and durability for individuals on methadone maintenance[73, 74]. Finally, as described below, we have recently adapted CBT4CBT specifically for individuals in office-based buprenorphine[75], as lack of access to high-quality, affordable, and disseminable evidence based behavioral therapies has been one barrier to wider adoption of buprenorphine in office based settings[76 77, 78]. CBT4CBT-COPES would greatly extend this work by enabling OAT providers, in a large range of settings, to provide a practical, inexpensive, easily disseminable, and standardized evidence-based intervention to those with chronic pain as well.

Toward a fully-integrated, technology-based approach for chronic pain patients in OAT. Manual-guided, clinician delivered approaches exist[79-81] and have demonstrated the feasibility and potential efficacy of integrated behavioral interventions for chronic pain and OUD: The Ilgen RCT[80] demonstrated significant reductions in pain in a VA population; the Barry RCT[79] indicated reductions in drug use but not significant reductions in pain by treatment group; the Morasco study[81] did not include a control group and only 7 participants had OUD. We will build on this pioneering work to

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develop the first fully-integrated technology-based intervention targeting chronic pain for individuals with OUD on opioid agonist treatment.

Provided they are carefully developed to retain the core active ingredients of the validated clinician-based approaches they are based on and are evaluated with appropriate and rigorous methodologic controls[82]; technology-based approaches have been demonstrated to be effective, feasible, cost effective and can help difficult-to reach and underserved populations access treatment[83-87]. Technology-based approaches also address some of the drawbacks of manualized clinician-administered approaches, including the high cost and time necessary to train and supervise clinicians, variations in fidelity and skill, and inevitable clinician 'drift' over time, all of which combine to result in weak implementation in many settings[88, 89]. Moreover, given rapidly growing numbers of individuals enrolling in OAT in response to federal, state, and local efforts to address the opioid crisis, it is unlikely there would ever be adequate numbers of trained clinicians to address this need.

It is of note that both Dr. Heapy and Dr. Carroll have not only developed effective clinician-delivered versions of CBT for chronic pain and SUDS, respectively, but have also developed feasible, effective, technology-based versions of them. We have demonstrated their comparability to clinician-delivered versions[90, 91], in terms of retention and patient satisfaction and have systematically evaluated mechanisms of action[92, 93]. Thus, in approaching the proposed integration, we will retain the critical unique (for COPES, monitoring and feedback, behavioral activation, pacing, addressing catastrophizing; for CBT4CBT; engaging, video-based examples of implementation of behavioral and cognitive self-control skills) and shared (skills practice, monitoring) components of the two versions of CBT while also addressing the complex interplay between chronic pain and the development and perpetuation of OUD.

To do so, we will produce a new set of video vignettes, portraying an individual who has chronic pain and OUD, newly enrolled in agonist treatment, who is learning to manage pain and opioid use via the target skills presented in each module. As we have learned in our series of CBT4CBT trials, presenting these vignettes through the course of highly engaging program in a continuous story arc ('soap opera'), with likeable characters facing common, realistic situations has been associated with very high rates of treatment completion and learning of CBT concepts[91, 94]. Uptake and retention in web-based approaches is important, high rates of retention in the various CBT4CBT trials suggests that users may be more highly engaged with compelling stories of individuals in difficult, realistic situations that parallel their own.

We will also be retaining the daily assessment feature of COPES that has been updated with current technology. This will involve daily texts with a link to a survey during the 12-week treatment program. This will be used to provide weekly personalized feedback, as done in the COPES trial[54, 90], to each participant enrolled in this condition, via a page on the CBT4CBT-COPES 'patient dashboard". Moreover, this will allow us to collect relatively fine-grained data on patient reports of pain and pain interference, craving, sleep problems and exercise for a comparatively large sample of individuals enrolled in buprenorphine or methadone treatment, another unique feature of the proposed trial. We anticipate this hypothesis-generating aspect of the trial will allow more detailed examination of relationships of these poorly-understood symptoms over time, exploration of these variables as mediators of treatment effects, and identification of changes in these variables that may be associated with OAT adherence. In addition, this will enable us to compare intensity and time course of symptoms for buprenorphine *versus* methadone patients, who may differ on multiple variables affecting pain and substance use treatment outcomes.

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4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

Overview

This is a Stage 1 treatment development project. In the first phase, we will consult with multiple experts and stakeholders to refine our plans to develop the integrated CBT4CBT-COPES program. This will involve developing a new introductory module that provides a rationale for integrated treatment of OUD and chronic pain, teaches functional analyses of the relationships between pain and opioid use, and introduces goal setting, the adaptive walking program, and the 5 A's. Two new modules drawn primarily from COPES will be developed (one covering chronic pain management, exercise, and pacing; the second on sleep and sleep hygiene; as well as using cognitive and behavioral skills to address other problems that frequently occur among individuals with chronic pain and OUD). The 7 existing CBT4CBT modules (functional analyses, coping with craving and strong affect, identifying and changing thoughts, decision making skills, assertiveness skills, problem solving, risk reduction) will be modified so that they (1) address pain, substance use and their interaction, (2) highlight how cognitive and behavioral skills can be applied to a range of problems to enhance generalizability.

Another key feature of development will be to create a system for daily feedback. Daily ratings of pain, interference, sleep, craving, steps, skill practice and goal attainment will be monitored during treatment via daily texts with a link to a survey to be completed; weekly ratings will be summarized in graphical form and presented with brief audio feedback from a study Coach, following existing COPES scripts via the Patient Dashboard. We will then conduct a brief feasibility trial with 5 individuals on agonist treatment who have chronic pain. Based on their feedback and those of the expert panel, the program will be finalized. In the 3-year R33 phase, we will conduct a randomized clinical trial in which 160 individuals will be randomized to standard care alone (buprenorphine or methadone with medical management and access to other services and counseling) or with access to the CBT4CBT-COPES program at the Liberation clinics and Connecticut Counseling Centers, Inc. over a period of 12 weeks, with a 6-month follow-up.

The study will be conducted in two phases:

Phase 1: Planning, Feedback and Development of Intervention (Years 1-2)

1. In the first month, our panel of experts on treatment of chronic pain in individuals with OUD (Jamison, Weiss, Martino, Becker, Sofuoglu) will review the planned integrated approach and provide feedback. They will have access to the existing CBT4CBT and COPES programs plus our plans for the integrated approach in advance of the meeting. We will then convene a one-day meeting in which the panel will offer feedback and advice on the adaptation. Minutes will be kept and sent to participants for review. Additional phone or web meetings will review progress, with another opportunity for feedback prior to the R33 Phase.
2. We will convene two other "panels", one composed of up to 20 individuals with OUD and chronic pain treated with buprenorphine or methadone from the Liberation or The Root Center programs or the ARC clinic, and up to 20 Liberation or Root Center or ARC clinic clinicians with experience with chronic pain patients. These "panels" will be used to develop videotaped vignettes for the new modules, as we have done successfully in the past[94]. These panels will meet individually via Zoom for1 hour, in a structured discussion format and audio taped to discuss the following topics:

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a. Special challenges for individuals with chronic pain and OUD on methadone or buprenorphine.
b. Discussion of interventions and strategies seen as particularly helpful/not helpful.
c. A 'wishlist' of tools and strategies for managing pain.

3. The audio tapes will be transcribed and redacted for any PHI. All tapes will be immediately destroyed upon transcription.In the next 12 months, we will develop the integrated CBT4CBT-COPES intervention. As in the existing CBT4CBT programs (a brief demonstration can be viewed on YouTube), emphasis is placed on the following core principles: First, ease of use and functionality (users require no previous experience with computers, material flows in a linear manner, all text is accompanied by audio so that only a 3th grade reading level is required, graphics are simple and straightforward). Second, using multimedia tools to convey key targeted skills in a highly engaging manner (skills and principles are conveyed via narration, animation, video vignettes with professional actors demonstrating targeted skills, interactive practice exercises, and multiple-choice questions at the end of each module). Consistent with the existing CBT4CBT programs, **the program will capture no identifying information or PHI**. The program tracks each user's movement through the modules (modules completed, time spent on each page, answers to multiple choice "Test Your Knowledge" questions, completion of homework, monitoring of goals and 5A's). Daily text link data will be used to add a new feature encompassing changes over time in pain and pain interference, sleep, craving, exercise, and goal attainment presented in simple graphics with brief personalized feedback allowing participants to see relationships and patterns among these variables.

Steps in this process, which parallel our previous successful adaptations[72, 75, 94] include:

- Development of the new modules: Integration and adaptation of the existing CBT4CBT program will be overseen by Drs. Heapy and MacLean, with Ms. Gordon as project manager. Initial scripts for narrations, videos, interactive exercises and quizzes will be generated by the core investigator group (Heapy, MacLean, Sofuoglu, Martino, Becker and Ms. Gordon) and reviewed by the Expert Panel. Their comments will be incorporated into final web scripts and detailed page-by-page storyboards will be developed.
- We anticipate each new module will have approximately 30 web 'pages', as well as about 8 total minutes of video 'episodes' and about 10 minutes of narration, with additional pages for interactive exercises, goal tracking, and quizzes. We also anticipate adding 5 new pages to each module of the existing CBT4CBT modules linking management of pain and drug use, pointing out similarity in skills used to manage drug use, pain, and related problems.
- Development of detailed scripts for 9 video episodes illustrating an individual with chronic pain and OUD learning and practicing the targeted skills for each module, with the videos comprising a compelling story arc so that users can see the pattern of progress, mistakes and setbacks, and learning that are common in this patient group. We arranged a Professional Service Agreement with Moving Pictures, Inc. The Moving Pictures team collaborated on the development of storyboards for the module flow, reviewed scripts, set up auditions for and casted actors, and produced and edited all video and audio content. In the original application we described working with Yale MedMedia, but due to other demands they were unable to meet the project deadline. Moving Pictures, Inc has worked on the development of earlier CBT4CBT version and were thus well suited to take on this task.
- Development of the program with Chess Health. We worked with web-based programmers at Chess Health to develop wireframes for all module content using the existing framework of previous CBT4CBT programs. In the original application we described working with Singlebrook Technologies, Inc., but since then, we worked with Chess Health to create an updated version of CBT4CBT with them, and were

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- able to use the existing program structure to integrate the new version of CBT4CBT-Copes.
- Ms. Gordon will collaborate to develop the wireframes for the new content/modules and work with the web developer, Chess Health., to create the integrated program, add the new audio, video, and practice components. Initially, we proposed to use an IVR system to; (1) engage with participants through a daily automated phone call, and (2) to deliver weekly personalized coach feedback via audio message. Dr. Heapy made the decision to fully integrate all components of CBT4CBT-Copes into the web-based platform in order maximizing efficiency of data collection and provide individuals with access to all features of the program contained with one platform. In this program, individuals will receive a daily text with a link to complete a 2-minute survey (the data will be linked to their program account). Having that data linked to the program account allows for coaches to provide feedback from daily surveys and module engagement. The weekly coach feedback (approximately 2-3 minutes) will be uploaded to the account and can be accessed as an audio clip on the individual's program dashboard. The 'beta' version of the CBT4CBT-COPES website will be carefully tested by the full research team.
- In the final 6 months, we will conduct a test of feasibility and acceptability in a small number of individuals on OAT with chronic pain (N=5). Once the initial CBT4CBT-COPES program is in development, it will be reviewed by 5 Liberation Clinic or Root Center clinicians, as well as 5 current OAT patients with chronic pain for usability, clarity and helpfulness of the material using Likert-type ratings forms questionnaires we have used successfully in past adaptations. We use both formal feedback questionnaires covering each component within each module as well as the "think aloud" protocol[126, 127] , in which users verbalize their reactions and thoughts while using the program. The think-aloud technique works particularly well with the patient groups targeted in our existing CBT4CBT programs (opioid, cocaine, marijuana, alcohol users) who may be unfamiliar with providing feedback through more formal means. These interviews will take place over zoom and for may be in group format or individual. Their comments will be integrated into the version of the intervention to be used in the R33 Phase

Phase 2: Randomized Clinical Trial (Years 3-5)

1. Evaluate the efficacy of CBT4CBT-COPES versus standard care (treatment as usual) at 3 months (primary endpoint) among 160 individuals with OUD and chronic pain enrolled in OAT at the Liberation clinics and Connecticut Counseling Centers Inc.. The primary outcome will be adherence to OAT (defined as continuous and verified enrollment at the 3-month timepoint); the primary pain outcome will be pain interference as measured by the PROMIS 6-item Pain Interference Short Form[128]. Hypothesis 1a: Individuals randomized to CBT4CBT-COPES will have greater retention at the 3-month point than those assigned to standard care. Hypothesis 1b: CBT4CBT-COPES will be associated with greater reductions in pain interference at the 3-month point.
2. Conduct a 6-month follow-up to evaluate the durability of effects on the primary outcomes. We hypothesize CBT4CBT-COPES will be associated with greater adherence and reduced pain interference compared with standard care at the 3 and 6-month follow-ups (6 and 9 months post randomization).
3. Conduct qualitative interviews with up to 44 individuals who participated in the study with a range of module completion (i.e., 1-9). Participants will be asked to evaluate the usability, measure the quality and give feedback on the CBT4CBT IMPACT program.
4. Conduct a sub-study consisting of a 1-time self-assessment with approximately 150 individuals evaluating stigma in the MOUD community. Participants will be asked a range of questions including, but not limited to stigma associated with race, substance use, chronic pain, physical issues, resilience, quality of life and perceived supports.

Procedures

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Initial Screening by Project Manager or Research Assistant: Individuals enrolled in the buprenorphine or methadone programs at Liberation and Connecticut Counseling Centers Inc. will be informed of the study via flyers, group meetings, or their clinicians. Individuals who indicate they are interested in hearing more about the study will be offered a meeting with the Project Manager or research assistant. At the first interview, study staff will provide an overview of the study and obtain written informed consent. We use a multiple-choice test to assess participants' comprehension of the protocol[129, 130], with ample time to review questions to assure understanding of the protocol, consent, and treatments offered. After determination of eligibility and informed consent, pretreatment assessments will be completed (see below). Randomization will occur as soon as participants have achieved a therapeutic dose of buprenorphine or methadone as confirmed by their clinician.

Urn randomization. To increase the likelihood that treatment groups are balanced with respect to demographic variables (gender, race), as well as likely prognostic variables (severity of opioid use disorder as moderate or severe via DSM-5 OUD symptom count, initial opioid experience of heroin versus prescription opioids, buprenorphine versus methadone treatment, pain severity (mild, moderate vs. severe) as operationalized by NRS average weekly pain rating). Participants will be assigned to treatment conditions through urn randomization[131, 132], using a Microsoft Access program that we have developed and implemented successfully in multiple previous trials [95, 119, 133, 134].

Treatment phase: Treatment conditions are described in detail below. Study treatments will last 12 weeks. During the treatment phase, all participants will meet weekly with the research assistant for completion of self-report and interview assessments preferably in-person, but with the option of virtual meetings. .

Clinical deterioration: We will closely monitor participant treatment response and safety in all conditions through weekly assessment sessions that will include brief assessment of psychiatric status. Although in our experience this is a very rare event, including during computer-assisted therapy[91], participants who show significant deterioration (e.g., increased drug/alcohol use or psychiatric symptoms that cannot be managed within the protocol, including significant suicidal or homicidal ideation) will be regarded as symptomatic failures, withdrawn from the treatment arm of the study, and referred for appropriate treatment (usually inpatient care). The project psychiatrist (Dr. Sofuoglu) will make the final withdrawal determination, using guidelines we have worked out in previous studies [109]. At the time of withdrawal, endpoint ratings will be made which include the full termination assessment battery (see below).

Termination and post treatment assessment: At the end of the 12-week treatment period, all participants will be re-interviewed by the research assistant, who will complete post treatment ratings (see Assessments, below). Access to the CBT4CBT-COPES program will be terminated; however, participants in all conditions will be strongly encouraged to continue in agonist treatment at Liberation clinics and Connecticut Counseling Centers Inc..

Follow-up: Follow-up interviews will be conducted 1, 3, and 6 months after termination (we find the one-month follow-up strengthens the relationship with the research staff and results in higher rates of follow-up). Follow-up interviews will include the full posttreatment battery (see Assessments, below), including assessment of utilization of other treatments and services. We will attempt to follow all participants in our intention to treat sample, regardless of their retention in treatment, using strategies that have been successful in multiple previous studies[91, 94, 135-137]. These include: (a) thorough explanation at the initial consent interview of the importance of follow-ups, (b) requiring that each participant provide at least 2 *verified* locators with knowledge of their whereabouts throughout follow-up, (c) use of multiple sources and locators to track participants[137], and (d) participant payment for each completed follow-up interview. *Using these procedures, our current rate of follow-up approaches 90-*

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95% across studies[138-140] for intention-to-treat analyses[99, 100]. For those who drop-out and cannot be re-engaged, we will ask them to complete a brief survey exploring their reasons for dropping out[141].

Rationale for study length: Given the 3-year limit for the R33 phase, in order to recruit a sample size for adequate power, we decided to evaluate primary outcomes at 3 months, with an additional 6 months of follow-up (9-month total study period). This will allow us to evaluate retention in OAT at the 6-month point. This should be adequate, as the bulk of attrition in OAT tends to occur earlier in treatment[142-145]. Three months will allow for adequate exposure to the CBT4CBT-COPES intervention for those assigned to that condition; the additional 6 months of follow-up will allow evaluation of durability of treatment effects, and importantly, pain symptoms and use of health services for an adequate period.

Rationale for design: While a 3- or 4-cell design would allow for the integrated CBT4CBT-COPES intervention to be tested against either CBT4CBT or COPES alone, because of the 3 year time limit for the R33 phase and the emphasis on adequate power for the trial, we decided the two-cell design would allow us to determine if the integrated approach improves adherence and pain outcomes over standard OAT treatment in an adequately powered trial. If determined to be effective here, subsequent studies could evaluate the efficacy of the integrated approach relative to CBT4CBT or COPES alone, which would also allow for detailed evaluation of mechanism. Recruiting from a large specialty program will allow us to recruit adequate numbers of both buprenorphine and methadone patients and hence enable some comparisons; this would be difficult in most primary care clinics. Both the Liberation evening clinic and Connecticut Counseling Centers Inc. are similar to many office-based buprenorphine settings.

Treatments

Standard care treatment as usual (TAU): Participants randomized to this condition will receive treatment-as-usual for the buprenorphine and methadone programs at Liberation Clinics and Connecticut Counseling Centers Inc., which includes regular medication management by the clinic physician, regular individual and group sessions and access to other services as needed (see letter of support). We have worked closely with Liberation Clinics and Connecticut Counseling Centers Inc. for over 20 years; we selected this program because they are high-quality, well-managed programs which have supported multiple clinical research programs (including both Yale and CTN multisite randomized trials of behavioral and pharmacologic approaches (see letter of support). All patients will also have access to counseling delivered onsite by highly experienced masters-level counselors employed at Liberation Clinics and Connecticut Counseling Centers Inc.. *Methadone and buprenorphine adherence will be monitored closely (via Timeline FollowBack as well as daily methadone visits, verification of buprenorphine prescriptions and counts, and evidence of buprenorphine/methadone in weekly urine toxicology screens).* Utilization of all services (including counseling, medical care, ED visits, legal services, pharmacological and non-pharmacologic treatments for pain, etc.) will be monitored closely throughout the trial and through follow-up, in all conditions, using the PACC-SAT (see Assessments).

CBT4CBT-COPES. Participants assigned to this condition will receive standard agonist treatment but also receive access to CBT4CBT-COPES. At the time of randomization, participants will be given a username and asked to select a password to access the CBT4CBT-COPES website. The Project Manager or research assistant will work with each participant to determine when, where, and how they will access the program (although participants will be free to access the program in a private area at the clinic as well). For the first session, she will guide the patient through the program to assure they are comfortable using the program and answer any questions they might have. Participants will be asked to spend at least one hour per week working with the program, either at the clinic or outside of the clinic (e.g. at their home). Participants will be asked to complete all 9 modules over the course of the 12-week study treatment period, repeating any modules, or sections, as they desire. At the start of each session, the program directory reviews the modules that the user has completed and directs users to either complete modules they have started or access new ones. The program tracks, for each

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participant, time logged onto the program, modules accessed, session progress, completion of practice exercises, and learning of CBT principles through multiple choice tests at the end of each module.

Participants randomized to this condition will also be provided with a pocket pedometer to facilitate their participation in the walking portion of the treatment. Study staff will measure each participant's stride length, adjust the pedometer stride length setting accordingly, and provide a brief demonstration of pedometer use. Pedometers will record only steps, distance and activity level. No personal information or GPS data will be recorded.

Daily texts with a link for survey: Following randomization to CBT4CBT-COPES, participants will undergo daily assessment via text that links to a web-based survey of pain intensity, pain interference, pedometer-measured step counts, sleep quality, sleep duration, and craving for seven days to establish a baseline of function for the purposes of treatment and providing regular feedback using questions derived from validated measures and used in our prior trials. After the baseline period, participants will continue to receive daily texts for the duration of the treatment. During treatment, two additional questions regarding practice of the treatment skills and progress toward the weekly meaningful activity goal will be included (see Table for treatment details). Patient-reported data collected on the daily texts with link to a survey will form the basis for regular feedback, which will be tracked and viewed in graphical form from the patient dashboard of the program. Participants will receive texts with a link to a survey each day at a time pre-selected by the patient.. Surveys will be no longer than 2 minutes in duration.

Assessments: Assessments include measures used to: 1) describe the sample, 2) measure primary/secondary outcomes during treatment and follow-up (both OUD and pain related), 3), evaluate likely mediators (e.g., CBT skills acquisition via multiple choice tests, catastrophizing) and moderators (e.g., psychiatric symptoms, medication dose, onset of pain versus OUD) in exploratory analyses, and 4) assess changes in functioning and impairment commonly affected in this sample (sleep, life role functioning). Urine toxicology screens are 13 panel and include opioids (buprenorphine, methadone, fentanyl, stimulants, cannabis, benzodiazepines). We rely on widely used, well-validated instruments, particularly those which have been recommended for clinical trials addressing pain[102] and substance use disorders[103, 146]. The battery is PHenX compliant [147, 148]. Hence, only the less well-known instruments are described below; all assessment instruments and the schedule of their administration are listed on the Table.

Instrument name	Rationale	Screen	Pre Tx	Weekly	Monthly	Post Tx/12 weeks	Follow-up 1, 3 6 mo.
Informed Consent Quiz [149]	Comprehension of protocol	x					
*PDC Screening Form	Demographics, treatment history	x					
Mini International Neuropsychiatric Interview (MINI)	Substance use & psychiatric disorders	x				X (OUD only)	X (OUD only)
Urine toxicology, breathalyzer	All drug use (13 panel)	x	x	x		x	x
Timeline Follow Back/ Substance Use Calendar	All types of substance use by day for full trial (baseline+84 days+6 months)	x		x		x	x
Brief Pain Inventory [151] and *Pain Characteristics and Treatment	Primary pain site, number of pain sites	X					
Brief Symptom Inventory [152-155]	Self-report of psychiatric symptoms		X	x		x	x
Addiction Severity Index (ASI) [156, 157]	Problems in life areas affected by substance use		X			x	x
CBT Knowledge test, Overdose knowledge[23]	CBT concepts, OAT knowledge, overdose risk		X			X	

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*PACC-SAT[158]	Utilization of medical, psychiatric, legal & other services		X		X	x	x
The PROMIS Sleep Disturbance 6a Form	Sleep duration, quality		X		X	X	X
Pain intensity-Numeric Rating Scale (NRS) [102]	Average pain intensity and pain interference over the past week	X	X	X		X	X
Pain Self-Efficacy Questionnaire[160]	Ability to accomplish common activities despite pain		X			X	X
Pain Catastrophizing Scale [161].	Catastrophizing (moderator)		X			X	X
Cold pressor test[41, 162, 163]	Pain sensitivity and threshold		X			X	
PROMIS 6-item Pain Interference Short Form[164-166]	Pain-related interference		X			X	X
PROMIS 6-item Pain Physical Functioning Short Form[164-166]	Pain-related functioning		X			X	X
PHQ-2 (Depression)	Self-report of depression (part of HEAL CDE for Pain studies)		X			X	
GAD-2 (Anxiety)	Self-report of Anxiety (part of HEAL CDE for Pain studies)		X			X	
Opiate Craving Scale	Self-report of current Opiate Craving		X	X		X	X
Patient Feedback for IMPACT program	Patient feedback about concepts and content included in the computer-based program			X (CBT only)			
Patient Evaluation of Treatment with GPIC question	Self-report of overall Global satisfaction					X	

- *The **Psychotherapy Development Center (PDC) Screening Form** has been used in multiple previous studies and provides general information, including demographic data, substance use history, previous substance use and psychiatric treatment history, medical history, recent life events, family history and social support, treatment attitudes and expectations, level of experience with computers and the internet.
- ***The Program and Client Cost-Substance Abuse Treatment (PACC-SAT)**[158], will be used to evaluate treatment and service utilization (including substance abuse, mental health, and medical care as well as social services, criminal justice) by participants in both conditions. It was adapted from the DATCAP [167, 168] by Yale health economist Dr. Jody Sindelar in order to provide a means of collecting cost and utilization data in addiction RCTs. It has been used successfully in multiple cost studies by our group[104, 105, 169-171]. While a full cost effectiveness analysis is beyond the scope of the Stage 1 project, use of this form will allow estimates of service use and costs by treatment condition as we have in previous trials [72].
- ***The Pain Characteristics and Treatment** form is a measure adapted from our prior trials[90, 117] and used to collect additional data on participant's pain conditions. We will assess pain condition (musculoskeletal, neuropathic, headache, etc.), primary pain site, number of pain sites, average, worst and least pain rating over the past week, current pain treatment regimen including pharmacological, non-pharmacological and complementary and integrative health approaches, and temporal sequence of pain and OUD.

5. Genetic Testing N/A ☒

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

In Phase 1, Panel 1 will be composed of up to 20 individuals with OUD and chronic pain treated with buprenorphine or methadone from the Liberation or The Root Center programs or the ARC clinic and up to 20 Liberation or Root Center or the ARC clinic clinicians with experience with chronic pain

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patients. This panel will be used to develop videotaped vignettes for the new modules, as we have successfully done in the past(94).
In Phase 1, Panel 2 will be composed of 5 Liberation or Root Center OAT patients with chronic pain and 5 Liberation or Root Center clinicians who will review the CBT4CBT-COPES program during development for usability, clarity and helpfulness.
In Phase 2, participants will be 160 individuals on agonist treatment at the Liberation Program clinics and Connecticut Counseling Centers Inc.. Currently, Liberation serves 1400 individuals with SUD each day; 970 are enrolled in OAT (500 methadone, 470 buprenorphine). A new buprenorphine evening clinic is opening in Bridgeport during 2019; thus, by the time the proposed project would begin, an additional 400 buprenorphine patients are projected. Current clinic data indicates that 40% report chronic pain; average length of retention in the methadone program is 1 years; average retention on buprenorphine is 6 months. Thirty-five percent are female; 30% are Latinx and 25% are African American.
Qualitative Interviews will be conducted on up to 44 individuals who present for their post-treatment interview or Follow-up 1, who were randomized to IMPACT and who completed at least 3 of the 9 modules. Participants will be offered the opportunity to partake in this additional interview which will take place over zoom and be audio-recorded. Once audio-recordings are transcribed they will be immediately destroyed, and all transcriptions will be coded only with the participants original study ID. No PHI will be collected at this time. Qualitative interviews will take approximately 1 hour to complete.
Sub-study self-assessment will be conducted on approximately 150 individuals who are currently on MOUD. Individuals will be recruited through clinicians, flyers and self-referral. No PHI will be collected and participants will use direct entry into an anonymous public link on REDCap.

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?
Inclusion/exclusion criteria will be as broad as possible to capture a representative sample of individuals with chronic pain enrolled in agonist treatment programs.

Inclusion criteria: Eligible participants will be 18 years of age or older, meet DSM-5 criteria for OUD and enrolled in methadone or buprenorphine treatment at Liberation and Connecticut Counseling Centers Inc.; report high impact (Grade 3) chronic pain defined by experiencing pain that limits life and work activities on most days or every day in the past 3 months (indicating chronicity); self-reported ability to walk at least one block (for the exercise component of CBT4CBT-COPES; we expect very few individuals would be ruled out based on this criterion. We will not require computer access, as participants without internet access will be able to access the program at the clinic, usually at the time of weekly assessment visits, in a separate room. The very few participants who

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do not have a cell phone will be supplied one for the duration of the study, using procedures we have worked out for previous studies.

Exclusion criteria include inability to read, write, and speak English at a third grade level (for reading informed consent); untreated or inadequately treated bipolar or psychotic disorder or current suicide risk as identified by the Demographic Form for the previous 2 weeks before screening, life threatening health conditions that would impede participation (e.g., end stage renal failure, malignant cancer requiring chemotherapy excluding melanoma); planned surgical treatment related to pain; and pending legal action or planned relocation that makes it unlikely they would be able to complete the study. Women of child-bearing age will be included, as there is no contraindication for CBT for pain or OUD for pregnant women.

9. How will eligibility be determined, and by whom? Write here

Phase 1

Clinicians who work directly with chronic pain patients in the Liberation or Root Center Clinic or the ARC clinic will be approached to comprise a panel (Panel 1) N=20 These clinicians will refer up to 20 individuals with chronic pain treated with buprenorphine or methadone from Liberation or The Root Center or the ARC clinic who will meet in a structured individual format via Zoom for about 1 hour to discuss 1. Challenges for individuals with chronic pain and OUD on OAT. 2. Interventions and strategies both helpful and unhelpful to this population and 3. A 'wishlist' of tool and strategies for managing pain. The Project Manager will meet with interested participants to explain the study and review the Verbal Consent form.

Panel 2 will consist of 5 Liberation or Root Center clinicians and 5 current OAT patients at Liberation or Root Center who are clinician referred to review the CBT4CBT-Copes program as it is being created and give feedback on characters, narration, content, screenshots, etc.. The Project Manager will meet with interested participants to explain the study and review the Verbal Consent form.

Phase 2

Initial Screening by Project Manager or Research Assistant: Individuals enrolled in the buprenorphine or methadone programs at Liberation and Connecticut Counseling Centers Inc. will be informed of the study via flyers, group meetings, or their clinicians. Individuals who indicate they are interested in hearing more about the study will be offered a meeting with the study staff. At the first interview, the Project Manager will provide an overview of the study and obtain written informed consent. We use a multiple-choice test to assess participants' comprehension of the protocol (10, 11), with ample time to review questions to assure understanding of the protocol, consent, and treatments

10. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Phase 1

No names, PHI or other identifying information will be recorded on any study documents. We will only collect information that is needed for research in order to develop the CBT4CBT-COPES program. A brief demographic form will be included to be sure there are varying demographics in the sample. Questions will include gender, race and years of pain experience as well as a Brief Pain Inventory questionnaire. Zoom audio tapes will be redacted if they contain any PHI and will be destroyed immediately following transcription. All contact information will be destroyed once payment is received by the participant.

Phase 2

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For all treatment conditions, frequent in-person or virtual monitoring (at least weekly) of the participant's clinical status by clinicians and research staff will ensure identification and withdrawal from the study of participants who show significant psychological or symptomatic deterioration.

Interventions.
The experimental intervention, CBT4CBT-COPES will be added to standard full-service opioid agonist treatment at Liberation and Connecticut Counseling Centers Inc., including counseling, medication and access to other services as needed. Computer-based interventions have been used safely in multiple investigations with a range of populations, and we are unaware of any reported risks associated with these interventions. A recent Agency for Healthcare Research and Quality (AHRQ) comprehensive review of computer-assisted interventions for a wide range of health and mental health issues found no reports of adverse events associated with these programs (24). Similarly, our previous trials have indicated that use of the CBT4CBT and COPES programs have been safe and effective. Thus, while we believe adverse events are likely to be rare, we will nevertheless continue to be vigilant in case of their occurrence. Thus, the study staff will be available to answer questions after the initial program orientation. The existing CBT4CBT intervention is highly secure and does not collect any PHI nor specific information regarding recent drug use or illegal activities. Moreover, the design of the program has closely followed recommended ethical and safety guidelines for use of computer assisted behavioral therapies developed by Sampson and Pyle (25), including (1) assurance of confidentiality, (2) determination of appropriateness of the specific form of training, in this case, CBT, which has been shown to be effective for a wide number of substance use disorders and populations, (3) adequate introduction to the computer program by staff to reduce possible anxiety about use of the system, (4) provision of follow-up consultation with a clinician if needed, and (5) supervision of the treatment process by a clinician (25, 26).

Urine and breath specimen collection.
Urine and breath (if Covid guidelines allow) specimens are collected primarily as safeguards to participants and should add no risks other than those normally associated with these procedures.

Rating scales and questionnaires
Phase 1
A list of questions will be generated by a panel of experts in the treatment of chronic pain. Panel 1 will "brainstorm" answers and ideas in individual sessions in an effort to help develop the CBT4CBT-COPES program. Panel 2 will review the CBT program content while in development for clarity and understanding at a time when adjustments to the program can still be made. Any identifying information collected on those who participate such as telephone number and email address for payment purposes will be immediately destroyed once payment is received by the participant.

Phase 2
These are all non-invasive, should add no risk, and have been used without difficulty or any adverse events in our previous studies with this population. The major disadvantage is the time taken to complete them. Our past experience with these measures indicates that they are acceptable to participants. Careful efforts aimed at maintaining confidentiality have been effective in previous research, and only participants' study code numbers will be recorded on the forms themselves to protect confidentiality.

IVR calls have been shown to be safe in a number of drug-using samples (27) and the questions to be used here (pain interference, sleep, pain, craving, steps) have been used in similar surveys

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without reactivity (28, 29). Therefore, we anticipate daily texts with a link to a survey will also prove safe and an effective means of data collection.

In the original COPES efficacy trial we used proactive weekly automated adverse event monitoring to identify adverse events, particularly for the walking component of the trial. We detected only one serious event that was related to the trial, a participant with an active diabetic foot ulcer that appeared to be aggravated by walking. We now screen for active diabetic foot ulcer in our studies. We anticipate that diabetic foot ulcer will be less common in the younger sample in the proposed study compared to our prior work in the Veterans Health Administration (VHA). In the COPES efficacy trial we found forty-seven participants (51%) experienced 92 AEs. The most commonly reported AEs were musculoskeletal events (42.4%) and worsening pain (16.3%). Among the worsening pain events, 24% were described as being related to increased activity, exercise, or stretching associated with study participation. This finding is consistent with prior studies that have assessed exercise related AEs among patients with chronic pain, serious adverse events were rare and often not related to the exercise intervention. Most AEs are classified as being increases in pain or common musculoskeletal injuries such as sprain or muscle soreness associated with exercise and resolved quickly. Overall, among a group of predominantly sedentary and obese/overweight patients with longstanding, moderately severe pain the walking intervention was well-tolerated and safe.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

Phase 1

Verbal Consent will be obtained and no identifying information will be collected aside from the phone number to conduct the interview and email address to send payment to the participant. These will be destroyed immediately following receipt of payment by the participant. All participation is voluntary.

Phase 2

Informed Consent

The Project Manager/Research Assistant will obtain written informed consent prior to any study related procedures. The informed consent process will be conducted in a private, quiet setting. The staff member and the participant will discuss the basic components described in the consent form. These include: participation is voluntary and participants may withdraw without consequences to clinic services received, purpose, procedures, randomization, visit schedule, risks and benefits, potential compensation, alternatives to study participation, and confidentiality. Potential participants will be provided an opportunity to ask questions and time to consider his/her decision to participate. We use study-specific comprehension quizzes to ensure the participant has an adequate understanding of study; any incorrect responses are reviewed with the prospective participant to assure they understand (10, 11). A copy of the consent form will be given to the participant.

For Qualitative Interviews a verbal consent will be sought by the interviewer before the session will begin on Zoom.

For the sub-study a verbal consent will be sought by the Research Assistant before the self-assessment will begin in REDCap.

Protection against risk.

As noted above, risks are minimal and not different from those of equivalent non-study interventions at this clinic. In all conditions, we will closely monitor participant treatment response and safety in all conditions through weekly assessment sessions; these will include breath and urine screens,

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and assessment of psychiatric status. participants who show significant deterioration (e.g., increased substance use or psychiatric symptoms that cannot be managed within the protocol, including significant suicidal or homicidal ideation) will be regarded as symptomatic failures, withdrawn from the treatment arm of the study, and referred for appropriate treatment (typically a more intensive level of care or agonist therapy). All research staff and clinicians at Liberation and Connecticut Counseling Centers Inc. are also trained to administer aerosol NARCAN which is available at all clinics. The independent evaluator (Dr. Sofuoglu) will make the final determination as to whether a participant should be withdrawn from the treatment arm of the study. At the time of withdrawal, endpoint ratings will be made which include the full termination assessment battery. We will recruit participants via postings and flyers distributed at the Liberation and Connecticut Counseling Centers Inc. opioid agonist clinics. The screening of individuals using the inclusion and exclusion criteria, as well as the screening instruments and diagnostic interview (MINI), will minimize the risk of including participants who are inappropriate for the study. Participants will be withdrawn from the treatment arm of the study if they show severe psychological or symptomatic deterioration, unacceptable levels of adverse events as determined by the study psychiatrist (Dr. Sofuoglu), if clinically necessary for ethical or safety purposes. Participants withdrawn from the treatment arm of the trial for these reasons or because they wish to withdraw from the study will be offered treatment as usual at the clinic or be referred to a higher level of care (or agonist treatment) when appropriate. Private referral and/or hospitalization may also be offered according to the participants' needs and wishes.

Confidentiality.
As noted above, the data collected from interviews and self-report forms, as well as urine and breath collection, carry no risk other than those normally associated with these procedures. All research staff and clinicians receive annual Good Clinical Practice, Human Subjects Protection, and HIPAA training through the Dr. Carroll's Psychotherapy Development Center (which provides training and ongoing reliability checks for all staff working on affiliated clinical trials such as the proposed project). Our data collection and management procedures are fully compliant with HIPAA. In addition:

- NIH provides Certificates of Confidentiality for all such trials.
- Our study forms have been designed to avoid collecting identifiable information (e.g., no PHI is collected on CRFs). The only dates collected are protocol session dates. These are changed to 'number of sessions completed' when data sets are anonymized and released to other investigators.
- Research data are collected on electronic CRFs, directly entered into the database. Any paper CRFs are scanned at the clinic site and electronically sent to data managers in our research offices on a closed secure network. All computers used by research staff are password protected. No identifying information is on CRFs.
- Confidentiality in regard to collected materials will be maintained via a numbered reference system maintained by the Project Director. Participants' names will appear only on the consent form, HIPAA authorization form, and "key" form kept by the Project Director.
- Limits to confidentiality include only disclosure of acute suicidality, homicidality, or abuse of a minor/elder, as is standard in clinical practice and indicated in the consent form.
- Data collected by the Yale RedCap system are stored at the Yale secure data center; data sets do not include any identifying information. At the conclusion of the study, all locator data are destroyed. Source data are generally destroyed 3 years after completion of the study at a secure location (the Principal Investigators office: Alicia Heapy, PhD; 950 Campbell Avenue, West Haven, CT) and destroyed per Yale IRB guidelines.

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12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

Overall level of risk for participants is minimal given the nature of this project and procedures in place for careful identification of potential subjects, informed consent process, and protection of confidentiality.

We have developed a standard DSM report form that is used in all of Dr. Carroll's trials and summarizes, *on a quarterly basis*:

1. Recruitment, retention, and follow-up rates for the study and compares them to target rates.
2. Rates of data completeness and availability of primary outcome data.
3. Occurrence of AEs and SAEs.
4. Report of study progress since the last report.
5. Rates of recruitment of women, minorities, and children with respect to targets.

DSM reports are forwarded to the Yale IRB at the time of the annual review and re-approval.

Because the projected effect sizes may not be large enough for detection during interim analyses, we are not proposing a preliminary analysis of accumulating efficacy and safety data by treatment assignment.

Participants who experience a significant psychiatric or medical problem requiring an overnight hospitalization at an acute care facility will be considered to have experienced an SAE. In general, most SAEs will result in inpatient care and thus in transfer to a higher level of care. All SAEs will result in the completion of an SAE Form and a verbal report within one hour to the Principal Investigator (Dr.Heapy) and timely notification to the Liberation and Connecticut Counseling Centers Inc. clinic director. Adverse events that are serious and unanticipated and probably, possibly, or definitely related or adverse events occurring with greater frequency than anticipated will be reported to the Yale Human Investigation Committee within 48 hours of discovery. The procedures for SAE reporting include written documentation using the clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel. Communication of recommendations and decisions from all parties (Yale Human Investigations Committee, and Liberation and Connecticut Counseling Centers Inc. Programs Administration) are made back to the investigator in a timely manner. We will report all protocol amendments or changes in the informed consent form to NCCIH as well as any temporary or permanent suspension of patient accrual.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A
    i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?

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ii. What provisions are in place for management of interim results?
iii. What will the multi-site process be for protocol modifications? *Write here*

13. Statistical Considerations: Describe the statistical analyses that support the study design.

Data management and analyses

Our data management system maximizes efficiency by front-loading quality control measures to insure accurate collection and rapid turnaround for identification and correction of omission and inconsistencies, in accordance with GCP guidelines. We have streamlined case report form (CRF) development for our studies by using the Yale-supported RedCap survey tool. The use of web-based direct entry provides immediate data capture and allows the data team to perform real-time data monitoring and analysis; it also prevents entry of illogical and out-of-range values and allows for timely response to address missingness or other collection errors. The data manager sets up the study in RedCap and creates the assessments The research assistant will access the assessments through RedCap for data collection. Any participant self-assessments will be collected through RedCap's secure survey tool. This web-based data collection system affords simple form creation and display through a web interface, while maintaining privacy and Yale/HIPAA data security standards. The data manager routinely exports the data to SPSS data files, where cross-form and accuracy checks are performed. Any inconsistencies or errors found during this process produce queries that are immediately sent to the research assistants for resolution.

Data analyses and power

Effect size estimates for CBT4CBT-COPES on retention come from our previous CBT4CBT research indicating a small to medium effect size for treatment adherence (*delta* .23 to .42) and opioid outcomes (*delta* .40)[69]. Our non-inferiority trial of COPES compared to clinician delivered CBT for primary chronic pain found no significant differences in pain outcomes by treatment (clinician CBT versus COPES), allowing us to infer effect sizes consistent with previous meta-analyses[51]. We used G*Power and estimated that for the primary endpoint analysis, with a sample size of 160 (80/group), power would be adequate (>.80) to detect a 20% difference in adherence, consistent with a small to medium effect. As a Stage 1 trial, a conservative estimate of a small to medium effect improves our chances of finding differences when they exist.

Specific Aim 1: Primary Hypothesis 1a. CBT4CBT-COPES, compared to standard treatment as usual (TAU), will improve OAT adherence at the 3-month point. The principal strategy will be logistic regression assessing retention defined by dichotomous continuous enrollment in agonist treatment, with evidence of agonist treatment adherence in the week prior to day 84, with OAT type as a covariate.

Secondary Hypothesis 1b. CBT4CBT-COPES will be associated with greater reductions in pain interference than TAU at the 3-month point. Changes in pretreatment to post treatment pain interference will be evaluated with a MANOVA assessing the 2 PROMIS Pain Interference Short Form scores by treatment condition with OAT type as a covariate.

Specific Aim 2: Primary Hypothesis 1a. CBT4CBT-COPES, compared to TAU, will have durable effects at 6-month follow-up (9 months post randomization). The principal strategy will mirror the post treatment analyses with logistic regression assessing adherence rates and MANOVAs evaluating PROMIS pain interference score change from baseline to follow-up.

Exploratory aims and hypotheses:

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1. CBT4CBT-COPES will show greater improvement in pain measures compared to TAU. Multilevel longitudinal models will be used to assess differences in the rates of change in pain severity by week from pretreatment levels through treatment completion using MIXED models with treatment and time as independent variables, and OAT type as a random effect. Similarly, changes in pretreatment to post treatment pain intensity and pain catastrophizing will be evaluated with MANOVAs, with treatment, time, and the interaction of treatment by time as the independent variables and OAT as a covariate.
2. CBT4CBT-COPES, compared to TAU, will reduce depressive and anxiety symptoms over time. These analyses will mirror those listed for improvement in pain severity– examining differences in rates of change by week by treatment condition.
3. CBT4CBT-COPES, compared to TAU, will reduce pain volatility compared to TAU. Intra-individual pain volatility will be measured as the average absolute magnitude of deviation in pain levels around each person's own pain level trajectory over time during the active treatment period[5, 172]. A pain volatility score for each participant will be obtained from multilevel models, with weekly assessments over time nested within individuals. Subsequent regression models will be conducted to evaluate differences in pain volatility by treatment condition with OAT type as a covariate. Baseline pain, the individual-level pain intercept and slope scores derived from the multilevel models, and demographic variables will be included as covariates.
4. Within CBT4CBT-COPES, reductions in pain volatility will be associated with greater adherence. Pain volatility scores will be created using the models described above, using the daily texts with link to a survey collecting daily pain severity scores by month. Using multilevel longitudinal models to evaluate volatility by month, we will assess the relationship between changes in pain volatility over time and treatment completion. We will also assess differences in monthly pain volatility, using data based on the fine grained daily data, by OAT type
5. CBT4CBT-COPES, compared to TAU, will reduce pain sensitivity. Changes in pretreatment to post treatment pain sensitivity will be evaluated with a MANOVA assessing the two Cold Pressor scores by treatment condition with the OAT covariate.

Moderators will be evaluated using general linear models with primary outcomes, independent variables, and covariates and include separate models for: a) psychiatric comorbidity b) type and dose of opioid agonist treatment (methadone vs. buprenorphine); c) chronicity of onset of chronic pain and OUD, for example. Mediators are clinical symptoms during treatment and include variables such as pain catastrophizing and pain related self-efficacy. We will use the Hayes & Preacher method and software macro[173] to evaluate mediators in models looking at the primary outcomes and exploratory mediators comparing CBT4CBT-COPES to TAU as we have in previous research[174, 175].

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

B. DRUGS/BIOLOGICS ☒N/A

C. DEVICES ☒N/A

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SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: Phase 1, Panel 1 N=40 (20 clinicians, 20 Liberation or The Root Center or the ARC clinic patients; Phase 1, Panel 2 N= 10 (5 clinicians, 5 Liberation patients) Phase 2 clinical trial N=160
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/web postings	☐ Radio
☒ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☐ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☐ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☒ Other: clinician referred and presentations in clinic groups		

* Requests for medical records should be made through JDAT as described at http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:
   a. Describe how potential subjects will be identified. Individuals enrolled in the buprenorphine or methadone programs at Liberation and Connecticut Counseling Centers Inc. will be informed of the study via flyers, group meetings, or their clinicians. Individuals who indicate they are interested in hearing more about the study will be offered a meeting with the Project Manager or research assistant.
   b. Describe how potential subjects are contacted. Potential participants will contact research staff from flyers or through clinician referral
   c. Who is recruiting potential subjects? Project Manager, Research Assistants and Clinicians

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:
   Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?
   ☐Yes, all subjects
   ☐Yes, some of the subjects
   ☒No

   If yes, describe the nature of this relationship. *Write here*

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)
   Choose one:
   ☐ For entire study
   ☐ For recruitment/screening purposes only
   ☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

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i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: *Write here*

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: *Write here*

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Phase 1:

Panel 1 (Months 2-6): This panel will be composed of up to 20 individuals with OUD and chronic pain treated with buprenorphine or methadone from the Liberation or The Root Center programs or the ARC clinic, and up to 20 Liberation or Root Center or the ARC clinic clinicians with experience with chronic pain patients. They will be utilized to develop videotaped vignettes for the new modules, as we have done successfully in the past. The potential participant will contact the Research Assistant directly either by phone call or text from flyer given to them by the clinic. The Research Assistant and potential subjects will discuss the basic components described in the HIC-approved Information Sheet via telephone. Potential participants of Panel 1 will be provided an opportunity to ask questions and time to consider his/her decision to participate in the development of the program. Verbal consent will be obtained by the RA prior to engaging a client or clinician in the pilot activities. A Zoom meeting will be set up by the RA with the interviewer and interviewee and an invite will be sent to each of them for the agreed upon time. The Zoom audio call will be audio taped for transcription at a later time. The tapes will be immediately destroyed upon completion of the transcription. A copy of the Information Sheet will be given to the participant by the clinic. RA will email gift card to participant once interview is completed. All contact information will be destroyed once payment is received.

Panel 2 (Months 18-24): Once the initial CBT4CBT-COPES program is in development, it will be reviewed by 5 Liberation Clinic or Root Center clinicians, as well as 5 current OAT patients with chronic pain for usability, clarity and helpfulness of the material using Likert-type ratings forms questionnaires we have used successfully in past adaptations. The Project Director/ Research Assistant and potential subjects will discuss the basic components described in the HIC-approved Information Sheet in a quiet, private setting over zoom. Potential participants of Panel 1 will be provided an opportunity to ask questions and time to consider his/her decision to participate in the development of the program. Verbal consent will be obtained by the Project Manager/RA prior to engaging a client or clinician in the pilot activities. A copy of the Information Sheet will be given to the participant.

Phase 2:

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At the first interview, the Project Manager or Research Assistant will provide an overview of the study and obtain written informed consent prior to any study related procedures in a quiet and private office space provided by the clinic to the research team. The Project Manager/RA and the participant will discuss the basic components described in the HIC-approved consent form. These include: participation is voluntary and participants may withdraw without consequences to clinic services received, purpose, procedures, randomization, visit schedule, risks and benefits, potential compensation, alternatives to study participation, and confidentiality. Potential participants will be provided an opportunity to ask questions and time to consider his/her decision to participate. A comprehension quiz will be given to ensure the participant has an adequate understanding of the study and a copy of the consent form will be given to the participant.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
   We use a multiple-choice test to assess participants' comprehension of the protocol with ample time to review questions to assure understanding of the protocol, consent, and treatments offered.
8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   N/A

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. *Please review the guidance and presentation on use of the short form available on the HRPP website.*

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒Not Requesting any consent waivers

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? In Phase 1, no PHI will be collected. In Phase 2, PHI that will be collected includes names, addresses, phone numbers, and email addresses for locator purposes.

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Phone numbers will also be used for daily text messages which will be pushed out by Chess. These phone numbers will be stored on a secure server and no data will be stored on the phone. For participants who do not want to use their own phones or do not have a phone a study cell will be provided. Our study assessments/forms have been designed to avoid collecting identifiable information (e.g., no PHI identifiers are collected on CRFs). The only dates collected are protocol session dates. These are changed to 'number of sessions completed' when data sets are anonymized and released to other investigators.

2. How will the research data be collected, recorded and stored? In Phase 1, "focus group" zoom audio recordings will be captured on an encrypted computer for security of the recording. The recordings will be zipped and password protected. They will be stored in Yale Box, which is HIPAA compliant, and securely transferred to transcriptionist. Once recordings are transcribed all recordings will be erased. Any identifying information or PHI contained in the recording will be redacted for further security. In Phase 2, Research data are collected on CRFs in the Yale RedCap secure platform. All computers used by research staff are password protected. No identifying information is on CRFs. Only authorized individuals will have access to CRFs.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☒Laptop Computer ☒Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   All portable devices contain encryption software Confidentiality, with regard to collected materials, will be maintained via a numbered reference system maintained by the Project Director. Participants' names will appear only on the consent form, HIPAA authorization form, and "key" form kept by the Project Director. The key form linking subject names to ID codes will be stored in a separate, locked file cabinet. Data are stored at our secure data management center; data sets do not include identifying information. In addition, we have designed all of our CBT4CBT websites such that no sensitive information (i.e., information on illegal behavior) or PHI is collected or stored by the website (including IP address). Moreover, to avoid participants inadvertently revealing sensitive information, the website does not use any 'blank fills', and the program shuts down after 10 minutes of inactivity.

   Chess Health, an outside vendor, will build and maintain the information system that will be used for the daily survey data collection. Chess Health uses Amazon Web Services to host the system in their secure environment. The environment is in line with Yale/HIPAA rules of privacy and security. Chess Health will have your phone number in order to send participants the link to the daily survey. At the Conclusion of this study, electronic files containing personal or confidential data will be destroyed according to Yale IRB guidelines. Phone number will not be connected to any other identifying information we collect.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

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Paper copies of participant records containing ID numbers will be moved to a secure archive in Temple Medical Building; 40 Temple Street, New Haven, CT. Source files with subject names will be stored in the regulatory coordinator's office separately under triple lock (building entry, office entry, separate locked file cabinet designated for name files only). The paper log linking subject names to ID codes will be stored in a separate, locked file in the regulatory coordinator's office. At the end of the required record retention period, data will be destroyed in accordance with Yale ITS policies 1609 and 1609PR.01. Source data are generally destroyed 3 years after completion of the study at a secure location by Shred-It.

6. If appropriate, has a Certificate of Confidentiality been obtained? In notice of award

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

There is no guarantee of direct benefit to study participants. The results will be directly relevant to NIDA and the NIH HEAL initiative. Potential benefits to participants include significant psychotherapeutic exploration through the provision of study therapies. Psychiatric examinations are also potential benefits. The major potential benefit in this study is in reduction of opioid and other substance use via the study treatments, which may, in turn, foster improvement in participants' legal, medical, interpersonal, psychological and occupational functioning.

The knowledge to be gained as a result of the proposed research is likely to be of considerable significance in understanding strategies to improve retention and treatment outcome for individuals with chronic pain who are maintained on buprenorphine or methadone. The study treatments and procedures to be evaluated carry low risk and are not significantly greater than the risks to individuals with opioid use disorder with chronic pain who do not participate in this research.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   Individuals who do not wish to participate or who are ineligible for the trial will be referred back to their clinician.

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
   Phase 1, Panel 1 will be compensated $60 for their feedback regarding relevant content for the proposed CBT4CBT-COPES program. A gift card will be emailed to participants immediately following the completed interview.
   Phase 1, Panel 2 will be compensated $60 for review the program and providing feedback on relevance of content and usability.
   Phase 2 , randomized trial: All participants will be offered compensation for time spent completing study assessments including $25 for screening, $35 for the baseline assessment, $20 for weekly assessments for each weekly assessment completed in the treatment phase of the study (total possible $180), $20 for each monthly assessment (total possible $40) and $35 for post-treatment assessments. Participants will also receive $50, $75 and $100 for each completed follow-up interview. Therefore, a total of $540 is possible. Incentives will be built in for completing assessments in-person which include $5 for weekly assessments totaling $45 ($5X9 weeks), $40

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for monthly assessments ($20X2 timepoints, $20 for each posttreatment and follow up attended for a possible total of $705.
Qualitative Interviews: Up to 44 individuals who were randomized to the IMPACT program will be offered $60 compensation for completing a 1-hour interview evaluating the IMPACT program.
Sub-study: Approximately 150 individuals on MOUD will be offered $35 for completing a 1-hour self-assessment associated with stigma across many domains of life.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
There will be no costs to subjects associated with participation in this study. Subjects will not be charged for study treatments or evaluations they receive at the clinic as part of this trial. Subjects may be charged for treatment as usual at the clinic; but most patients receive treatment with no-out of pocket expenses or on a sliding scale

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

    a. Will medical treatment be available if research-related injury occurs? *Write here*

    b. Where and from whom may treatment be obtained? *Write here*
    c. Are there any limits to the treatment being provided? *Write here*
    d. Who will pay for this treatment? *Write here*
    e. How will the medical treatment be accessed by subjects? *Write here*

Because we are evaluating standard behavioral approaches with strong empirical support and no known adverse consequences, study related injuries are expected to be extremely rare. There will be no compensation and/or medical treatment available if injury occurs. Participants or their insurance carrier will be expected to cover costs of any medical treatment.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?
Yes ☐ No ☒

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