HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2016-1)

Protocol Title: Title of Research Project: Pilot study of galantamine and CBT4CBT to reduce post-taper relapse for MAT

Principal Investigator: Kathleen M. Carroll, PhD

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(*If applicable*) **Clinicaltrials.gov Registration #:** Click or tap here to enter text.

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.

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
We are proposing a randomized pilot feasibility study to evaluate the effects of galantamine, a reversible and competitive inhibitor of acetylcholinesterase, versus placebo, on preventing relapse to opioid use following tapering from methadone or buprenorphine maintenance (Medication Assisted Treatment, or MAT) among adults with opioid use disorder, with additional behavioral therapy (web-based cognitive behavioral therapy) provided across all conditions to help individuals successfully transition from MAT to a drug-free state.

   We aim to evaluate the feasibility and potential efficacy of up to 16 mg/day galantamine treatment among 30 adults aged 18 or over who have recently chosen to be tapered off methadone or buprenorphine. Participants will be randomized to receive galantamine (extended release) or matched placebo to be initiated within a week of initiating of a standard medically monitored buprenorphine or methadone taper and continue until 4 weeks after the end of the taper (length of taper is determined by the CMU physician; for most patients it occurs over 4-6 weeks; thus we expect the duration of treatment to be 8-10weeks for most participants). Participants will then be followed for three months to evaluate the durability of treatment response.

   This dose and treatment duration are similar to those used in our previous studies with substance using patients, including those maintained on methadone (1-4). Primary outcomes will include: (1) successful completion of taper (2) opioid withdrawal symptoms, and (3) opioid use, assessed by self-report and urine samples during and up to 3 months after the end of opioid taper.

   Exploratory Aims: To explore the potential mechanisms underlying galantamine's effect on the main study outcomes. These include measures of cognitive function and inflammation, which will be measured at the beginning of treatment, immediately after the taper ends, and at the end of treatment.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
Approximately 12 months

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.

   Improving outcomes after methadone or buprenorphine maintenance for individuals with opioid use disorder.

   The efficacy and public health significance of treating opioid-dependent via maintenance therapies (methadone or buprenorphine) is compelling. Compared to no medication or detoxification, maintenance therapies are associated with significantly less morbidity and mortality (5, 6). The appropriate focus of current public heath efforts is on making maintenance therapies more widely available as a strategy to address current high rates of opioid use and mortality in the US (7). At the same time, there is no consensus on the length of time most opioid-dependent individuals should be maintained on either methadone or buprenorphine (6). Moreover, although not all individuals wish

to remain on buprenorphine or methadone indefinitely, rates of relapse among individuals seeking to taper off methadone or buprenorphine are extremely high (estimated at 80% or higher) (8-10) and relapse carries significant risk over overdose and death (11-13). Strategies for increasing the likelihood of successfully tapering individuals from methadone/buprenorphine maintenance to abstinence are clearly needed.

Multiple factors likely contribute to these unacceptably high rates of relapse, including physical and psychological stress associated with reducing methadone/buprenorphine dose over time, adjusting to the lack of support/structure and monitoring of the programs in which MAT is delivered, and so on. Moreover, individuals maintained on methadone typically have multiple problems with cognitive function, including deficits in memory, attention, and problem solving (14); these are likely exacerbated with the stress of detoxification and transitioning from methadone maintenance programs. We therefore propose a randomized pilot feasibility study evaluating a combined behavioral therapy/pharmacotherapy approach to help individuals successfully transition from MAT to a drug-free state.

Rationale for computerized CBT

To provide cognitive and behavioral tools for the transition to abstinence, we will provide computerized cognitive-behavioral therapy, starting about one month before the taper ends and extending up to a month after. Cognitive-behavioral therapy consists of multiple strategies aimed at helping individuals achieve greater control over cravings and urges, and improve decision making and problem-solving skills. CBT is one of the most widely studied and well-validated treatments for the addictions and other mental health disorders (15, 16). A particular advantage for this study is CBT's focus on strategies to help individuals remain abstinent; in fact, in its first application to substance use disorders it was called 'relapse prevention' therapy (17). For the proposed study, we will use a computerized version of CBT, called computer-based training in CBT (CBT4CBT) developed at Yale and demonstrated to be safe, effective and durable in a range of substance-using populations (18-20), including methadone-maintained individuals (21) (17). As CBT4CBT is computer-based and can be used at home on smartphones, laptops, and other devices, it appears well suited to individuals who are transitioning from regular clinic visits for methadone dosing and counseling.

Acetylcholine (Ach) *and opioid use disorder*

Ach is one of the key neurotransmitters in the central nervous system (CNS) and participates in multiple functions including sensory and motor processing, sleep, nociception, mood, stress response, attention, arousal, memory, motivation and reinforcement (22-24). The neural substrate of drug reinforcement is the mesolimbic dopamine (DA) transmission which projects from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). The mesolimbic DA is anatomically and functionally linked to ACh. While VTA receives ACh projections from the laterodorsal and pedunculopontine tegmental nuclei, NAc has cholinergic interneurons that are closely linked to DA function. In the reward circuit, especially in the NAc, DA and ACh have opposing effects. For example, ablation of the cholinergic neurons in the NAc enhanced the rewarding effects of morphine, assessed by the conditioned place preference (CPP) and the negative reinforcement of morphine withdrawal in mice (25). In contrast, increased ACh levels induced by treatment with

inhibitor donepezil blocked the CPP for morphine (25). In another study, galantamine, another cholinesterase inhibitor, attenuated the reinstatement of opioid-seeking behavior in rats that were trained to self-administer heroin (26). Following its release from nerve endings, ACh activates two types of receptors: nicotinic and muscarinic acetyl cholinergic receptors, based on their differential sensitivity to the exogenous ligands, nicotine and muscarine, respectively. The observed effects of cholinesterase inhibitors on morphine reinforcement seems to be mediated by the activation of nicotinic acetylcholine receptors (nAChR). In a recent study, treatment with acetylcholinesterase inhibitor, rivastigmine or donepezil, blocked the acquisition and expression of CPP for morphine (27). In addition, cholinesterase inhibitors also blocked the reinstatement of CPP for morphine by a priming dose of morphine. Treatment by a nAChR antagonist mecamylamine, reversed the effects of cholinesterase inhibitors, suggesting that these effects of cholinesterase inhibitors are mediated by the nAChRs (27). In other studies, cholinesterase inhibitors enhanced the nociceptive effects of opioids in mice (28). Similar findings were observed in uncontrolled human studies. In patients who are receiving chronic opioids, addition of a cholinergic inhibitor medication enhanced opioid analgesia and reduced the sedative effects of opioids (29-31). Together, these findings support the potential efficacy of cholinesterase inhibitors for the treatment of opioid use disorder.

Galantamine

In this study, we will use galantamine, a cholinesterase inhibitor to help individuals to taper off from opioid medications including methadone or buprenorphine. Cholinesterase inhibitors are a group of medications that are marketed for the treatment of Alzheimer's disease. Following its release to the synaptic cleft, ACh is hydrolyzed by acetylcholinesterase. This enzyme is inhibited by a group of medications called acetylcholinesterase inhibitors. These medications increase synaptic levels of ACh available at both the nicotinic and muscarinic type cholinergic receptors (32). Many acetylcholinesterase inhibitors including tacrine, rivastigmine, donepezil and galantamine, are clinically used as cognitive enhancers in the treatment of dementia. Galantamine, similar to other cholinesterase inhibitors, increases the synaptic concentrations of ACh. As a unique feature, galantamine also directly stimulates the nicotinic receptors: it is an allosteric modulator of the α_7 and $\alpha_4\beta_2$ subtypes (33). Because of its additional nAChR potentiating effects, we hypothesized that GAL could be more effective than other cholinesterase inhibitors.

For this study, study medication, galantamine extended release (ER) will be administered at an initial dose of 8 mg/day for 4 weeks, with the option of going to 16 mg during the final 4 weeks of treatment. Capsules will be prepared by the APT Foundation pharmacist. Matching placebo capsules will also be prepared for participants randomized to the placebo arm.

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.

This is a randomized pilot study to examine the potential use of galantamine as an adjunct to the standard buprenorphine or methadone taper in the context of behavioral support. Early abstinence from opioids is associated with high relapse rates and there is a great need to develop interventions

that will prevent relapse to opioid use. Cumulating evidence suggest the cholinergic system is a promising target for relapse prevention.

In this randomized pilot, 30 adults enrolled in the methadone or buprenorphine maintenance programs at the APT Foundation and who have sought a medically supervised, voluntary taper from these medications will be offered participation in a double-blind, placebo controlled, randomized trial of galantamine as an adjunct to standard tapering procedures at this clinic along with the combined approach utilizing concurrent behavior therapy. Primary outcomes will be: (1) successful completion of taper (achieving a methadone/buprenorphine dose of 0), (2) opioid withdrawal symptoms, and (3) opioid use, assessed by self-report and urine samples during and up to 3 months after the end of opioid taper. We will also closely monitor patient comfort and safety (assessed by opioid withdrawal symptoms, adverse events, with measures of stress, sleep and pain) as well as cognitive function (assessed by the CANTAB).

PROCEDURES

Initial Screening
Participants will be recruited from individuals stabilized in the methadone maintenance program or buprenorphine maintenance programs of the APT Foundation who have recently chosen to taper off MAT. They will be identified by their clinicians, fliers, and clinic postings. Individuals who indicate they are interested in hearing more about the study will be offered a meeting with the Research Assistant. At the first interview, the Research Assistant will provide a brief overview of the protocol and obtain informed consent. To enhance the quality of informed consent procedures, we will use a multiple choice test to assess prospective participants' understanding of key aspects of the protocol (34), and provide ample time to review questions and concerns to assure individuals' understanding of the protocols and treatments offered. After determination of eligibility, the pretreatment assessments will be completed by the Research Assistant (see Assessment Table below).

Pretreatment evaluations and physical examination
Eligible individuals will meet with the Research Assistant to complete baseline interview and self-report scales (see Table below) including the CANTAB which is an optional assessment for which participants will be paid. They will also be examined by Dr. Shi to assure they are healthy, meet medical inclusion/exclusions, and are sufficiently stable for tapering. Routine laboratory studies will include CBC, BUN/creatinine, electrolytes, serum glucose, cortisol, liver function tests, and urine toxicology. Following final confirmation of eligibility by Dr. Shi, participants will be randomized to condition using a computerized urn randomization program (35) to balance treatment conditions on key prognostic variables (buprenorphine versus methadone; severity of substance use disorder, gender) and begin their tapering.

Treatment phase
Tapering typically takes 4 to 6 weeks and will follow standard clinical procedures as established by Dr. Shi at the Central Medical Unit (CMU) of the APT Foundation over almost 30 years. At the start of each participants' taper, the participant will be offered weekly CBT4CBT sessions, which they are free to complete on site at CMU or at home (see CBT4CBT description, below). These sessions will last about 35 minutes. CBT4CBT is intended to provide support during the taper and transition to abstinence.

As the taper begins, patients will initiate the study medication (4-6 weeks during taper and 4 weeks after completion of the taper). The medication will be continued after the taper ends, as we anticipate it may be helpful in coping with protracted withdrawal. Participants will receive study medication at weekly research meetings. These will take place at the Central Medical Unit at the same time as weekly visits with Dr. Shi. We anticipate these will last no longer than 10 minutes. Participants will be dispensed up to 16 mg/day of galantamine or matched placebo at the CMU with weekly monitoring of symptoms, adverse events, and urine collection. Medication increases will take place at the discretion of Dr. Shi, based on lack of adverse reactions to study medication. Medication compliance will be assessed at every visit. Participants will be free to use CBT4CBT as they wish through the end of follow-up (3 months after completion of taper). At the end of the active treatment, an endpoint interview will be conducted. Follow-up assessments will occur two weeks, one month and three months following the end of the taper.

Study design & Timeline	
Week -0	Informed consent, baseline assessment, inclusion/exclusion criteria
Week 1 to week 4-6	Reduced methadone/buprenorphine dose per standard CMU procedure
Week 1 to week -4-6	Initiate CBT4CBT and galantamine or placebo, continue tapering, weekly check-in
Week 4-6	Last dose methadone or buprenorphine
Week 4-6 to Week 8-10	Continue CBT4CBT and study medication, weekly check-in
Week 8-10	Endpoint interview
Week 10-12	Two week follow-up assessment
Week 12-14	One month follow-up assessment
Week 20-24	Three month follow-up assessment

Treatment Conditions

1. Medications

Galantamine 8mg or placebo will be dispensed weekly with directions for daily dosing at the start of taper and continue 8-10 weeks, with the option to increase to 16mg at the end of Week 4. Participants will receive a weekly supply during weekly research assessment visits. Adverse events will be monitored closely; urine and breath samples will be collected weekly during taper and at each follow-up.

In this study, we will use galantamine extended release (ER). Galantamine ER is used once daily (36). The recommended initial dose is 8 mg/day and the maintenance dose is 16-24 mg/day. With once daily dosing, steady-state plasma levels are reached within one week (36). Common adverse events (>5%) include weight loss (5% to 7%), diarrhea (6% to 12%), loss of appetite (7% to 9%), nausea (13% to 24%), vomiting (6% to 13%, dizziness (9%), headache (8%). Other less common adverse events include bradyarrhythmia (2%), cardiac dysrhythmia (infrequent), heart failure (infrequent), esophageal perforation (rare), gastrointestinal hemorrhage, rectal hemorrhage (infrequent), thrombocytopenia (infrequent) and death (very rare). When the taper begins, participants will receive the first dose of the medication in the CMU clinic at the time they come in for their methadone/buprenorphine. Participants

will meet briefly with Dr. Shi and study staff weekly during the first week and weekly thereafter to ensure that they tolerate the study medication well.

Galantamine's safety and efficacy have been evaluated in different patient populations including Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Attention Deficit Hyperactivity Disorder (ADHD), chronic fatigue syndrome, schizophrenia and alcohol dependence (37-43).

In our most recently completed randomized clinical trial evaluating galantamine versus placebo among 120 methadone maintained individuals with cocaine use disorder, galantamine was safe and well tolerated by patients (3). The most frequently reported adverse events were nausea/vomiting (reported at least once by 21% of participants), headache (17.7%), loss of appetite (15.9%), fatigue (15%), and diarrhea/constipation (13.3%), but there were no significant differences in frequency of these symptoms by medication condition (galantamine versus placebo). Four participants reported significant weight loss; all were in the placebo condition (galantamine versus placebo, X^2=3.54, p=.06). Rates of serious adverse events occurred infrequently (8.3% of all those randomized, n=10; 3 for medical reasons, 6 for substance use hospitalization, and 1 for psychiatric reasons) and did not differ by treatment condition (galantamine versus placebo).

To minimize the adverse effects of galantamine in our study, following precautions will be taken:

1) Following the manufacturer's recommendations, the galantamine dose will be started at 8mg/day. Participants will be maintained on this dose for 4 weeks and if they tolerate the 8 mg dose, the dose may be increased to a maximum of 16 mg/day. Galantamine doses over 16 mg/day are associated with more frequent adverse events and will not be used in this study.
2) We chose methadone- and buprenorphine-maintained patients voluntarily seeking to taper off MAT as our participant population. Participants will come to the clinic to attend weekly research visits and obtain weekly supply of study medication. This will allow close monitoring of compliance as well as any adverse effects from galantamine treatment (44). Participants will be briefly evaluated before methadone/buprenorphine administration by the clinic nurse. In addition, participants will see the clinic nurse weekly for a systematic evaluation of any adverse events.
3) Potential participants will be carefully screened to rule out medical conditions that may increase the possibility of adverse events. These include asthma or chronic obstructive lung disease, history or current gastrointestinal ulcer, hepatic or renal impairment and cardiac rhythm disturbances (44).
4) Participants will be warned and closely monitored for concomitant use of drugs that may cause drug interactions with galantamine. These include: a) drugs that slow heart rate (eg, beta-blockers), which may increase the risk of bradycardia and AV block, and b) NSAIDs; increased potential for developing ulcers/active or occult gastrointestinal bleeding (44).

2. CBT for CBT

All participants will also be offered CBT4CBT, which they can access onsite at CMU, or if they wish, at home on their own smartphone, laptop, or tablet. Research staff will provide detailed instruction and support in the use of the computer and the program, and be available to answer questions about the program. Research staff will check in weekly with study participants. Time spent using the program

will be tracked by the computer and can be entered into the data analyses as a possible predictor of outcome.

The CBT4CBT program has been evaluated in multiple clinical trials with a range of substance using samples (cocaine, opioid, alcohol, marijuana users) and has been shown to be effective, durable, and safe (18-21). Furthermore, this proposal follows ethical guidelines for use of computerized behavioral therapies developed by Sampson and Pyle (45), including (1) assurance of confidentiality, (2) determination of appropriateness of the specific form of therapy (in this case, CBT, which has been shown to be effective across a wide range of substance use disorders), (3) adequate introduction to the computer program to reduce possible anxiety about use of the systems, (4) provision of follow-up consultation with a clinician if needed, (5) computer system uses current information on the disorder, and (6) supervision of the treatment process by a clinician.

The CBT4CBT program has the following features:

- *Password protection*. Each patient will access the program through an ID/password system that protects confidentiality and is linked to an imbedded database that tracks, for each patient, time logged onto the program, modules accessed, progress through the program from session to session, completion of homework assignments, progress in treatment, and learning of CBT principles through multiple choice tests after each module.
- *User-friendliness*. Given that many patients have minimal background in the use of personal computers, the program is user-friendly, with extensive use of point-and-click features (as opposed to typed-in responses) so that no prior experience with computers or software is necessary. Presentation of didactic material is done through graphics and cartoons, videotaped examples, and audio voice-overs, thus requiring very little reading of text. When text is used in presentation of material, audio voice-overs accompanies the text, as many patients may become impatient or uncomfortable with reading large amounts of material. CBT concepts are presented in a simple, straightforward style without jargon and in a visual style that is engaging and enjoyable (e.g., modeled on computer learning games).
- *Topics covered*: The 'CBT for CBT' program will is modeled closely on a validated NIDA-published CBT manual (46). Seven core skill modules cover the following topics, which correspond to the major session topics in the manual:
    - o Understanding and changing patterns of drug use,
    - o Coping with craving,
    - o Substance refusal skills,
    - o Seemingly irrelevant decisions,
    - o Planning for emergencies, and
    - o Problem-solving skills.
    - o HIV/STD risk reduction
- *Choice of topics*: Although all patients will be able to access all 7 key CBT topics ('skill modules'), patients have the option of choosing the order in which they access skill modules as well as items within modules as often as they wish. Prior to log-off, patients are reminded to immediately report any concerns or uncomfortable feelings associated with use of the program to the research assistant, their APT clinician, or Dr. Carroll.

Assessments: Assessments will include measures of substance use, withdrawal symptoms and severity, stress, cognitive function, sleep and pain.

i. **Assessment of Outcome**.

The primary outcome will be successful transition to abstinence, defined as providing an opioid-free urine at the one- and three-month follow-up. On-site urine testing system we use is the ToxCup Drug Screen Cup We will use a 5 panel Screen Cup on-site ToxCup system for detection of cocaine, methamphetamine, THC, benzodiazepine, and opioids at each assessment visit. Breathalyzer samples will be collected at each assessment to monitor alcohol use. Individuals who miss follow-ups or re-initiate methadone or buprenorphine will be considered to be relapsed.

- The 11-item **Clinical Opioid Withdrawal Scale (COWS**) (47, 48), a widely used and validated rating scale, will be used at each assessment visit during taper to evaluate withdrawal symptoms
- The **Perceived Stress Scale** (49) is a brief, widely used measure of perceived stress.
- The **Sleep Problems Questionnaire**, a 4-item measure of insomnia during the past 1 month(50), will be used to monitor sleep patterns (51-53).
- Pain will be assessed at baseline, during taper, and at each follow-up using the **Brief Pain Inventory-Short form** (54)
- **Adverse events** will be monitored at each visit through use of the **SAFTEE** (55), which has been used in a large number of pharmacotherapy trials (56, 57).
- **Inflammatory markers**. Opioid medications are known to enhance inflammatory markers and the serum level of these markers may potentially predict treatment outcomes. For this reason we will collect serum levels of pro-inflamatory cytokines including Interleukin-1 beta (IL-1β), Interleukin-2 (IL-2), Interleukin-6 (IL-6), Interleukin-10 (IL-10), Interleukin 12 p70 (IL12p70), Interferon gamma (IFNg), Tumor Necrosis Factor alpha (TNFα), Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF). Serum samples will be obtained at baseline, and at the end of taper and at 4-week post taper. The samples will be assayed using electrochemiluminescence multi-array technology (Meso Scale Discovery, Gaithersburg, MD).
- **CANTAB.** (Optional) We will include tests from the well-validated computerized CANTAB battery (58, 59) selected specifically for their likely sensitivity to effects of mifepristone and used in similar ongoing trials with alcohol dependent populations (60). Paired Associate Learning (PAL) which assesses episodic memory and learning of geometric patterns and spatial locations, Delayed Pattern Recognition Memory (PRM), which assesses short-term recognition memory for geometric patterns, and Rapid Visual Information Processing (RVIP), a test of visual sustained attention with a small working memory component.

Instrument name	Rater	Screen	4-6 week taper	End of taper	4 weeks post taper	Follow-up 2 week 1, 3 mo
Informed Consent Quiz	P	x				
Baseline Demographics, including DSM-V screener	RA	x				
Inclusion/Exclusion	RA	x				
Follow-up contact & tracking sheet	RA	x				x
BASIS	RA	x				
Urine toxicology screen, breathalyzer	RA	x	weekly	x	x	x
Inflammatory markers	MD	x		x	x	
COWS (withdrawal symptoms)	MD	x	weekly	x		x

Substance Use Calendar (SUC)	RA	x	weekly	x	x	x
Perceived Stress Scale	P	x		x	x	x
Sleep Problems Questionnaire	P	x		x	x	x
CANTAB subtests (Optional)	RA	x		x	x	
Brief Pain Inventory	P	x	weekly	x	x	x
Patient satisfaction	P, PC			x	x	
SAFTEE (adverse events)	MD		weekly	x	x	x
SAE Reporting Form (as needed)	PC					

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.

Participants will be 30 opioid-dependent adults enrolled the methadone maintenance or buprenorphine programs of the APT Foundation and who provide written informed consent. Participants will be recruited from those enrolled in methadone or buprenorphine treatment and stable for at least one year and are voluntarily requesting taper. In this and other community programs in which we have worked, we have recruited samples that are roughly 40% members of racial and ethnic minority groups. We will not include individuals younger than 18, as MAT program require patients to be 18 or older. Health in our samples is generally good, but participants often experience a variety of comorbidities related to chronic substance use.

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?

Eligibility will be determined by the project physician, Dr. Shi, following screening/baseline assessment and physical exam.

Individuals will be included who:

- Are male and females, between the ages of 18 and 65
- Are enrolled in the APT methadone or buprenorphine program, have been stabilized for at least one year, and who voluntarily wish to taper off MAT.

- For women of child-bearing age, have a negative serum pregnancy test at screening, agree to adequate contraception to prevent pregnancy, and agree to have monthly urine pregnancy tests at the clinic.
- Are fluent in English and have a 6th grade or higher reading level.
- Can commit to at least 12 weeks of treatment and are willing to be randomized to treatment

Individuals will be excluded who:

- Are undergoing administrative (non-voluntary) tapering (e.g., example due to non-payment of program fees, program rule infractions).
- Meet DSM-V psychiatric classifications for lifetime schizophrenia or bipolar disorder, or have a depressive or anxiety disorder with current use of a prescribed psychotropic medication that cannot be discontinued;
- Current DSM-V diagnosis of drug or alcohol use disorder (other than opioids or tobacco);
- Demonstrate significant medical conditions, including asthma or chronic obstructive lung disease, history or current gastrointestinal ulcer, hepatic or renal impairment and cardiac rhythm disturbances or any other medical conditions that the study physician deems contraindicated for galantamine treatment;
- Use of other medications including a) drugs that slow heart rate (e.g., beta-blockers),which may increase the risk of bradycardia and AV block and b) NSAIDs; increased potential for developing ulcers/active or occult gastrointestinal bleeding (44);
- Have a screening liver function test (AST or ALT) greater than 3 times normal;
- Known allergy or adverse reaction to galantamine

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

Eligibility will be determined by the project physician, Dr. Shi, following screening/baseline assessment and physical exam

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

a. Tapering

Standard methadone or buprenorphine tapering procedures well-established and in place at the Central Medical Unit. Risks therefore are no different from standard procedures at this setting.

b. Computer-assisted training program

The 'CBT4 CBT' program will be delivered in addition to standard tapering procedures at the clinic. The program is modeled closely on the CBT treatment manual that has been evaluated in several randomized clinical trials (46) and which is widely accepted as an empirically validated treatment for substance dependence (51). We have completed several large trials of the program and have found it safe and effective for this population (18-21). We have not observed any adverse effects related to use of the program in over 300 outpatients with substance use disorders.

Thus, while we believe adverse events, such as increases in craving or suicidal ideation associated with the use of the computer program, are likely to be rare, we will nevertheless continue to be vigilant in

case of their occurrence. Thus, the research assistant will supervise the participants' use and understanding of the program closely, and Dr. Carroll will be available to monitor patients' reactions to the program and to answer any clinical issues. A member of the research staff will check-in with participants on a weekly basis. In addition, participants will be notified at both login and logoff that any feelings or thoughts that concern them (such as craving, anxiety, and particularly thoughts about harming themselves or others), should be discussed immediately with their counselor, the Dr. Carroll and Dr. Shi.

Thus, psychological risks appear to be minimal and not different from those of equivalent non-study psychotherapeutic interventions. For each treatment condition, frequent monitoring (at least weekly) of the patient's clinical status by research staff will insure identification and withdrawal from the study of participants who show significant psychological or symptomatic deterioration.

c. Galantamine

Galantamine is a generally well-tolerated medication and has a good safety profile in related populations at the same doses as proposed here (e.g., chronic alcohol dependent males undergoing alcohol detoxification). The doses proposed here (initial dose of 8 mg up to a maximum of 16 mg/day) is lower than the typical maintenance dose of 16-24 mg/day. Common adverse events (>5%) include weight loss (5% to 7%), diarrhea (6% to 12%), loss of appetite (7% to 9%), nausea (13% to 24%), vomiting (6% to 13%, dizziness (9%), headache (8%). Other less common adverse events include bradyarrhythmia (2%), cardiac dysrhythmia (infrequent), heart failure (infrequent), esophageal perforation (rare), gastrointestinal hemorrhage, rectal hemorrhage (infrequent), thrombocytopenia (infrequent) and death (very rare). To minimize the risk of adverse events, participants will be closely monitored during study participation with daily visits to the CMU during taper and weekly post-taper and close monitoring of adverse events by the program nurse and physician as well as the research staff.

In previous clinical trials, galantamine's safety and efficacy have been evaluated in different patient populations including Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Attention Deficit Hyperactivity Disorder (ADHD), chronic fatigue syndrome, schizophrenia and alcohol dependence (37-43, 61-63). A recent meta-analysis of 10 clinical trials which included 6805 patients with Alzheimer's disease or mild cognitive impairment (41). The adverse events reported include tremor; anorexia; vomiting; nausea; weight loss; headache; abdominal pain; diarrhea; dizziness; and agitation. For the 8mg/day dose, none of the adverse events was statistically significantly more frequent than placebo treatment. At 16mg/day dose, nausea, vomiting and diarrhea were statistically significantly more frequent than placebo. Similarly, at 24 mg /day dose nausea, vomiting, dizziness, weight loss, anorexia, tremor and headache were statistically significant. This analysis concluded that, galantamine was generally well-tolerated and the frequency of adverse events seem to be dose-related (41).

Altogether, these studies support the safety of galantamine in different patient populations including those with alcoholism. Adverse effects of galantamine seem to be dose-related, with more frequent adverse effects over the 16 mg/day dose.

d. Urine and breath specimen collection

Urine and breath specimens are collected primarily as safeguards to participants and should add no risks other than those normally associated with these procedures.

e. Blood draws

Less than 50cc's of blood will be drawn for routine laboratory evaluations and for inflammatory markers and should add no risks other than those normally associated with these procedures.

f. Rating scales and questionnaires.

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

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

The screening of patients using the inclusion and exclusion criteria, medical exam and the urine toxicology screens are intended to identify participants who are appropriate for the study. Conducting the study at a primary care center with on-site medical staff and frequent visits and monitoring by medical and research staff will minimize the risks of adverse events and assure that they are managed quickly if they do occur. Confidentiality in regards to collected materials will be maintained via a numbered reference system maintained by the research assistant. Participants' names will appear only on a consent form and "key" form kept by the research assistant. Participants will be withdrawn from the treatment arm of the study if they show severe psychological or symptomatic deterioration if clinically necessary for ethical or safety purposes. Participants withdrawn from a study for these reasons or because they wish to withdraw from a study will be offered treatment as usual at the clinic or be referred to a higher level of care when appropriate. Private referral and/or hospitalization may also be offered according to the participants' needs and wishes.

To minimize the risk adverse effects of galantamine in our study, following precautions will be taken:

1) Following the manufacturer's recommendations, the galantamine dose will be started at 8mg/day. Participants will be maintained on this dose for 4 weeks and if they tolerate the 8 mg dose, the dose may be increased to a maximum of to16 mg/day. Galantamine doses over 16 mg/day are associated with more frequent adverse events and will not be used in this study.
2) We chose methadone and buprenorphine maintained patients voluntarily seeking taper off MAT as our participant population. Participants will come to the clinic to attend weekly research visits and obtain weekly supply of study medication. This will allow close monitoring of compliance as well as any adverse effects from galantamine treatment (44). In addition, participants will see the clinic nurse weekly for a systematic evaluation of any adverse events.
3) Potential participants will be carefully screened to rule out medical conditions that may increase the possibility of adverse events. These include asthma or chronic obstructive lung disease, history or current gastrointestinal ulcer, hepatic or renal impairment and cardiac rhythm disturbances (44).
4) Participants will be warned and closely monitored for concomitant use of drugs that may cause drug interactions with galantamine. These include a) drugs that slow heart rate (eg, beta-blockers), which may increase the risk of bradycardia and AV block and b) NSAIDs; increased potential for developing ulcers/active or occult gastrointestinal bleeding (44).

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? Greater than minimal
    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

A Data and Safety Monitoring Board (DSMB) will monitor this and all Center projects because this population might be considered vulnerable due to their substance use. The overall risks are moderate and adverse effects of Galantamine include weight loss (5% to 7%), diarrhea (6% to 12%), loss of appetite (7% to 9%), nausea (13% to 24%), vomiting (6% to 13%, dizziness (9%), headache (8%). Other less common adverse events include bradyarrhythmia (2%), cardiac dysrhythmia (infrequent), heart failure (infrequent), esophageal perforation (rare), gastrointestinal hemorrhage, rectal hemorrhage (infrequent), thrombocytopenia (infrequent) and death (very rare). These will be monitored and recorded by study staff and reported to the DSMB per protocol. This board, already in place for Dr. Carroll and Sofuoglu's other NIH-supported projects, is composed of Yale investigators who are independent of the trial and experienced in various aspects of the conduct of clinical trials for the treatment of addictive disorders We use a standard DSMB report form that is used in all Center and Center-related trials that 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 targeted rates.

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. Instead, we propose to submit a quarterly report of aggregate data to the DSMB members that contains screening data, baseline demographics, retention data, serious adverse events data, as well as accrual status including projections, times to milestones, and any other data that will help in the assessment of the clinical trial. Based on this report, each DSMB member will complete a form making one of two recommendations: 1) continue recruitment as planned; or 2) schedule formal DSMB meeting immediately. If any DSMB member recommends a meeting, this will be scheduled within one week, minutes will be kept, the report will be reviewed with the PI, and the committee will vote on whether the study should: 1) continue recruitment unchanged; 2) continue with a protocol amendment; 3) stop recruiting pending further investigation. If, after this meeting, any DSMB member votes to stop recruitment or requests a protocol modification, the Yale IRB will be informed.

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 from the methadone/buprenorphine clinic. All SAEs will result in the completion of an SAE Form and a verbal report within one hour to the Principal Investigator (Dr. Carroll), the Co-Investigator (Dr. Shi) and the CMU Clinic Director (Ms. Henry). Within 24 hours, the following additional individuals will be informed: 1) all co-investigators; 2) the DSMB. All of these individuals will receive a copy of the SAE Form within one week at which point a decision will be made whether to convene a meeting of the DSMB. 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 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 (DSMB, IRB, and APT 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 NIDA 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? *Write here*
   ii. What provisions are in place for management of interim results? *Write here*
   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.
Write here

This is a small randomized pilot trial to evaluate the safety and feasibility of galantamine versus placebo plus CBT4CBT to improve successful transition from methadone or buprenorphine maintenance to abstinence. The primary outcome will be relapse to opioid use within the follow-up period. While not powered to detect a significant difference between treatment conditions in the primary outcome, given estimates of relapse as high as 80% in this population, a success rate of 40-50% would warrant further evaluation in a larger study.

Because Dr. Carroll has a potential conflict of interest in this protocol, the following procedures will be followed per the plan approved and on file with the Yale COI committee for Dr. Carroll's other projects that involved CBT4CBT: Dr. Carroll is not directly involved with the consenting of participants, determination of eligibility of participants, direct collection of study data; furthermore, and analysis of study data are conducted by multiple staff, with study condition not revealed until analysis is complete.

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

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# applied for ☐RDRC oversight (RDRC approval will be required prior to use)

B. DRUGS/BIOLOGICS ☐N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☒
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☒
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☒
4. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☒
5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Galantamine, a reversible and competitive inhibitor of acetylcholinesterase, elevates synaptic concentrations of acetylcholine which leads to increased stimulation of both nicotinic and muscarinic receptors. Galantamine also directly stimulates the nicotinic alpha7 and alpha4-beta2 receptors, as an allosteric positive modulator. This results in dopamine release in the mesolimbic/mesocortical dopaminergic pathway[22], providing an additional mechanism by which galantamine may enhance cognitive function and reduce stimulant use[19, 21, 23].

Few studies have evaluated galantamine, either in terms of direct effects on substance use or as a strategy to improve cognitive impairment: Among 114 alcohol-dependent individuals, galantamine was

associated with significant reductions in cigarette smoking compared with placebo[24]. A trial evaluating effects of galantamine in 149 recently detoxified alcohol-dependent patients reported no significant effects on relapse, but some evidence of reduced drinking among those who relapsed[25]. In a randomized placebo controlled pilot study with 14 cocaine-dependent methadone-maintained individuals, 16 mg/day galantamine was associated with fewer cocaine positive urine specimens, (45% versus 95%, *P*=.15) as well as a higher proportion of days of abstinence from cocaine 80% versus 60%, *P*=.06) relative to placebo, with participants reporting moderate nausea and fatigue[26]. Differential effects on cognitive functioning were not seen. In a 10-day proof-of-concept trial with 34 abstinent cocaine users, 8/mg/day of galantamine was associated with significant improvement in the Rapid Visual Information Processing task (RVP) of the CANTAB (Cambridge Neurologic Test Battery) compared with placebo[27]. These two pilot studies by our group suggested evaluation of galantamine on cocaine use and cognitive functioning was warranted in an a full randomized clinical trial.

2. Source: Identify the source of the drug or biologic to be used.

   Purchase from Razadyne ER, Ortho-McNeil Neurologics, 1125 Trenton Harbourton Road, Titusville, NJ 08560

   a) Is the drug provided free of charge to subjects? ☒YES ☐NO
   If yes, by whom? Study

f. Storage, Preparation and Use: Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

This is a double-blind study. Medication will be packaged by the clinic pharmacy and administered by the clinic nurses. Only the clinic pharmacist will hold the key and will be able to break the blind if necessary. All participants will be given a wallet card with emergency numbers in case of emergency or if the blind needs to be broken.

Check applicable Investigational Drug Service utilized:

☐ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☐ None
☒ Other: APT Foundation Pharmacy

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

g. Use of Placebo: ☐Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.
There are no approved therapies to improve relapse after methadone/buprenorphine taper. The computerized CBT program will be provided to all participants as behavioral support this exceeds current standard of care.

b) State the maximum total length of time a participant may receive placebo while on the study.

10 weeks

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
Relapse to drug use is extremely high in this population and no effective medications have been identified. In the case of relapse, all participants can be re-admitted to APT methadone or naltrexone programs or seek treatment elsewhere.

d) Describe the procedures that are in place to safeguard participants receiving placebo.
Regular monitoring by Dr. Shi and study staff will alert staff to patients whose relapse risk is particularly high; they will be referred as indicated to a higher level of care. The computerized CBT program is also being offered to provided additional support to patients and exceeds current standard of care.

h. **Continuation of Drug Therapy After Study Closure** ☐Not applicable to this project

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ **Yes** If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☒ **NO** If no, explain why this is acceptable.
This is an initial pilot study of galantamine for this population. If galantamine appears to have benefit for this population, we will apply for funding for a larger randomized controlled trial.

B. DEVICES ☒N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. Targeted for enrollment at Yale for this protocol: 30
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:		

*** 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. Fliers in APT clinics, referrals from APT clinicans

b. Describe how potential subjects are contacted. Potential participants will be asked to contact Dr. Shi or research staff.

c. Who is recruiting potential subjects? Research staff, CMU staff.

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.

Dr. Shi and Central Medical Staff provide physical examinations for all patients entering buprenorphine or methadone at APT. CMU staff also typically supervise medical care of APT patients undergoing taper.

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.) N/A

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.

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.

A trained research staff member at the performance site 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. Study medical personnel will meet with potential participants during the consenting process, before signatures, to review the medical content. 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 study. 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 require participants to read and write, and we will use a multiple-choice test after review of the consent form to determine that participants understand the key points of the research. The Project Coordinator reviews the test with the participant and clarifies any question which was incorrectly answered

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?

- Our study forms have been designed to avoid collecting identifiable information (e.g., no PHI is collected on CRFs). We generally collect only names and protocol session dates. The latter are changed to 'number of sessions completed' if data sets are released to other Yale investigators. As below, names appear only on the consent and HIPPA forms and the 'key form'.
- The health information collected for this study are substance use history, adverse reaction symptoms, current medications, previous hospitalizations and health related services used.
- Research data are collected on CRFs, and 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.
- The screening of patients using the inclusion and exclusion criteria, and the comprehensive evaluations will minimize the risk of including subjects with insignificant substance use (or who are otherwise inappropriate for the study).
- Confidentiality in regards 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, HIPPA 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, as is standard in clinical practice.
- Data are stored at our secure data management center; data sets do not include identifying information. At the conclusion of the study, all locator data are destroyed. Source data is generally destroyed 3 years after completion of the study at a secure location (Iron Mountain) and destroyed by Iron Mountain or Shred-It.
- The funding agency, NIDA, may access the data for routine audits.
- All research staff and clinicians receive annual Good Clinical Practice training through the Core.
- Our data collection and management procedures are fully compliant with HIPAA.

2. How will the research data be collected, recorded and stored? *See above*

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?

See above

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.

   Data are stored at our secure data management center; data sets do not include identifying information. At the conclusion of the study, all locator data are destroyed. Source data is generally destroyed 3 years after completion of the study at a secure location and destroyed by Shred-It.

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

Per the Notice of Changes to NIH Policy for Issuing Certificates of Confidentiality (NOT-OD-17-109), effective October 1, 2017, this research is covered by a Certificate of Confidentiality.

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.)

Benefits to subjects include significant psychotherapeutic exploration through the provision of the computerized cognitive behavioral training program. The major potential benefit in this study is in reduced risk of relapse which may, in turn, foster improvement in subjects legal, medical, interpersonal, psychological and occupational functioning.

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 to standard treatment at the APT Foundation methadone or buprenorphine program or other appropriate programs in the New Haven area.

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.

   All subjects will be offered a material inducement for participation in study evaluations including $25 for screening, $25 for the pretreatment assessment, these payments will be in the form of a gift card. Participants will be offered the optional CANTAB assessment at 3 separate timepoints (screening, end of taper and 4 weeks post taper) for which they will be paid $20 at each timepoint. However, they must complete the first timepoint (screening) to be considered to participate in the remaining 2. Participants will be paid $10 for each weekly research assessment visit completed and $10 each week for urine toxicology screen during the 8–10 week treatment phase of the study ($20/week for 8 -10 weeks), $30 for end of taper interview, $35 for an endpoint interview, $40 for 2-week follow-up, $45 for one-month follow-up, and $50 for three-month follow-up, these will be cash payments. For a possible total of $470 - $510. Payments to the participants will be prorated for those who withdraw prematurely; that is, they will receive payment only for those assessments they complete.

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.
   Subjects will not be charged for ancillary treatments (the CBT4CBT program) or evaluations they receive at the clinic. Subjects will be charged for treatment as usual at the clinic; where most patients receive treatment with no-out of pocket expenses or on a sliding scale. Study medication will be provided at no cost to subjects.

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).

   Should injuries occur, the participant would be assessed and referred appropriately by the staff of the Central Medical Unity of the APT Foundation. The participant's insurance carrier will be expected to pay the costs of medical care. No additional financial compensation for injury is available

   a. Will medical treatment be available if research-related injury occurs? *Yes*
   b. Where and from whom may treatment be obtained? *At the Central Medical Unit of the APT Foundation*
   c. Are there any limits to the treatment being provided? Limited *outpatient care only.*
   d. Who will pay for this treatment? *Patient insurance*
   e. How will the medical treatment be accessed by subjects? *CMU referral*

IMPORTANT REMINDERS

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

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

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 ☒

If Yes, please answer questions a through c and note instructions below.
a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered “no” to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

Literature cited

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