Oxytocin reduces noradrenergic-induced opioid-like withdrawal symptoms in individuals on opioid agonist therapy

CLINICAL PROTOCOL

Carolina L. Haass-Koffler, PharmD, PhD
121 South Main Street
Providence, RI 02903
Tel: 401-863-6624; Fax: 401-863-6697
carolina_haass-koffler@brown.edu

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Clinical trial registration: Clinicaltrials.gov; NCT04051619

IND/FDA: 135570, oxytocin and yohimbine (Holder: Haass-Koffler)

Brown University
Application for Full Board / Expedited IRB Review

Protocol Title:

Oxytocin to reduce stress-induced craving in individuals with opioid use disorder

Principal Investigator (PI): Carolina Haass-Koffler
Department: CAAS, Psychiatry and Human Behavior
PI Phone number & email address: 401-836-6624; carolina_haass-koffler@brown.edu
Is this an undergraduate student project?[1] ☐ Yes ☒ No
If yes, name of undergraduate student:

Human Subjects CITI training is complete (PI, student & advisor): ☒ Yes ☐ No
Good Clinical Practices (GCP) training is complete (clinical trials only): ☒ Yes ☐ No ☐ N/A
HIPAA training is complete (if using PHI): ☐ Yes ☐ No ☒ N/A

Are there multiple sites involved with this study? ☐ Yes ☒ No

- If "yes," review the Application for IRB Authorization Agreement

Funding Source(s):

- If there is no external funding for the project, write "University;" if funded by a specific internal funding mechanism (e.g., Mellon Mays Fellowship, Royce Fellowship, UTRA, OVPR Seed funds, etc.) please specify**:** NIH
- If externally funded, the project title and grant/contract # must be provided: **Centers of Biomedical Research Excellence (COBRE) P20 GM130414-01**

PART I. HUMAN SUBJECTS RESEARCH SCREENING

Full Board/Expedited studies must meet the federal definition of "Human Subjects Research." Answer the following questions to determine if your proposed study meets the federal definitions of both "Research" and "Human subjects."	
☒ Yes ☐ No	Is this study a systematic investigation?
☒ Yes ☐ No	Is the *primary design intent* of this study to contribute to generalizable knowledge?
☒ Yes ☐ No	Is the information being obtained *about* living individuals?
☒ Yes ☐ No	Will you collect information through some type of intervention or interaction? **OR** Will you have access to individually identifiable information? **OR** Will you have access to private information?
STOP	If you answered "no" to any of the above questions, your study does not meet the definition of "Human Subjects Research." You are not required to submit an Application for IRB review to the Brown HRPP.

[1] Most Undergraduate student projects do not require IRB/HRPP review and oversight. Before completing this application, please refer to Brown's Guidance Regarding Undergraduate Work Involving Human Subjects Research.

Before proceeding, be sure to review the revised Common Rule categories for Exemption to determine if your study meets criteria for Exempt review and the Application for Exemption.

PART II. RISK ASSESSMENT & EXPEDITED ELIGIBILITY SCREENER

1. Minimal Risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

Using this definition, do you believe this research presents:

☐ No greater than minimal risk (**Expedited**)	Briefly justify this selection (and proceed to Question 2):
☒ Greater than minimal risk (**Full Board**)	Briefly justify this selection (and proceed to Part III): This protocol include the administration of two medications; oxytocin intranasal (IN) and yohimbine oral (PO).

2. Below are Research Categories *eligible* for Expedited Review. Select one or more of the categories that are applicable to your proposed research, if any.

☐ Category 1	Clinical studies of drugs and medical devices only when condition (a) or (b) is met (please select one): ☐ (a) research on drugs for which an IND application is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review); OR ☐ (b) research on medical devices for which (i) an IDE exemption application is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
☐ Category 2	Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: ☐ (a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these participants, the amounts drawn must not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; OR ☐ (b) from other adults and children, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.
☐ Category 3	Prospective collection of biological specimens for research purposes by noninvasive means. Examples may include: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicated a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removal at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routing prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

	(j) sputum collected after saline mist nebulization.
☐ Category 4	Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples may include: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
☐ Category 5	Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). NOTE: Some research in this category may be Exempt. Review the categories for Exemption before selecting this option.
☐ Category 6	Collection of data from voice, video, digital, or image recordings made for research purposes.
☐ Category 7	Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. NOTE: Some research in this category may be Exempt. Review the categories for Exemption before selecting this option.

PART III. RESEARCH DESIGN & METHODS

1. Introduction and Background in lay language.

Although stress has long been linked to substance use, craving and relapse, there are no available medications that target stress-induced substance use disorder (SUD). In particular, with the rise in opioid use, there is still a crucial need for developing effective pharmacological treatments that target and integrate the complexity of this disease. The long-term goal of this project is to identify the key neuroendocrine pathways that are responsible for stress-induced craving in individuals with opioid use disorder (OUD) in order to better understand how they can be effectively treated. To achieve this goal, we will utilize oxytocin, as a putative pharmacological intervention, because: 1) oxytocin's neuroanatomical-neuroendocrine pathways are shared with stress hormones; 2) oxytocin modulates dopaminergic transmission, lowers stress response and mitigates drug seeking-behaviors; and 3) an increasing number of studies suggest that the **oxytocin** neural circuits closely interact with the endogenous opioid system.

One of the most challenging aspects in designing a human laboratory study is the inclusion of an acute stress condition that represents a comprehensive naturalistic environment for OUD individuals. Hence, testing pharmacotherapies in stress-induced opioid use models in laboratory paradigms is critical for the identification and development of therapeutic interventions to prevent drug use. Pharmacological challenges such as yohimbine, an *α*-2 adrenoceptor antagonist, have been shown to activate central stress response in addition to increasing sympathetic nervous system activity, facilitating recall of traumatic memories and increasing heroin craving in opioid-dependent individuals. Thus, for this proposal we will integrate oxytocin (pharmacological therapy), with a cue-reactivity paradigm (specific for opioid cues) and yohimbine (neuroendocrine stress activation) in individuals receiving opioid replacement therapy (ORT) with buprenorphine/naloxone or methadone.

The proposed research is significant because, using pharmacological probes, it will provide a much needed insight into the fundamental neurobiological mechanisms underlying stress-induced opioid craving with the goal to improve therapeutic outcomes and prevent relapse for this population.

2. Specific Aims and Study Objectives

With the dramatic rise in opioid use, there is a critical need for effective pharmacological treatments for opioid use disorder (OUD). Although stress has long been linked to substance use, craving and relapse, no medications for OUD target stress-related pathways involved in the development and maintenance of OUD.

The goal of this research is to evaluate whether oxytocin, a hormone with anti-stress properties, dampens the effects of stress and opioid-associated cues on opioid craving and thus may be an effective adjunctive treatment for OUD.

The central hypothesis of this research is that oxytocin will reduce stress-induced opioid craving in patients with OUD treated with buprenorphine/naloxone or methadone as opioid replacement therapy (ORT). This hypothesis is based on the model of addiction (Koob, *Neuron* 2008) in which chronic substance use and stress lead to neurobehavioral counter-adaptations that dysregulate biobehavioral response.

In this double-blind, placebo controlled, randomized trial, individuals with OUD (*N*=50) who are currently receiving treatment with buprenorphine/naloxone or methadone will be randomized to intranasal oxytocin (40 international units, IU) and oxytocin-matched placebo, administered twice/day for 7 days with a minimum of two days between the opposite condition (oxytocin or placebo). On days 5 and 7, and on days 14 and 16, participants will complete two counter-balanced sessions in which they receive yohimbine (32.4 mg) or yohimbine-matched placebo, and responses to opioid cues are assessed.

Aim 1: assess the effects of oxytocin on cue-induced opioid craving after yohimbine stress-induced. We hypothesize that opioid craving will be reduced in the oxytocin condition, compared to the oxytocin-matched placebo, after yohimbine stress induction.

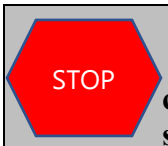
Aim 2: assess whether baseline levels of stress affect the effects of oxytocin on cue-induced opioid craving after yohimbine-matched placebo. We hypothesize that after yohimbine-matched placebo administration, opioid craving will be reduced in the oxytocin condition only among individuals with higher levels of stress at baseline.

Aim 3: to assess the safety and tolerability of oxytocin and yohimbine in OUD individuals receiving buprenorphine/naloxone or methadone. Participants will complete a laboratory session that includes a battery of medical/physiological/psychological assessments to monitor adverse events.

Aim 4:

Exploratory Aims: we will examine the effect of oxytocin, as compared to placebo, on neuroendocrine fluctuations of salivary cortisol (three points area under the curve) and blood neurotensin, orexin and substance P by comparing hormones concentrations at baseline and after study medication and placebo administration (visit 3, 4, 5 and 6).

This research will be the first to assess the clinical efficacy of repeated oxytocin administration to prevent opioid stress-induced relapse. Considering the high comorbidity between OUD, anxiety disorder and PTSD, this proposal will pave the avenue for testing oxytocin as an adjunct opioid replacement therapy (ORT) for an as needed personalized pharmacotherapy for this population.

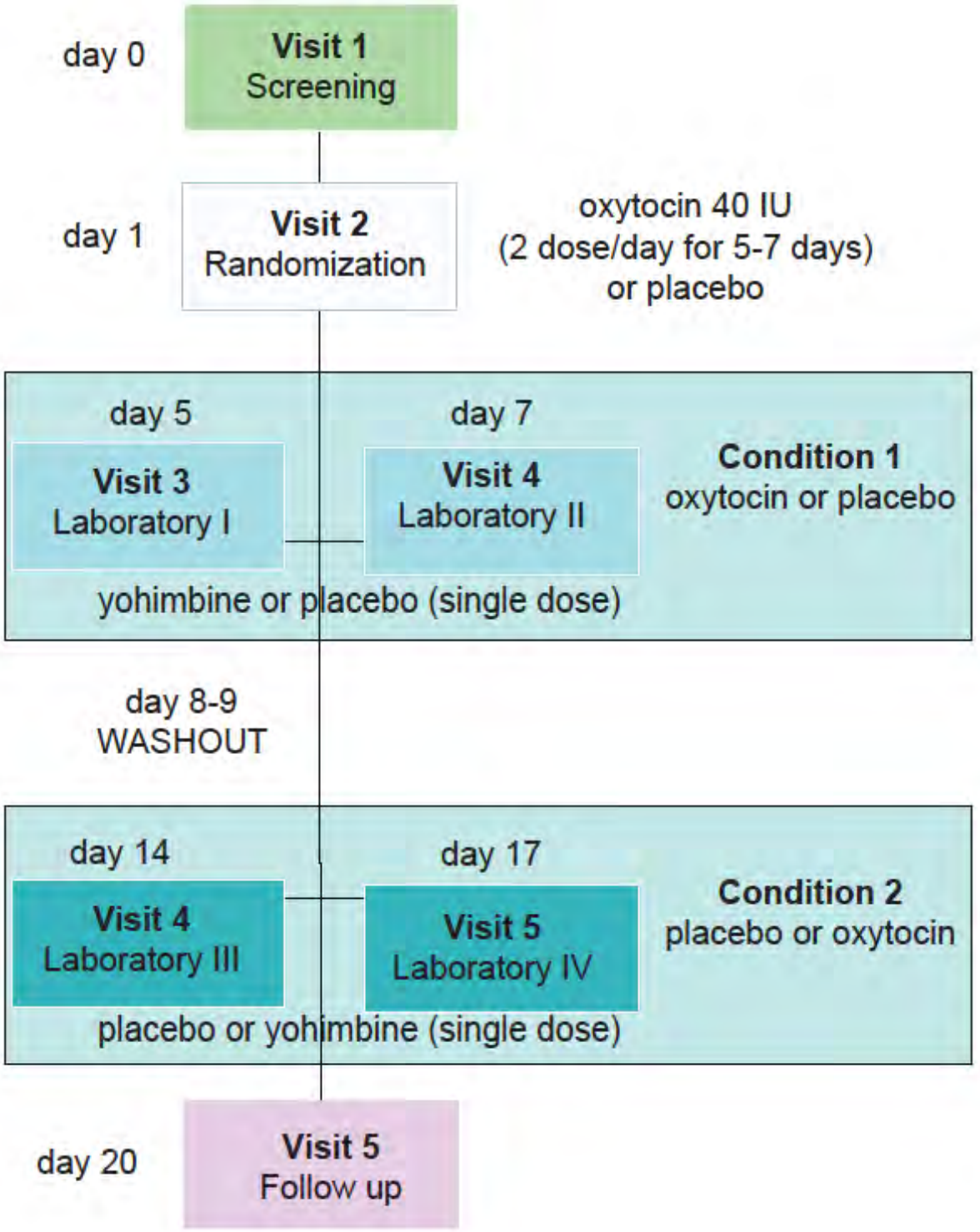


If your study ONLY involves the use of identifiable secondary data / biospecimens, including coded data from which you may be able to ascertain identity, skip to PART VI. Otherwise, please continue.

3. Materials, Methods and Analysis.

This study will use a within subject design with oxytocin vs. oxytocin-matching placebo and yohimbine vs. yohimbine-matching placebo. The cue reactivity (CR) (opioid craving induced by personalized opioid cues) will follow the physiological symptoms (triggered by yohimbine) to isolate the stress signal associated with opioid. Eligible participants will be randomized to use intranasal oxytocin or placebo spray under double-blind conditions for 7 days. On days 5 and 7, participants will complete a session in which they receive yohimbine and one in which they receive placebo, under double-blind conditions, with the order of these conditions randomized across participants. After a two-day wash-out period, participants will receive the opposite condition within the oxytocin group (oxytocin or placebo, counterbalanced) to be administered for 7 days. On days 14 and 16, participants will complete an additional two labs where they will receive yohimbine and yohimbine matched placebo (counterbalanced). In a follow-up visit, we will complete final assessments before concluding the study (**Figure 1**).

FIGURE 1 – Pharmacological interventions during the study



Drugs and Doses Participants will receive intranasal oxytocin (40 IU) and oxytocin-matched placebo twice a day for 14 days; there will be one week of oxytocin administration and one week of placebo administration with two days of washout between the two conditions. They will receive two oral doses of yohimbine (32.4 mg) and two oral doses of yohimbine-matched placebo in the laboratory sessions.

Dr. Haass-Koffler already obtained the Investigational New Drug (IND: 135570) from FDA for this study (**Appendix A**).

Oxytocin: The oxytocin and oxytocin-matched placebo will be formulated at 5mg/0.1mL (5mg/spray) and dispensed as 10-mL nasal spray, twice a day (2 sprays per nostril) for 7 days (total daily dose: 40 international units, IU). Previous pilot studies have demonstrated that oxytocin administered either as single dose (73) or daily for two weeks (72) was well-tolerated in individuals with co-occurring opioid and cocaine disorder. The intranasal dose was chosen based on earlier work (102, 103) and previous studies (69, 104) have shown that 40 IU is well-tolerated in healthy populations with minimal to no side effects or adverse events. The administration period (7 days) is within the confines of an acceptable timeframe based on previous studies and ongoing oxytocin clinical trials (NCT: 02407340 and NCT: 02548728). A study conducted by the PI's mentor, Dr. Leggio and his team (105), indicated that both intranasal and intravenous exogenous (labelled) oxytocin cross the blood brain barrier and reach the CSF in rhesus macaques (106). As most of the neurohypophysial hormones, oxytocin has very short half-life, however, the pharmacological effect of oxytocin may extend from the transient kinetic effects. Intranasal oxytocin has shown to blunt stress effects on hippocampal synaptic plasticity and memory in rats via acting on oxytocin receptors and regulating phosphorylated extracellular signal-regulated kinases (pERK)(107). As such, oxytocin may induce compensatory mechanisms regulating secretion of magnocellular neurons in the hypothalamus which are operant on other hormones (108).

Yohimbine: Patients will receive a single oral dose of 32.4mg yohimbine or yohimbine-matched placebo in the lab, approximately one hour prior to the cue reactivity procedure, which correspond to the yohimbine time to reach maximum concentration (t_{max}=1 h). Yohimbine 32.4mg is based from multi-dose yohimbine administration to heroin-dependent/buprenorphine stabilized volunteers which increased opioid-seeking behaviors (15). The PI has already obtained an IND from the FDA for the use of yohimbine in this study and she is currently using this same oral dose in another trial funded via her K01 (NCT: 02243709; IND: 121984)]. Further supporting the safety of yohimbine, other prior studies have used yohimbine to examine neuroendocrine probes to boost stress signal in human studies (20, 22, 109). Ample data support the safe use of yohimbine to induce craving in alcohol-dependent individuals (22), and the safe induction of stress in PTSD veterans (110) and gamblers (96).

Telephone prescreening (**Attachment J**)

Visit 1 (Screening) Before starting any procedure the participant will sign the Consent document (**Attachment K**). Participants will be assessed on inclusion/exclusion criteria according the CADRE psychometric scales, vital signs, ECG, blood, saliva and urine analysis standardized format. Specific for this project, we will include an additional blood analysis ensure the presence of buprenorphine and absence of opioids. Females will report their last menses and the use of hormone-based contraceptives (111).

Visit 2 (Randomization) – Day 1 After medical clearance, blood will be collected for clinical laboratory tests to assess basal β-endorphin, and other stress hormones (neurotensin, orexins and substance P) during five visits (Visit 1, 3, 4, 5 and 6) (one vial). Basal salivary oxytocin and cortisol will be collected by passive drooling (one vial). Since oxytocin has shown to decrease cortisol release and anxiety in response to social stress (6), samples of salivary cortisol will be collected at three time points (stress induction, cue reactivity and end of the experiment) to measure cortisol levels as a biomarker of oxytocin's effect on acute stress. Then, participants will be randomized to either oxytocin or oxytocin-matched placebo group that will be dispensed as a nasal spray and the session will include a 30 min

discussion of the proper administration of the nasal spray, the potential side effects and drug-drug interactions.

Visit 3 (Laboratory Session I) – Day 5 Participants will provide a urine sample (drug toxicology), and a one vial blood sample (β-endorphin, hormone levels). Participants will then complete a series of assessments (**Table 1**) and receive a single oral dose of yohimbine or yohimbine-matched placebo. Fifteen minutes later, participants will administer a dose of oxytocin or oxytocin-matched placebo (40 IU, 4 sprays per nostril), after 30 min the first sample of saliva (cortisol and oxytocin) will be collected and the cue-reactivity will begin (112). Cue-Reactivity (CR) Task will be administered in a similar manner to other published studies (72, 73) for individuals with OUD with cues selected based on patients' drug experience. To measure cue-induced opioid craving, participants will a view images of neutral stimuli and then of opioid drug use (24). Participants will rate their craving via drug visual analog scale (VAS) and the second sample of saliva cortisol will be collected (45 min later). Vital signs will be monitored during the entire procedure. Participants will then complete Post-Cue measures, will have their vital signs measured and conduct the last sample of saliva.

Visit 4 (Laboratory Session II) – Day 7 Participants will come back after two days. The procedure will be similar to Visit 3 but they will receive the opposite condition (yohimbine or yohimbine-matched placebo).

A two-day washout period will occur followed by initiation of the opposite intranasal medication condition (i.e. oxytocin and oxytocin-matched placebo) to be administered for one week starting at day 9.

Visit 5 (Laboratory Session III) – Day 14 Participants will complete the lab procedures as described in Visit 3 and 4, however, this time will be administered the opposite oxytocin condition (i.e. oxytocin or oxytocin-matched placebo). Participants will also receive yohimbine or yohimbine-matched placebo (counterbalanced).

Visit 6 (Laboratory Session IV) – Day 17 Participants will come back after two days. The procedures will be completed as described in Visits 3-5, but they will receive the opposite condition (yohimbine or yohimbine-matched placebo).

Visit 7 (follow-up) – Day 20 After three days, participants will come to the lab for the final assessments (**Table 1)**.

For those that have previously completed the study and will be re-enrolled in the opposite medication conditions, they will go through an additional two visits for safety criteria and to once again confirm eligibility: visit A and Visit B

Visit A: Participants will review their brief medical history questionnaire with the nurse practitioner, and compete assessments about any anxious or depressive symptoms.

Visit B: Upon completion of visits 5 and 6 where participants were randomized to the opposite medication condition, they will once again come to the lab to complete the final assessments **(Table 1)**.

Medication compliance: To ensure study medication compliance, oxytocin levels will be measured at screening (to determine oxytocin baseline values), at Visit 3, 4, 5 and 6. Buprenorphine levels will be checked by urine at each visit, in order to ensure ORT compliance and reduce the risk of withdrawal after study conclusion.

Assessments Demographic and baseline characteristics will be assessed according the CADRE standardized format (**Attachment B**). Additionally, specific for this project, we will include (**Attachment G**):

Opioid craving/withdrawal. a) Clinical Opiate Withdrawal Scale (COWS) (113) an 11-item scale that measures the stage or severity of opiate withdrawal and the level of physical dependence, b) Opioid Craving Scale (OCS) a 3-item scale adapted from the 3-item Cocaine Craving Scale (114), that assesses opioid craving and c) Opioid Timeline Follow-back (115) a calendar-assisted interview that will help participants estimate their amount of opioid use over the last 90 days.

Mood, Anxiety and Trauma Measures, in addition to the CADRE standardized assessments, we included anxiety and stress measure: a) Hamilton Anxiety Rating Scale (HAM-A) (116) is a 14-item scale that measures anxiety symptoms (psychic anxiety and somatic anxiety), b) Hamilton Rating Scale for Depression HAM-D a 21-item scale designed to assess potential depressive symptoms, and c) State-Trait Anxiety Inventory (STAI) (117) is 40-item measure that is split into state anxiety (20 items) and trait anxiety (20 items).

The list of the CADRE standardized assessments and measures is attached (**Attachment B**) and *ad hoc* assessments administer during the study period is described in **Table 1** (**Attachment G**). Other potential effects of oxytocin as pharmacotherapy for OUD on relapse, drug-taking or subjective rating of drug effect will be monitored throughout the study.

TABLE 1 – Assessments						
Measure	**Visit 1** Screening	**Visit 2** Randomization	**Visit 3, 4, 5 and 6** Laboratory	**Visit 7** Follow-up	**Visit A**	**Visit B**
Adverse Events Evaluation (AEE)		x	x	x		x
Clinical Opiate Withdrawal Scale (COWS)	x	x	x	x	x	x
Concomitant medications, nicotine and marihuana use	x	x	x	x	x	x
Prior and Concomitant Medications Log	x	x	x	x	x	x
Hamilton anxiety rating scale (HAM-A)	x	x	x	x	x	x
Hormone blood collection (blood and saliva)	x		x			
Opioid Craving Scale (OCS)	x	x	x	x		x
State Anxiety Inventory-State (STAI-State)	x		x		x	
Trait Anxiety Inventory-Trait (STAI-Trait)	x					
Study medication accountability			x			
Buprenorphine urine level	x	x	x	x	x	x
Menopausal Health Questionnaire	x					
Hamilton Rating Scale for Depression HAMD	x				x	
PTSD PCL 5		x				
Drug Attention Scale (DAS)			x			

Desire for Drug Questionnaire (DDQ)			x			
Obsessive Compulsive Drug Use Scale (OCDUS)			x			
Drug or Treatment Drug Craving Questionnaire			x			

Clinical Laboratory Core (CLC)

Measures Aim 3 of the CADRE's Clinical Laboratory Core (CLC) is to build a center-wide database of transdiagnostic biological and environmental factors associated with the development and progression of SUDs and chronic disease. This database will enable CADRE project and pilot investigators to test multi-causal models of the relationships between SUDs and chronic disease. Measures to be included in all projects in service of this aim include: the MINI 7.0.2. (brief patient-completed structured clinical interview for DSM-5 disorders), measures of stigma, trauma, family history of alcohol/substance use, affective dysregulation (anhedonia), behavioral dysregulation (impulsivity), sleep, physical activity, health-related quality of life, and blood samples from which DNA will be extracted and biobanked for future analysis. All measures are described in the CLC Research Plan. The CLC measures will be included in each project's baseline assessment battery, along with project-specific measures, by the CLC's data management team to ensure uniformity in item wording and response format across projects.

Assessments: The CADRE CLC will provide a core assessment battery to all RPs to measure mechanisms underlying chronic disease. As described in the CLC Research Plan, these include measures of pain, trauma, family history of AUD/SUD, affect, behavioral dysregulation, physical activity, sleep, and health-related quality of life. Biomarkers collected in all projects include: enzymes aminotransferase and alanine aminotransferase (AST, ALT), markers of liver damage; creatinine and blood urea nitrogen, markers of kidney function; salivary cortisol, a marker of stress response; soluble CD14 (sCD14), a marker of monocyte activation; tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), pro-inflammatory cytokines; kynurenine/tryptophan ratio (Kyn/Tryp), implicated in neuropsychiatric symptoms associated with immune activation; and monocyte chemoattractant protein 1 (MCP-1), a chemokine that regulates migration and infiltration of monocytes/macrophages and is involved in various neuroinflammatory disorders.

THE BLUE TEXT IN THE FOLLOWING SECTIONS IS A GUIDE TO ENSURE ALL RELEVANT INFORMATION IS INCLUDED IN YOUR APPLICATION. YOU MAY DELETE THE BLUE TEXT BEFORE SUBMISSION

4. **Participant Population.**

One hundred individuals receiving buprenorphine/naloxone as opioid replacement therapy (ORT) will be screened randomized. We included individual receiving ORT because we specifically target risk of relapse in a treatment-seeking population. No vulnerable population will be included in the study.

- INCLUSION CRITERIA
  - ~Male or female (50%), 18 to 70 (inclusive) years of age;
  - Currently meets DSM-5 criteria for OUD;
  - Currently on a stable dose of buprenorphine/naloxone or methadone for at least 3 months;
  - In good health as confirmed by medical history, physical examination and blood work (AST/ALT; bilirubin, creatinine clearance within normal limit);
  - Willing to take medication and adhere to the study procedures;

- Understand informed consent and questionnaires in English at an 8th grade level;
- Clinical Opiate Withdrawal Scale (COWS) = 0 at study screening and prior laboratory sessions.

➢ EXCLUSION CRITERIA

- Women who are breastfeeding, test positive for pregnancy or are unwilling to use medically-approved birth control;
- Liver function within 5x the Upper normal limits (AST/ALT) and renal function within 2x the Lower Normal Limit (bilirubin, creatine clearance).
- Suicide attempts in the last three months;
- Current substance disorder other than marijuana, nicotine and caffeine as assessed by self-report and urine toxicology screen at baseline;
- Current use of medications that may interact with study medications;
- History of hypersensitivity to study medications;
- Clinically significant electrolyte abnormalities, current rhinitis or use of vasoconstricting medications or prostaglandins.

NOTE: the exclusion criteria are based in reducing participants' safety.

Participants need to speak English and be able to understand informed consent and questionnaires in English which will be written exclusively at an 8th grade level.

One hundred individuals receiving buprenorphine/naloxone or methadone as opioid replacement therapy (ORT) will be screened, 80 will be randomized, with 50 expected to complete the study. Potentially eligible participants will be invited for an in-person screening, where they will provide written informed consent and undergo a physical examination in the NEW Clinical Laboratory Core (CLC).

The **sample size estimate** is based on recent findings reporting that baseline levels of stress significantly predicted oxytocin effects on cue-induced craving (Mitchell et al., *J Addict Med*, 2016). Effect sizes were calculated based on a between-subjects in oxytocin study with alcohol related responses (Pedersn et al., *ACER*, 2013). The estimate of opioid craving (measured by the OCQ) were calculated from the *M* and the *SD* of alcohol-related outcomes: oxytocin was superior to placebo in reducing alcohol withdrawal (*i.e.* less lorazepam required to complete detoxification: 3.4 mg±4.7, vs. 16.5 mg±4.4, $p<0.01$), lower mean CIWA scores (4.3 mg ±2.3 vs. 11.8 mg ± 0.4, $p<0.01$). We estimated that with a standard threshold, $\alpha = 0.05$, for med-large effect ($f = 0.35$), two group independent variable and three covariates in ANCOVA, the *N* is 67 to detect 0.80 power. With an additional 0.20 to account for attrition [*N* = 50 (completers) + 13 = 80 (enrolled)]. The estimated power at *N* = 67, with the addition of an interaction term (for Aim 2) would be = 0.63. Therefore, the calculated sample size is well powered to address the hypothesis of the main medication effect (Aim 1) and of the interaction effect with stress and anxiety (Aim 2).

5. Recruitment Methods

We will recruit equal numbers of men and women in this study since not only stress affects prescription opioid misuse, but also sex. This target population should be feasible to recruit considering that the prevalence of prescription opioid use among women is substantial. Participants will respond to the recruitment materials by telephone or email and will be pre-screened on the telephone for initial eligibility by the RA. Dr. Josiah Rich, PI of COBRE Opioid grant, will collaborate with Dr. Haass-Koffler for the recruitment of this project (letter of support to the CADRE PI: Dr. Monti).

Potentially eligible participants will be invited for an in-person screening by the RA and the nurse practitioner, where they will provide written informed consent and undergo a physical examination,

blood work and electrocardiogram (ECG). After confirmation of eligibility by the study physician (Dr. Swift), participants will be enrolled in the study by the PI (Dr. Haass-Koffler) with the support of the RA.

The biomedical assessments (urine test and ECG) will be performed by a trained RA under the supervision of the nurse practitioner and the blood will be collected by a phlebotomist or nurse practitioner.

The RA will receive training in administer the screening assessments by trained research personnel (either by the PI or the nurse practitioner). Screening test and procedure to ensure that potential participants are eligible to participate.

TABLE 1 – Assessments at screening, Visit 1

Measure	Personnel administering the assessment
Blood test clinical analysis, buprenorphine blood level	NP, PL
Clinical Opiate Withdrawal Scale (COWS)	RA
Concomitant medications, nicotine and marihuana use	RA
Hamilton anxiety rating scale (HAM-A)	RA
Hormone collection (blood and saliva)	Blood (NP), Saliva (RA)
Opioid Craving Scale (OCS)/Timeline Followback (TLFB)	RA
State Anxiety Inventory-State (STAI-State)	RA
Trait Anxiety Inventory-Trait (STAI-Trait)	RA

Legend - PI: Dr. Haass-Koffler, NP: Nurse Practitioner (TBD), RA: Research Assistant (TBD), PL: Phlebotomist (TBD)

NOTE: The de-identified screening data (study code) will be kept after eligibility is determined for research purpose. The document that links the study code with identifiable information will be destroyed after conclusion of the trial. The screening consent process is fully described in Part V. All screening material will be in English.

Standard care: opioid replacement therapy (ORT) with buprenorphine/naloxone or methadone.

Intervention: standard care + oxytocin 40 IU intranasal, twice a day

6. Compensation / Reimbursement

Compensation schedule and amount is described below:

Visit 1 will take ~ 4 hours and participants will receive $40 for the visit.

Visit 2 ~1 hour and participants will receive $40 for the visit.

Visits 3, 4, 5 and 6 will take ~3 hours and participants will receive $100/visit.

Visit 7 will take ~1 hour and participants will receive $20 + a $50 bonus for completing the study.

Total possible compensation is $550. Participants will be compensated in cash or Clincard and for the sessions that they complete. The amount of compensation is based on the time spent in each session and based on other similar study conducted by the PI or Dr. Swift at Brown University. Participants will receive parking validation or RIPTA tickets (both ways) as reimbursement for travel cost.

Participants that have previously completed the study and are re-enrolled in the opposite medication condition counterbalanced, will receive an extra $20 for Visits A and B both; these visits are for safety criteria and to ensure eligibility once again. A sum of $590 compensation is possible for these individuals.

7. Potential Research Risks / Discomforts to Participants.

1) discomfort from answering questionnaire items,
2) issues associated with undue inducement,
3) issues associated with coercion,
4) side effects or drug interactions with oxytocin,
5) craving for opioids,
6) discomfort from opioid craving during cue reactivity, and
7) discomfort from the neuroendocrine activation produce by yohimbine.

Participants will be protected against any potential risks and will be closely monitored throughout the study.

1. Participants may experience some discomfort when answering questionnaires items, however we expect that the risks will be low. Based on past and current research by Drs. Haass-Koffler and Swift, participants have not had any discomfort or issues that have arisen from questionnaires.
2. The risk of breach of confidentiality is low and strict precautions will be taken to minimize the risk of breach of confidentiality. A Data Safety Monitoring Plan (DSMP) will be in place that follows Brown's IRB guidelines.
3. The risk of undue inducement is low. Monetary compensation for this study is commensurate with the amount of time and effort that is required for the study.
4. The risk of coercion is low, since we have a well formulated "alternatives to participation" section of the consent so subjects don't believe enrolling is the only way to get help with OUD.
5. Participants may experience some side effects associated with oxytocin administration and there is some risk of drug-drug interactions. However, oxytocin will be administered intranasally and will have reduced first-pass metabolism. Also, based on past research, oxytocin has minimal side effects and is well-tolerated by participants. A detailed procedure to minimize risk associated with oxytocin is defined below.
6. Participants may experience some discomfort from opioid withdrawal, but these should be minimal since the participants are taking ORT. As outlined below, several precautions will be taken to help minimize any opioid withdrawal symptoms that participants may experience.
7. Participants may experience craving for opioids after being exposed to opioid cues. Past research by Drs. Swift and Haass-Koffler have shown that participants do not have significant craving or subsequent drug use after cue exposure.

In this study, yohimbine (32.4 mg), formulated by JB Pharmacy is administered below the therapeutic index to a dose considered unsafe (>100 mg). Furthermore, yohimbine will be administered only once, during the laboratory session. Dr. Haass-Koffler has already obtained the Investigational New Drug (IND:135570) from the FDA that determined that it is safe to proceed to clinical investigation using oxytocin and yohimbine in patients receiving buprenorphine/naloxone or methadone therapy (**Appendix A**).

~~Finally, Dr~~. Haass-Koffler has a current and ongoing human laboratory study (PI and IND holder: NCT: 02243709; IND: 121984) using the same dose of yohimbine within a similar laboratory paradigm formulated by the same pharmacy with no adverse events that have been reported to the FDA, NIH or IRB.

As detailed in the Description of Potential Risks, the following will be set forth to protect against risks of the study:

1. To protect against or minimize discomfort from answering questionnaire items, participants may refuse to answer questions that they do not feel comfortable answering. Participants with discomfort may withdraw from the study with no penalty and will be referred to Dr. Swift for a clinical assessment if distress continues.
2. To protect against a breach of confidentiality, all data acquired during the study will only be accessible by the research staff and used for research purposes only. All research data will be kept in a locked filing cabinet or on a password-protected computer database in the study office. Only participant code numbers will be used to identify participants. Consent forms and logs with participant's names and codes will be locked in a separate cabinet in the PI's office as an extra layer of security. All biological samples will be guarded in a similar manner. Only participant code numbers will be labeled on biological samples and will be locked in a laboratory suite. All interviews and assessments will be conducted in an interview room with a closed door to ensure participant privacy and confidentiality. The NIH Certificate of Confidentiality will protect against disclosing any identifying information/characteristics of participants in legal demands such as court orders or subpoenas. The Certificate will ensure further protection of participants' confidentiality.
3. To protect against issues associated with undue inducement, participants will be compensated appropriately for their time and effort. The study involves about a week of participation and given the considerable time commitment and involvement, compensating participants for their time and travel costs is appropriate and comparable to other study protocols. Those who drop out of the study early will be compensated for sessions that they completed.
4. To protect against issues associated with coercion, participants will be informed that participation is not required to get help treatment help with OUD. Also, we are not enrolling vulnerable populations.
5. To protect against or minimize any risk of side effects associated with oxytocin, yohimbine or any drug-drug interactions, potential risks will be judiciously outlined to participants and thorough screening procedures will be in place to minimize recruitment of those that might be at a higher risk of adverse events. The study physician (Dr. Swift) and the CADRE NP will carefully review all participant screens and the PI will evaluate the individual medication profile to minimize any risk association with the medication. The participants will be instructed on the proper administration of the medication and they will return the spray bottle at the last visit. The safety of oxytocin is supported by other work with intranasal oxytocin spray (102, 103). No adverse events or side-effects were reported during the studies. Dr. Swift's contact information will be provided to participants so that participants can contact him between visits if necessary.
6. To protect against or minimize any discomfort from opioid withdrawal, participants will be closely monitored throughout the study. Opioid withdrawal will be assessed before each visit and since individuals with a COW > 0 will be excluded from the study at screening, we don't expect withdrawal from opioids to be severe. Dr. Swift and/or the CADRE NP will be accessible 24/7 during the study and participants will be instructed to call if they experience any withdrawal symptoms. Emergency medical services will be immediately called if a serious adverse event arises during the study. Opioid withdrawal symptoms can be uncomfortable but are not dangerous.
7. To protect against or minimize any discomfort from opioid craving during cue reactivity, participants will be closely monitored throughout the laboratory session. Buprenorphine/naloxone or methadone level will be assessed at visit 3 to ensure ORT compliance. Participants' vital signs (BP, HR and MAP) and opioid craving with behavioral assessments will be monitored during the entire session.
8. The safety of yohimbine (32.4mg), formulated by Bayview Pharmacy is administered below the therapeutic index to a dose considered unsafe (>100mg). Furthermore, yohimbine will be administered only once, during the laboratory session.

The protocol involves an intervention proposed as an adjunct therapy to the standard care. There are minimal risk for participants in their daily lives, however they may feel discomfort during the

laboratory procedures (stress-induction). See below additional consideration to prevent the additional risks:

- *JB Pharmacy* will provide the oxytocin (40 IU intranasal) and yohimbine (32.4 mg, oral) that will be administered at CAAS under team supervision prior to the laboratory session. Risks of medications will be minimized through careful and detailed screening of participants by the PI, (Dr. Haass-Koffler) who is a trained pharmacist and pharmacologist and the co-I, and study physician (Dr. Swift) who is a practicing physician and addiction psychiatrist, to minimize recruitment of those who might be at higher risk for adverse events, as well as careful and detailed monitoring of adverse events and participant well-being during the study.

- *Oxytocin*. There are usually no side effects in individuals that administer intranasal oxytocin spray at the dose provided in this proposed project. The half-life of intranasal oxytocin in serum is 3-17 minutes and therefore side effects should be minimal. Common side effects include: relaxation, irritability and stomach cramps. Less common side effects that are reported at higher doses include: mild dizziness, dry mouth, nausea, vomiting, nasal irritation, runny nose, or tearing of the eyes are common with medication given by nasal spray. Participants will be instructed on how to properly administer the nasal spray by the CADRE NP, with an empty sprayer bottle. The participant will administer the first dose while at the CADRE laboratory to ensure correct administration. Participants will be instructed to stop taking the medication and to call the PI if any side effects or adverse events as a result of the medication occur. The PI will then contact Dr. Swift and/or the CADRE NP who will recommend next steps. Participants may withdraw from the study at any time if they do not feel comfortable administering the medication and will be compensated for sessions that they have completed. To protect against or minimize any risk associated with opioid craving after the opioid cue-reactivity task, participants' vital signs and opioid craving with behavioral assessments will be monitored. If a clinically significant increase in craving were to occur, participants may require clinical management. Dr. Swift and/or the CADRE NP will be immediately called and will evaluate each participant on a case-by-case scenario.

- *Yohimbine:* The oral dose of yohimbine for this study is based on prior studies, in particular from an ongoing study of Dr. Haass-Koffler's (PI and IND holder: NCT: 02243709; IND: 121984) in which yohimbine was administered to examine neuroendocrine probes in human studies. Ample data supports the safety of yohimbine to induce craving in alcohol-dependent individuals, and the safe induction of stress in PTSD veterans and gamblers. In this study, yohimbine (32.4mg), formulated by Bayview Pharmacy is administered below the therapeutic index to a dose considered unsafe (>100mg). Furthermore, yohimbine will be administered only once, during the laboratory session and under direct supervision of the study personnel. It will be given at a safety-tested dose to increase noradrenergic activity already being evaluated in psychiatric patients with clinically relevant stress conditions such as PTSD, anxiety, and depression. Finally, yohimbine's short half-life ($t_{1/2}$ = 1-2 hour) provides a transient effect. The protocol includes close monitoring of vital signs (BP, HR and MAP) and cortisol levels. Dr. Swift and/or the CADRE NP will evaluate any possible adverse effect due to yohimbine administration. In addition, we will administer the standardized CADRE assessment to determine stress and anxiety at baseline. If anxiety is higher at the end of the study we will call Dr. Swift and/or the CADRE NP to have him meet with the patient before being released. The most common side effects reported by the use of yohimbine are: an allergic reaction, irregular or fast heartbeat, confusion, dizziness, anxiety, irritability, or nervousness, tremor, headache, skin flushing and we have not encounter these effect in our ongoing trial (PI and IND holder: NCT: 02243709; IND: 121984).

- *Drug-drug interactions* There are no known drug-drug interactions between buprenorphine or buprenorphine co-formulated with naloxone and yohimbine and or methadone and yohimbine. To protect against any risk of additional drug-drug interactions, participants will be thoroughly screened for any prescriptions or over-the-counter medications that may interact with oxytocin and yohimbine. Dr. Haass-Koffler will oversee the possible drug-drug interactions that may arise from the co-administration of existing medications taken by participants with the study medications. She will evaluate the medication profile for each screening visit and she will prepare a full pharmacokinetics/ pharmacodynamics (PK/PD) report for the final review of Dr. Swift using the Clinical Pharmacology database provided by Brown. Participants will be instructed to immediately call the PI if they start taking new medications. The PI will then contact Dr. Swift who will recommend next steps. Participants will be asked to avoid any medications that could interact with oxytocin and yohimbine. To further minimize any risk associated with drug-drug interactions, participants will receive a wallet card with contact numbers of the PI, study physician, as well as emergency numbers. Participants will be instructed to carry the card at all times and to call Dr. Swift 24/7 in case of an emergency

Data and Safety Monitoring Plan (DSMP) is attached to this protocol **(Attachment D)**

8. Potential Benefits of the Research. NOTE: Compensation for participation is not a benefit and should not be included in this section.

- Potential benefits to human subjects and to others There are no direct benefits to participants in this study. However, considering the potential benefits and the knowledge to be gained, we believe that the benefits outweigh the risks. The risk-benefit ratio provides a justification for conducting this study, which could ultimately lead to more effective treatment options for opioid use disorder.

- Importance of the knowledge to be gained With the serious health and economic consequences associated with opioid use disorder, this study provides a much needed understanding of the behavioral and biological factors involved with opioid craving and use. This study aims to examine the potential efficacy of a novel pharmacological treatment for opioid dependent individuals during stress conditions. If effective, the findings of this study could lay the groundwork for an effective treatment strategy for opioid use disorder and individuals with other addictive disorders.

PART IV. APPENDICES SCREENER		
Please complete & attach the following Appendices to this Application, as applicable.		
Incl.	**N/A**	
☐	☒	Appendix A. Children as Subjects *To be attached when minors are included as participants [please be aware of the age of majority for your specific research site(s)]*
☐	☒	Appendix B. Prisoners as Subjects *To be attached when prisoners are included as participants.*
☒	☐	Appendix C. Use of Drugs *To be attached when the research includes the use of FDA-regulated or unregulated drugs.*
☐	☒	Appendix D. Use of Devices *To be attached when the research includes the use of FDA-regulated or unregulated devices.*

☒	☐	Appendix E. Prescription Drug / Medication Management *To be attached when study procedures include administering prescription medications to study participants.*
☐	☒	Appendix F. Mental Health Safety Plan *To be attached when participants may experience significant emotional distress, or be at risk of themselves or others.*

LIST OF ATTACHMENTS

- **A.** FDA IND#135570 (Specific for this project)
- **B.** CADRE CORE Standardized Assessments and Measures
- **C.** Use of Drugs (oxytocin and yohimbine)
- **D.** Data and Safety Monitoring Plan (DSMP)
- **E.** Prescription Drug / Medication Management
- **F.** Mental Health Safety Plan
  F. 2 CADRE Suicidality Mental Health Monitoring
- **G.** Project ad hoc Assessments and Measures
- **H.** Oxytocin Drug Manual
- **I.** Yohimbine Drug Manual
- **J.** Telephone pre-screening
- **K.** Informed Consent Document
- **L.** Recruitment material

PART V. INFORMED CONSENT

Informed consent is a *process*, not just a form. The IRB must ensure the informed consent process clearly discloses and facilitates the understanding of all information needed to make an informed decision to participate while promoting the voluntariness of participation.

Please review the Consent/assent templates and related guidance on the HRPP Forms & Templates page before developing your consent forms.

1. Describe the informed consent process:

In a private room in Dr. Haass-Koffler' laboratory, following a breath alcohol content (BrAC) = 0.00, participants will provide a written informed consent to participate. Participants will be asked to read the document thoroughly and indicate that they have done as much in order to proceed to the study. Potential participants have the option of refusing to participate in the study, withdrawing their participation at any time, and/or refusing to answer any questions that they feel uncomfortable responding to (**Attachment K**).

2. Facilitate Understanding

To ensure that participants understand the informed consent, participants will read each page. All participants will be informed of the study procedures, study rationale and any potential risks and benefits. The PI or Research Assistant will answer any questions about the informed consent and study that participants may have.

Being fluent in English is part of the study inclusion criteria and thus participants will not be permitted to enroll in the study unless they meet this criterion

We will ensure ongoing consent by adding language to remind participants that they have the option of refusing to participate in the study, withdrawing their participation at any time, and/or refusing to answer any questions that they feel uncomfortable responding to.

3. Documentation
Participants will be asked to sign a copy of the consent form that the researcher will keep on file in a locked storage cabinet. A second copy of the consent form will be provided to study participants to keep.

4. Additional Considerations
All study participants will be consented. This study does not involve minors, any deception, and all data including biospeciments will be full de-identified.

Proceed to PART VII. DATA SECURITY ASSESSMENT

PART VI. USE OF SECONDARY DATA / BIOSPECIMENS

1. From what source(s) will you acquire or access the data / biospecimens?

2. Do any of the source(s) require a Data Use Agreement (DUA) or other Agreement that requires institutional signature to obtain, access or use the data / biospecimens? ☐ Yes ☐ No

If "yes," please include a copy of the Agreement(s) with this submission and also follow the Data Use Agreement review and signature processes.

3. Describe the type(s) of data and date range(s) of the data you will use and the characteristics of the study research population (e.g., age range, sex, and any other pertinent demographic information.)

Proceed to PART VII. DATA SECURITY ASSESSMENT

PART VII. DATA SECURITY ASSESSMENT

1. Do the study data / biospecimens include identifiers? Video and audio recordings are considered identifiable.

☒ Yes ☐ No*

If "no," I affirm that I have read and will abide by the Level 1 Risk Minimum Security Standards: ☐ Yes ☐ No
Proceed to Part VIII.

If "yes," answer the following questions.

A. Describe the identifiers associated with the data / biospecimens.
Biospeciments will be coded by de-identified study numbers immediately after collection. The file connecting the participant ID to their study code will be kept in a secured password protected department folder, the destroyed after conclusion of the trial.

B. Justify why identifiers are required to conduct the research.
This is a biomedical study that requires blood and saliva collection for screening eligibility, safety measure and to answer research question.

C. Described the proposed research use of the identifiable data / biospecimens.
The de-identified data will be used for the purpose of this study and the other CADRE projects.

D. Self-classify the Risk Level of these data / biospecimens (select the *highest level of risk* for all data / biospecimens being collected).

☒ Level 2 Risk
☐ Level 3 Risk

2. How will study data / biospecimens be collected?

☐ Brown desktop
☐ Laptop
☒ Departmental server
☐ CIS managed server
☐ Brown Qualtrics
☐ REDCap; Please describe what instance of REDCap is being used (Brown does not have an instance of REDCap):
☐ MTurk (AMT)
☐ Text messaging → You must complete the Text messaging section after completing Qs 3 – 5.
☐ Mobile App (on tablet, iPad, Phone) → You must complete the Mobile App section after completing Qs 3-5.
☐ Zoom
☐ Other audio / videoconferencing tool; please describe the tool:
☒ Paper records, including photographs. Please describe, including how you will securely store the paper records:

Subject's identifiable information (i.e. screening questionnaires) will be stored separately from individual data. Paper records will be maintained in locked file cabinets in locked offices. The file connecting the participant ID to their study code will be kept in a secured password protected department folder, the destroyed after conclusion of the trial.

☐ Web-based site / survey / other tool not listed above → You must complete the Web-based Other section after completing Qs 3 – 5.

☐ Other; please describe:

3. Who will have access to the study data / biospecimens?

☐ A. Brown PI only. How will unauthorized access by others be prevented?

☒ B. Brown PI and other Brown research team members. How will unauthorized access by others be prevented?

Data will be stored on a Brown University protected drive. Unauthorized access by others will be prevented by password protecting the folder that the file is located in, as well as the file itself. All computer and biospeciment information will be de-identified and referred to by a subject identification number following collection. All electronic records will be maintained on password protected fileservers in a locked office, further protected by firewalls and other security procedures

☐ C. Data will be shared with research collaborators external to Brown. This data sharing intent **must** be described as part of your consent process / form. Please describe how you will securely share / transfer the data outside of Brown:

*Note that an Outgoing Data Use Agreement **is required when sharing identifiable data external to Brown**. Please follow the procedures outlined here. You do not need to submit a copy of a DUA to the HRPP. This will be linked by the ORI administratively.*

4. Where will the study data / biospecimens be stored?

☒ Departmental server
☐ CIS managed server
☐ Stronghold
☐ Campus file storage
☐ REDCap
☐ Other. Please describe:

5. If traveling with your data, describe how your data will be secured.

NA

6. For how long will you retain identifiable data / biospecimens? How will you destroy identifiers when no longer required?

We will be deleting the file connecting the participant ID to their study code at the completion of the study.

Text Messaging (only complete if instructed above.)

1. Are you using the current text messaging service available on the device?

☐ Yes ☐ No	If "no," you must also complete the Mobile App section.
2. Whose device will be used? ☐ Participant's personal phone ☐ Brown-issued phone	
3. Content of messaging: (If brief, insert here; otherwise, please provide as an attachment)	
4. Is the communication one-way or two-way? ☐ One-way ☐ Two-way	
Mobile App (only complete if instructed above.)	
1. Name of the mobile app:	
2. Has this site / tool been reviewed by CIS IT Security?	
☐ Yes ☐ No	If "no," answer the following: a. Who created the site / tool (vendor name or off the-shelf app creator name)? b. Where is it hosted? c. Is the site / tool scanned for security vulnerabilities? ☐ Yes ☐ No d. What version of software is being used, if applicable: ☐ N/A or e. How are the data encrypted?
3. Whose device will be used? ☐ Participant's personal phone ☐ Brown-issued phone If Participant's person phone: a. How is the app downloaded to the device? b. Is a password or PIN required for the app? ☐ Yes ☐ No	
4. Will data be stored on the device for any period of time?	
☐ Yes ☐ No	a. If "yes," please describe (i.e., queue on phone and then transmitted to server): b. Is the app data encrypted on the device? ☐ Yes ☐ No
5. Device features mobile app can access ☐ N/A ☐ Device ID and call information ☐ Identity ☐ Contacts ☐ Camera ☐ SMS or chat ☐ Storage ☐ Device and application history ☐ Phone ☐ Photo / media / files ☐ Microphone ☐ Location ☐ Other; please describe:	
6. Will a third-party have access to research data through this app? ☐ Yes ☐ No	
7. Is data transmitted by the device?	
☐ Yes ☐ No	If "yes," how is it encrypted in transit?
8. Are phone numbers or mobile identification numbers stored with the data? ☐ Yes ☐ No	
Web-based Other (only complete if instructed above.)	
1. Name of the site / tool:	
2. Has this site / tool been reviewed by CIS IT Security?	
☐ Yes ☐ No	If "no," answer the following:

	a. Who created the site / tool (vendor name or off the-shelf app creator name)? b. Where is it hosted? c. Is the site / tool scanned for security vulnerabilities? ☐ Yes ☐ No d. What version of software is being used, if applicable: ☐ N/A or e. How are the data encrypted?
☐ Yes ☐ No	If "no," answer the following: a. Who created the site / tool (vendor name)? b. Where is it hosted? c. Is the site / tool scanned for security vulnerabilities? ☐ Yes ☐ No d. What version of software is being used, if applicable: ☐ N/A or e. How are the data encrypted?
3. Is informed consent being obtained via this site / tool?	
☐ Yes ☐ No	If "yes," how is re-identification prevented?
4. Does the technology allow for the explicit exclusion of the collection of IP address of the participant's connection?	
☐ Yes ☐ No	If "yes," will you use this option to exclude the collection of IP address? ☐ Yes ☐ No

Brown Qualtrics: CIS has pre-vetted Brown Qualtrics for collection/storage of up to Risk Level III data. Qualtrics is the preferred survey tool for all Brown research data collection.

REDCap: Brown does not currently have its own instance of REDCap. Access to REDCap through a Lifespan collaborator must be explicitly identified.

Data collection: The expectation is that data collection *devices* will only store data during active data collection. Data must then be transitioned to more secure long-term storage solutions.

Departmental/CIS managed servers: If data are collected/entered directly onto a Departmental or CIS managed server, **you must ensure** that the server meets the security standards described in the Minimum Security Standards for Servers based on the Risk Level of the data identified in 1D.

Proceed to PART VIII. INTERNATIONAL RESEARCH

PART VIII. INTERNATIONAL RESEARCH

1. Does the research involve human subjects activities outside of the United States?

☐ Yes ☒ No

a. If "yes," please list the countries. If "no," you are not required to complete this Part of the application. Proceed to PART IX. ATTACHMENTS.

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b. What is the status of permissions / approvals from local ethics boards or committees?

☐ Received; please append to this Application.

☐ Pending

☐ N/A. Please explain:

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c. Will this research take place in a non-public setting (including a school, hospital or clinic) for which local permission is required? ☐ Yes ☐ No

If "yes," please append a letter(s) of support or permission(s) to this Application.

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d. Describe how you have taken into account any social, political, or cultural issues that may impact participants.

☐ I have reviewed the current version of the *International Compilation of Human Research Standards* and agree to abide by relevant local laws, regulations and guidelines.

☐ I have reviewed the *General Data Protection Regulations guidance* and will abide by any requirements.

☐ I have reviewed ORI's export control guidance on international travel, international collaborations, and international shipping (*if applicable*)

Proceed to PART IX. ATTACHMENTS

PART IX. ATTACHMENTS

Please attach the following materials to this Application for Full Board / Expedited IRB Review, as applicable.

Incl.	N/A	
☒	☐	Informed consent documents / scripts
☒	☐	Data collection materials (questionnaires, surveys, interview scripts, etc.)
☐	☒	Permissions, approval documents, and/or support letters identified in PART VII.
☒	☐	Recruitment materials (emails, flyers, letters, scripts, posters, brochures, etc.)
☐	☒	Application for IRB Authorization Agreement
☐	☒	Data Use Agreement from data provider(s)
☒	☐	Data Safety Monitoring Plan
☒	☐	Other: **IND**

LIST OF ATTACHMENTS

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  F. 2 CADRE Suicidality Mental Health Monitoring
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PART X. CONFLICT OF INTEREST

The *Brown University Conflict of Interest Policy for Officers of Instruction and Research* *("COI Policy")* defines the term "Investigator" as "the project director or principal investigator and any other person, regardless of title or position (e.g., full or part-time faculty member, staff member, student, trainee, collaborator, or consultant), who is **responsible** for the **design, conduct, or reporting** of sponsored research."

Using this definition of "Investigator," please ensure that all Investigators on this protocol answer questions (1) and (2) below. Attach additional sheets for any Investigators who are not the PI; additional sheets are available on the HRPP website.

1. Have you completed a conflict of interest disclosure (i.e. *COI Reporting Form*) within the past 12 months and is it accurate and up-to-date as of the time of this submission, as required by Brown's COI Policy? (You may access the InfoEd system here to confirm.)	
☒ Yes ☐ No	If "no," please do so before submitting this Application
2. Do you have a significant financial interest (SFI) that is related to this research protocol? "Related" could mean the research involves products, technology, intellectual property, or services made, owned, or provided by the entity/ies in which you have an SFI. It could also mean that the SFI could be affected by the proposed research or its results.	
☐ Yes ☒ No	If "yes," please identify the SFI and explain the relatedness:
☐	Additional COI sheets for Investigators are attached to this Application. ***(Required for Advisors)***

PART XI. INVESTIGATOR & FACULTY ADVISOR AGREEMENTS / PRINCIPAL INVESTIGATOR RESPONSIBILITIES

A. Conduct of the Research

1. I accept responsibility for the ethical conduct of this research and protection of participants as set forth in the Belmont Report, Common Rule, and Brown University policies.
2. I accept responsibility for ensuring this research is conducted in accordance with:
   a) Sound research design and methods;
   b) The parameters of the research plan and activities described in this Application;
   c) The applicable terms of the grant, contract, or other signed funding agreements;
   d) Applicable laws and regulations, including those protecting the rights, safety and welfare of human subjects.
3. I certify that I am, or my faculty advisor is, sufficiently qualified by education, training and experience to assume responsibility for the proper conduct of this research. I accept responsibility for ensuring that all member of the research team have or will complete human subjects CITI training before any work with participants or identifiable data / biospecimens begins.
4. I accept responsibility to personally conduct and/or directly supervise this research. I certify that I have sufficient time and resources to properly conduct and/or supervise this research.

B. Ensuring and Maintaining Compliance

1. I will comply with relevant regulatory and institutional reporting requirements, including Brown University's *Reportable Events Policy*.
2. I understand that it is my responsibility to ensure that any research personnel, including myself, responsible for the design, conduct or reporting of the research declares any conflicts of interest related to this research. I will ensure that any changes that impact my or other research personnel's answers to the questions in PART IX. Conflict of Interest, are reported promptly to Brown's HRPP.
3. I will ensure that prospective agreement and/or informed consent is obtained and a copy is provided to participants, when appropriate.
4. If there are changes to the research described in this Application for Full Board / Expedited IRB Review that may impact the study's classification as Full Board or Exepdited research, I will promptly notify the Brown HRPP of such changes.

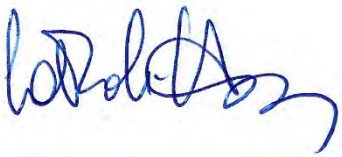
5. I will notify the Brown HRPP when I have completed all activities involving human subjects or identifiable participant data or identifiable biospecimens.
6. I will maintain approval, as applicable, with collaborative parties, including approvals from other countries or jurisdictions.
7. I will cooperate with any post-approval monitoring or auditing of study activities and/or study records as requested and/or required by the Brown ORI, the Brown IRB, funding entities, sponsors, and/or any federal or state regulatory agencies.

C. Study records, Reports and Documentation

1. I will maintain all research protocol materials and consent materials for the duration of this study.
2. I will maintain research records for at least three years following the end of this research, or for a longer length of time if specified in applicable regulations or sponsor requirements. I will take measures to prevent accidental or premature destruction of these records.
3. I will abide by all terms of any Data Use Agreement (or equivalent agreement) related to this study, including those agreed to electronically (through an online attestation).
4. I will ensure that the data security measures for acquisition, collection, transfer and use of study data described in PART VI. of this Application are adhered to by all members of the research team.

By my signature below, I certify that I have read and agree to uphold all of you and/or Advisor Responsibilities in PART XI.

Principal Investigator signature: **Date:** 4/29/2019



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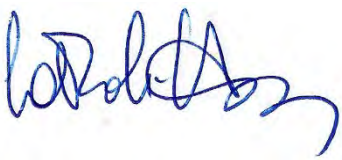
An Advisor's signature is required for all graduate/medical student projects

Advisor certifies the following: Advisor has read the complete protocol, approves this project, and will remain available to advise the student throughout the course of the proposed human subjects research, or will transfer responsibilities to another Advisor if unable to advise for the entirety of the project.

Advisor's name (please print):

Advisor's signature: **Date:** Click here to enter a date.



For IRB Use Only

Signature of the IRB:

Date of IRB approval: Click here to enter a date.