Prolonged Exposure Therapy for PTSD and Opioid Use Disorder

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Human Subjects Research Protocol

PROTOCOL SUMMARY

Project Title:

Prolonged Exposure Therapy for PTSD and Opioid Use Disorder

Principal Investigator: Kelly R. Peck

PURPOSE AND OBJECTIVES

Purpose: The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.

The current U.S. opioid epidemic represents the most devastating public health crisis of our time, with nearly 12 million Americans reporting opioid misuse in 2016 (SAMHSA, 2017). Opioid use disorder (OUD) is associated with a host of adverse consequences including infectious disease, overdoses and premature death, as well as significant economic costs estimated at over $78 billion annually (Birnbaum et al., 2011; Clausen et al., 2009; Florence et al., 2016; Hser et al., 2001; Jonas et al., 2013; Rudd et al., 2016). Psychiatric comorbidities are prevalent among individuals with OUD with approximately 50% meeting criteria for mood and anxiety disorders (Brooner et al., 1997; Callaly et al., 2001; Gros et al., 2013; Kidorf et al., 2004; Roncero et al., 2016; Strain, 2002). These prevalence rates far exceed those found in the general population (Kessler et al., 2008) and likely confer additive vulnerabilities upon individuals with OUD.

Posttraumatic stress disorder (PTSD) is a chronic and debilitating psychiatric condition that is highly prevalent in this population. Over 90% of individuals with OUD report lifetime trauma exposure, and 33% of these individuals meet criteria for PTSD (Mills et al., 2005, 2006; Pierce et al., 2009). Although opioid agonist treatment (OAT; e.g., methadone, buprenorphine) is the most efficacious treatment for OUD (Mattick et al., 2009, 2014), patients with PTSD generally experience worse treatment outcomes, including continued psychiatric distress, greater treatment dropout, and relapse to illicit opioid use (Ecker et al., 2017; Peirce et al., 2016; Schiff et al., 2010; Teeson et al., 2005; Villagomez et al., 1995).

Within the general population, prolonged exposure therapy (PET) is a widely-used, empirically-supported and manualized therapy that is regarded as a first-line cognitive-behavioral treatment for PTSD (Foa et al., 2008). PET is designed to disrupt the cycle of anxiety and avoidance that characterizes PTSD via sustained imaginal and in-vivo exposure exercises that deliberately and systematically expose patients to painful memories and current, real-life trauma reminders that were previously avoided, yet not inherently harmful (Foa et al., 2019). Overall, PET has well-documented efficacy for reducing PTSD symptom severity in both civilian and veteran populations (Foa et al., 1999, 2005, 2008; Jonas et al., 2013; Powers et al., 2010; Schnurr et al., 2007). Moreover, PET is effective for reducing symptoms of PTSD regardless of whether it is delivered remotely or face-to-face (Acierno et al., 2017; Morland et al., 2020). Recent data also suggest that PET can improve PTSD symptoms without exacerbating substance use or craving among patients with substance use disorders when PET and substance use disorder (SUD) treatment are delivered concurrently (Coffey et al., 2016; Foa et al., 2013; Mills et al., 2012; Roberts et al., 2015; Torchalla et al., 2012; van Dam et al., 2012).

Despite these promising findings, little is known about the effects of PET among patients with concurrent OUD. In three recent studies by our group and others, PET has been associated with reductions in PTSD symptom severity among patients receiving treatment for concomitant OUD (Peck et al., 2018; Schacht et al., 2017; Schiff et al., 2015). In an initial small, uncontrolled feasibility study, twelve female methadone patients who were survivors of sexual abuse received up to 19 weekly 90-minute individual PET sessions delivered by trained social workers (Schiff et al., 2015). Participants reported significant reductions in PTSD and depressive symptoms and no relapse to illicit opioid use was observed. In a second study, Schacht et al. (2017) evaluated the effects of PET among 58 methadone-maintained patients with PTSD. Because of the notoriously poor PET adherence rates reported among patients with SUDs (Belleau et al., 2017), attendance-contingent monetary incentives were included in one of the PET experimental conditions to support PET session attendance. Specifically, participants were randomized to receive standard PET alone (i.e., 12 weekly 60-minute individual PET sessions with a trained doctoral- or master's-level therapist) or PET plus monetary incentives delivered contingent upon attending scheduled PET sessions. Participants randomized to the PET + incentives condition attended significantly more therapy sessions than participants who received PET alone (7.11 vs. 1.80,

respectively; p<.001). They also demonstrated greater decreases in PTSD severity compared to controls, with 78% vs. 48% meeting criteria for clinical improvement at the Week 12 follow-up, respectively (p=.029). Finally, a third study conducted by the PI of this proposal (Peck et al., 2018) involved a secondary analysis of data from a randomized trial in which 126 adults with co-occurring PTSD were recruited from an inpatient SUD treatment program and randomly assigned to receive either PET or a non-trauma-focused comparison treatment in addition to SUD treatment as usual (Coffey et al., 2016). Peck and colleagues (2018) compared participants with OUD (n=52) versus those with other SUDs (n=74) and found that adults with OUD presented with higher baseline levels of psychiatric distress and SUD severity. Furthermore, when PTSD- and SUD-related outcomes were examined among the 85 participants who were randomized to receive PET, participants with OUD achieved significant reductions in PTSD and psychiatric symptom severity that were comparable to those reported by participants in the non-OUD group despite experiencing more severe symptoms at baseline.

Together, these studies provide promising initial evidence that PET may reduce PTSD symptom severity among patients with concurrent OUD. However, because none of the above studies included a condition to permit evaluation of PTSD symptoms over time in patients receiving standard OAT without additional PTSD-focused therapy, it is unclear to what extent observed improvements in PTSD symptom severity were a function of PET versus the psychopharmacological effects of OAT. Furthermore, though patients receiving PET + incentives reported the greater clinical improvements in the Schacht et al. (2017) study, control participants who were not incentivized for attendance also reported statistically-significant improvements over time despite attending only two sessions of PET on average, translating to essentially no delivery of PTSD-focused therapeutic content.

Accumulating evidence from preclinical and clinical studies suggests that the opioid agonist medications buprenorphine and methadone may themselves have antidepressant and anxiolytic effects (Dean et al., 2004; Falcon et al., 2015, 2016; Fingleton et al., 2015). Although both methadone and buprenorphine are associated with improvements in psychiatric symptoms, including anxiety, stress, depression and psychological quality of life (Dean et al., 2004; Fingleton et al., 2015), buprenorphine's combination of mu opioid receptor agonism and kappa opioid receptor antagonism may exert particularly promising anti-depressive effects (Ahmadi et al., 2018; Gerra et al., 2006; Karp et al., 2014; Pick et al., 1997). Additionally, a recent retrospective chart review of 2,015 veterans with PTSD found that buprenorphine was associated with significantly greater reductions in PTSD symptom severity compared to selective serotonin reuptake inhibitors, the first-line pharmacotherapy for PTSD (Lake et al., 2019).

Recent data from our group also suggest that provision of buprenorphine alone, without counseling, may be associated with significant improvements in psychiatric symptoms (Streck et al., 2018a). In that randomized clinical trial, waitlisted adults with OUD were randomized to one of two 12-week conditions: Interim Buprenorphine Treatment (IBT; N=25) consisting of buprenorphine maintenance with bi-monthly clinic visits and technology-assisted monitoring, or Waitlist Control (WLC; N=25) wherein participants remained on the waitlist of their local clinic. Participants randomized to receive IBT (i.e., low-barrier buprenorphine dosing without counseling) demonstrated significant reductions on all measures of psychiatric distress examined, with scores significantly lower at Weeks 4, 8 and 12 post-randomization compared to baseline (Figure 1). In contrast, there was no evidence of change in psychiatric symptoms among WLC participants. Despite the clinical implications of these findings, our study did not specifically recruit patients with PTSD and did not evaluate trauma-related symptoms.

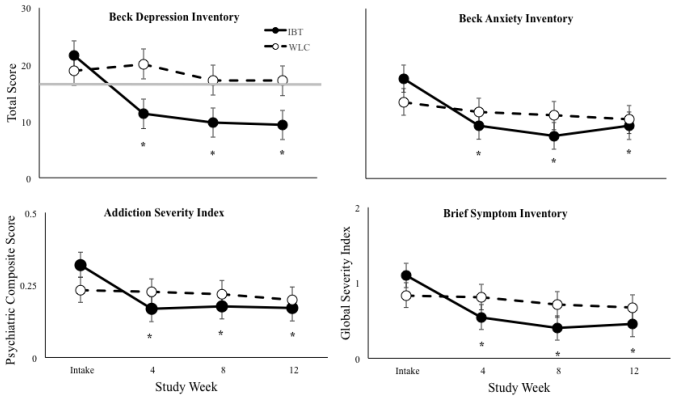

Figure 1. Changes over time in psychiatric symptoms for individuals who received buprenorphine versus who remained on the waitlist

In summary, the question of whether OAT alone may attenuate PTSD symptomatology even in the absence of intensive cognitive-behavioral therapy remains unanswered and is important given the prevalence and deleterious effects of PTSD among OAT patients, as well as the ever-present constraints on mental health resources in SUD treatment settings. Indeed, if a meaningful subset of patients with PTSD experiences improvements in psychiatric distress in response to standard OUD pharmacotherapy, limited available clinical resources could be more effectively allocated to those who require more intensive PTSD treatment in order to achieve favorable outcomes. This question is particularly urgent given the increasing numbers of opioid-

dependent individuals receiving methadone or buprenorphine maintenance treatment for OUD (Alderks, 2017; Wen et al., 2018).

References. Include references to prior human or animal research and references that are relevant to the design and conduct of the study.

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Objectives: Clearly state the primary and secondary objective(s) of the study.

The primary objective is to evaluate the effects of PET above and beyond OAT for reducing PTSD symptomatology among patients with concurrent PTSD and OUD.

METHODS AND PROCEDURES

Study Design: Describe the research design, including a description of any new methodology and its advantage over existing methodologies.

For this randomized parallel-group study, we propose to recruit 135 participants. Participants will be randomized to receive OAT as usual (*n* =45), OAT + PET (*n* =45), or OAT + Incentivized PET+ (*n* =45). Prior to conducting the randomized trial, we will recruit and enroll 30 participants who will serve as pilot participants with 10 participants randomized to receive one of three experimental conditions:

(a) OAT as usual - Participants randomized to the OAT as usual condition will continue to receive standard buprenorphine or methadone maintenance treatment from their current treatment provider and complete assessments of PTSD symptom severity, psychosocial functioning and drug use at intake and Study Weeks 4, 8, and 12.

(b) OAT + PET - In addition to receiving standard buprenorphine or methadone treatment and completing monthly assessments, participants randomized to OAT+PET will receive PET consisting of 12 weekly, individual sessions with a trained doctoral- or master's-level therapist.

(c) OAT + Incentivized PET (OAT+PET^{+}) - Participants randomized to the OAT+PET^{+} condition will receive the procedures noted above for the OAT+PET group plus monetary incentives delivered contingent upon completion of PET sessions. The inclusion of attendance-contingent incentives will permit us to rigorously evaluate the effects of PET under conditions in which patients receive a sufficient 'dose' of trauma-focused therapy.

Piloting will allow us to make necessary adjustments prior to the initiation of the main trial. Based on prior experience piloting voucher-based incentive interventions in new populations (e.g., Dunn et al., 2008; Streck et al. 2018b), we are confident that 30 pilot participants will be sufficient for addressing any logistical issues regarding participant adherence to study procedures, PET, incentive schedule, or other aspects of the study protocol.

As noted above, following completion of the pilot study, we will conduct a Stage II randomized trial evaluating the effects of PET above and beyond OAT for reducing PTSD symptomatology among 135 adults who are maintained on buprenorphine or methadone and have a current diagnosis of PTSD. We hypothesize that participants randomized to the OAT+PET+ condition will attend more therapy sessions and demonstrate greater decreases in PTSD severity relative to those randomized to the OAT or OAT+PET conditions. Additional outcomes will include symptoms of psychiatric distress (e.g., anxiety, depression) as well as opioid treatment outcomes (e.g., OAT retention, illicit opioid abstinence, opioid craving).

Procedures: Describe all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc.

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

Participants. Participants will be 165 adults (30 in pilot study, 135 in RCT) who are maintained on buprenorphine or methadone and have a current diagnosis of PTSD. Participants will be recruited using the following sources: IRB-approved flyers posted on bulletin boards in our Chittenden Clinic (CC) opioid treatment program; referrals by CC staff and prior study participants; self- and provider-referrals from other office-based buprenorphine practices and methadone programs throughout the community; IRB-approved advertisements posted throughout the community, on Craigslist and

social media platforms (e.g., Facebook) and in the main daily and the free "alternative" newspapers serving Vermont. We have successfully used these methods in our prior IRB-approved studies of individuals with OUD and other co-occurring health conditions and anticipate no difficulties doing so for this trial (Dunn et al., 2008, 2010; Sigmon et al., 2013, 2015, 2016b).

Contact between participants and study staff will be initiated by the participants. Potential participants will respond to advertisements that contain a study description and the contact information for the RA. When interested individuals contact the RA, s/he will briefly describe the study and use a brief phone screen to make a preliminary determination about the potential participant's eligibility. Those who are interested in participating and appear to be eligible will be scheduled for a longer intake screening that will begin with a full study description of study procedures, including potential risks and benefits.

For inclusion in the trial, participants must be >18 years old and be currently maintained on methadone or buprenorphine for OUD. They must also endorse >1 traumatic event on the Life Events Checklist for DSM-V (LEC-5; Weathers et al., 2013) and meet current DSM-V PTSD criteria (American Psychiatric Association, 2013) based on the Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013). Participants also must be willing to have therapy sessions audio recorded for the purpose of completing weekly homework assignments and have clear memory for the traumatic event. Consistent with our prior IRB-approved studies among OAT-enrolled patients, eligible participants must be maintained on a stable methadone or buprenorphine dose for $\geq$1 month prior to the study (Dunn et al., 2008, 2010; Sigmon et al., 2016ab). At intake, participants will sign a written release to allow study staff to confirm medication dose and clinical stability with the participant's OAT provider.

Individuals with an acute psychotic disorder, bipolar disorder with an active manic episode (but not simply the presence of bipolar disorder), imminent risk for suicide, a medical condition that may interfere with consent or participation (e.g., organic brain syndrome, dementia, head injury, neuropathy, etc.) will be excluded, as well those who demonstrate illiteracy in English. Participants must provide written informed consent to participate. Those meeting the above criteria and interested in the study will be eligible to participate. Individuals who meet the study criteria described above and provide written informed consent will be eligible to participate.

Experimental conditions.

OAT as usual. Participants randomized to OAT as usual will continue to receive standard buprenorphine or methadone maintenance from their current treatment provider and complete assessments of PTSD symptom severity, psychosocial functioning and drug use at Study Weeks 4, 8, and 12. Follow-up assessment visits will be conducted in-person at our clinic at UHC following all relevant COVID-19-related CDC guidelines and UVM safety protocols. However, study measures may also be administered remotely via phone or UVM's institutionally supported Zoom platform to reduce the risk of COVID-19 transmission. Standard OAT generally includes daily doses of buprenorphine or methadone, medical management, urine toxicology testing, regular attendance at individual or group counseling and case management as needed. As the type and quantity of clinical services received may vary across programs, time and patients, we will administer a TLFB at each study visit specifically assessing the amount and types of services that each participant receives from their OAT provider as well as in the community more generally (e.g., NA/AA support meetings, individual or group counseling, case management).

OAT + PET. In addition to receiving standard buprenorphine- or methadone-maintenance treatment as described above and completing monthly assessments, OAT+PET participants will also receive 12 individual sessions of PET. Beginning in Study Week 1, OAT+PET participants will complete weekly 60-minute PET sessions provided by a doctoral- or master's-level therapist trained in PET. Therapy sessions will be conducted at our research clinic in UHC or remotely via UVM's institutionally supported Zoom platform to reduce the risk of COVID-19 transmission. During Sessions 1-2 and prior to beginning the imaginal and in vivo exposures that are the focus of later PET sessions (Foa et al., 2019), participants will receive education about PTSD, the rationale for PET, and breathing retraining techniques as a method for managing PTSD-associated arousal. During Session 3, participants will work with the therapist to provide an initial description of their traumatic event, develop an exposure hierarchy for in vivo exposures, and the first in vivo exposure exercise will be assigned for homework. Weekly in vivo exposure exercises will be assigned at each subsequent session and involve intentional and gradual exposure to real-life trauma reminders that have been previously avoided but are not inherently harmful. Session 4 will be the first session to include imaginal exposure, in which the participant will describe the traumatic event in detail. Each imaginal exposure will be recorded and participants will be instructed to listen to the recording daily as part of their weekly homework assignment. This process is repeated until the final session, which will also include a review of treatment progress. Although PET sessions will be largely informed by conventional prolonged exposure (Foa et al., 2019), we will make the following modifications to support the effective delivery of PET in a clinical population with concurrent PTSD and OUD and facilitate future dissemination efforts: (a) sessions will be approximately 60 minutes in duration, as 60-minute PET sessions promote similar reductions in PTSD symptoms as the more traditional 90-minute sessions (Nacasch et al., 2015); (b) participants will receive psychoeducation regarding the association between PTSD and SUD symptoms; and (3) participants will complete diaphragmatic breathing at the end of each

imaginal exposure exercise in order to reduce distress to baseline levels.

OAT + Incentivized PET. Participants randomized to the OAT+PET+ condition will receive the procedures noted above for the OAT+PET group plus monetary incentives delivered contingent upon completion of PET sessions. The incentive program will follow the general parameters of the program we developed to promote and sustain abstinence from licit and illicit drugs across a variety of clinical populations (Alessi et al., 2004; Dunn et al., 2008, 2010; Heil et al., 2003, 2004; Higgins et al., 1991, 2004; Roll et al., 1996; Roll & Higgins, 2000; Sigmon et al., 2016). Participants will earn vouchers that have monetary value for attending scheduled PET appointments. Vouchers will be given to participants immediately following completion of each session. No cash will be provided to patients; rather, subjects will be able to submit vouchers to a research assistant in exchange for gift cards that they can use for purchase of retail items and services in the local community. The initial session will be worth $20. Each consecutive attended session will increase the voucher amount by $5 such that the 2nd consecutive session will be worth $25, the 3rd $30 and so on (Table 1).

Table 1 – OAT+PET+ incentive program

Session	Incentive	Bonus
1	$20	
2	$25	$50
3	$30	
4	$35	$50
5	$40	
6	$45	$50
7	$50	
8	$55	$50
9	$60	
10	$65	$50
11	$70	
12	$75	$100
Total earnings	$570	$350

To support completion of the full 12-week PET protocol, we will incorporate additional strategically-placed bonuses into the reinforcement schedule with the goal of maximizing the percentage of subjects who complete the full 12-session protocol. Bonuses have been a mainstay of our voucher-based interventions with other challenging populations (Alessi et al., 2004; Dunn et al., 2008, 2010; Higgins et al., 1991; Roll et al., 1996, Roll & Higgins, 2000; Sigmon et al., 2016). First, to support consistent (vs. sporadic) attendance, participants will receive a $50 bonus for every two consecutive sessions attended (Table 1). Second, to support completion of the full PET protocol, participants will receive a $100 bonus upon completion of Session 12.

Missed sessions will earn no vouchers and will reset the voucher values for the next attended session back to the initial $20 value. Two consecutive attended PET sessions following a reset will return the voucher value back to the value immediately prior to the missed appointment. In prior studies, we demonstrated that this reset mechanism helps to maintain the momentum of behavioral change (Roll et al., 1996; Roll & Higgins, 2000). Overall, participants who are randomized to the OAT+PET+ group and who attend every PE session as scheduled can earn a maximum of $920 combined across both regular and bonus incentive schedules.

Describe required screening procedures performed before enrollment and while on study.

When interested individuals contact the RA, s/he will use a brief phone screen to make a preliminary determination about the potential participant's eligibility. Those who are interested in participating and appear to be eligible will be scheduled for a longer intake screening assessment.

Following a brief description of study details, individuals expressing interest in participating will complete an intake assessment that includes: the LEC-5 (Weathers et al., 2013), the CAPS-5 (Weathers et al., 2013), PCL-5 (Weathers et al., 2013), Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994), Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), Addiction Severity Index (ASI; McLellan et al., 1985 Beck Depression Inventory-II (BDI-II; Beck et al., 1996), Beck Anxiety Inventory (Beck & Steer, 1993), Brief Pain Inventory – Short Form (BPI-SF; Cleeland et al., 1994), The Monetary Choice Questionnaire (MCQ; Kirby et al., 1999), Insomnia Severity Index (ISI; Morin et al., 2011), Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000), a Demographic and Drug History Questionnaire developed by our group, and a Time Line Follow-Back (TLFB; Sobell & Sobell, 1996) of opioid use, illicit and licit non-opioid drug use, alcohol use, and access to support services. Participants will provide a urine specimen for immediate onsite testing for opioids (e.g., heroin, methadone, buprenorphine, oxycodone, fentanyl) as well as other, non-opioid drugs (e.g., cocaine, amphetamines, benzodiazepines). Finally, if impairment is suspected, participants may be asked to provide a breath sample to monitor for recent alcohol use (ALCO-SENSOR III, Intoximeters, Inc., St. Louis, MO).

At each therapy session, participants will complete the PCL-5 (Weathers et al., 2013) and TLFB (Sobell & Sobell, 1996) in order to assess self-reported PTSD symptomatology, opioid use, illicit and licit non-opioid drug use, alcohol use, and access to support services. Therapy sessions may be conducted in-person or remotely via Zoom platform. At 4-, 8-, and 12-weeks post-randomization, all participants will complete follow-up assessments consisting of an abbreviated version of the intake and participants randomized to receive PET will also complete the Working Alliance Inventory Client Form (WAI; Horvath & Greenberg, 1989). A participant satisfaction questionnaire will also be administered at Week 12. Follow-up assessment visits will be conducted in-person at our clinic at UHC. However, study measures may also be administered remotely via phone or Zoom platform. Furthermore, if a participant is at high-risk and/or currently experiencing COVID-19 symptoms, urine collection may be excused and study measures can be administered remotely via phone or Zoom platform. Regardless of experimental group, all participants will receive $60 for completing the initial intake assessment and $150 for completing follow-up assessments at 4-, 8-, and 12-weeks post-randomization.

For research involving survey, questionnaires, etc.: Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation.

☐ **Not applicable**

Study procedures will be conducted in-person at UVM Substance Abuse Treatment Center or remotely via phone or UVM's institutionally supported Zoom platform. The intake assessment will include the LEC-5 (Weathers et al., 2013), the CAPS-5 (Weathers et al., 2013), PCL-5 (Weathers et al., 2013), Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), Addiction Severity Index (ASI; McLellan et al., 1985), Beck Depression Inventory-II (BDI-II; Beck et al., 1996), Beck Anxiety Inventory (Beck & Steer, 1993), Patient Health Questionnaire - 9 (PHQ-9; Kroenke et al., 2001), Generalized Anxiety Disorder 7-Item Scale (GAD-7; Spitzer et al., 2006), Brief Pain Inventory – Short Form (BPI-SF; Cleeland et al., 1994), The Monetary Choice Questionnaire (MCQ; Kirby et al., 1999), Insomnia Severity Index (ISI; Morin et al., 2011), Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000), a Demographic and Drug History Questionnaire developed by our group, and a Time Line Follow-Back (TLFB; Sobell & Sobell, 1996) of opioid use, illicit and licit non-opioid drug use, alcohol use, and access to support services. Participants will also provide a urine specimen for immediate onsite testing for opioids (e.g., heroin, methadone, buprenorphine, oxycodone, fentanyl) as well as other, non-opioid drugs (e.g., cocaine, amphetamines, benzodiazepines). Finally, if impairment is suspected, participants may be asked to provide a breath sample. Participants randomized to the OAT+PET and OAT+PET^{+} conditions will complete therapy sessions with research clinicians once per week while receiving PET as described above. Therapy sessions may be conducted in-person or remotely via Zoom platform. At each therapy session, OAT+PET and OAT+PET^{+} participants will complete the PCL-5 (Weathers et al., 2013) and Time Line Follow-Back (TLFB; Sobell & Sobell, 1996) in order to assess self-reported PTSD symptomatology, opioid use, illicit and licit non-opioid drug use, alcohol use, and access to support services. Participants randomized to receive OAT as usual will continue to receive standard buprenorphine or methadone maintenance from their current treatment provider, though all participants will complete follow-up assessments at 4-, 8-, and 12-weeks post-randomization. A participant satisfaction questionnaire will also be administered at Week 12. Follow-up assessment visits will be conducted in-person at our clinic at UHC. However, study measures may also be administered remotely via phone or Zoom platform. Furthermore, if a participant is at high-risk and/or currently experiencing COVID-19 symptoms, urine collection may be excused and study measures can be administered remotely via phone or Zoom platform. Follow-up assessments will consist of an abbreviated version of the intake and participants randomized to receive PET will also complete the Working Alliance Inventory Client Form (WAI; Horvath & Greenberg, 1989).

TYPES OF PROCEDURES (Please do not use the "other" option unless the procedure is not listed.)
Check all that apply.

X	Survey (mail, telephone, in-person, on-line)		Blood drawing:	Vol.		Over days, weeks?	
	Medical exams/history					Type & Amt.	
	Deception ***see below**		Surgery		X	Collection of Urine and/or Feces	
	Observation		Drug Administration			HIV Testing	
	Photographs		Device Use			Ultrasound (e.g. echocardiogram)	
X	Audio Recording		Exercise			Imaging (e.g. CT scan, DEXA, mammogram, PET scans, SPECT)	
	Video Recording		Diet			Use of Radiation treatment	
X	Interviews in person or by phone		Pathology Specimens (retrospective)			Use of Radioactive substances (e.g. radiolabeled antibodies, drugs or contrasts)	
	Focus Groups		Genetic Materials (DNA)*			MRI (for treatment studies)	
	Review of prospective data	X	Questionnaires			MRI (not for treatment studies)	
X	Review of retrospective data		Diaries			Tissue (obtained for clinical purposes)	
	Recording of Identifiable Data		Pregnancy Tests			Tissue (obtained solely for research)	
	Electrocardiograms						
X	Sensitive Data (criminal or sexual conduct, drug or alcohol conduct or use)			(specify):		Information related to traumatic life events, opioid use, and other illicit drug use.	

***If genetic information is being collected, GINA language must be added to the consent form.**
***Deception typically involves withholding information from the potential subject and would require an alteration to the consent process.

Statistical Considerations: Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.

Statistical Methods

The three experimental groups will be compared on baseline characteristics using analyses of variance for continuous variables and chi-square tests for categorical variables. If characteristics differ significantly and are predictive of outcome, they will be considered as potential covariates in subsequent analyses. Primary analyses will include all randomized subjects independent of early dropout, consistent with an intent-to-treat approach (Armitage, 1983). For our primary outcome of PTSD severity (CAPS-5) and secondary outcomes of psychiatric distress (BDI, BAI) and drug use (e.g., ASI subscales), mixed-models repeated measures analyses with subjects as random effects (SAS, PROC MIXED) will be used to compare the three groups across Week 4, 8, and 12 assessments. Fixed factors will include treatment condition and the within-subject factor, assessment timepoint, along with their interaction. Linear contrasts will be used to compare experimental conditions on changes from baseline to post treatment assessments, partial F-tests will be used to examine simple effects and pairwise comparisons will be based on Fisher's Protected LSD.

For the primary outcome of PTSD symptom severity, we hypothesize that participants randomized to the OAT+PET+ condition will demonstrate greater decreases in PTSD severity relative to those randomized to the OAT or OAT+PET conditions. We also hypothesize that OAT+PET+ participants will demonstrate greater decreases in psychiatric distress as measured by the BAI and BDI relative to the other conditions. Additional secondary outcomes will be exploratory in nature and include PTSD trauma type as well as measures of opioid treatment response (e.g., OAT retention, illicit opioid abstinence, opioid craving). For example, repeated measures analyses for dichotomous data based on generalized estimating equations utilizing a logit link function (SAS, PROC GENMOD) will be used to compare groups on percentage of participants retained in OAT and abstinent for illicit opioids across Week 4, 8, and 12 assessments, with post hoc testing based on Wald chi square tests. Analyses will be performed using SAS Statistical Software V9.4 (SAS Institute, Cary, NC). Statistical significance will be determined based on $p<.05$ for all analyses.

Sample Size Justification

The proposed sample of 135 participants for the randomized trial is based on having sufficient power for detecting group differences on the primary outcome of mean PTSD symptom severity score (CAPS-5). Power is estimated to be 80% using α=.05 to detect a difference in the mean change from baseline to Week 12 between any two groups of 8 points on the CAPS-5. These estimates are based on prior studies of PET in patients with concomitant SUD (Mills et al., 2012; Peck et al., 2018; Schacht et al., 2017), with slightly greater reductions expected in our OAT+PET+ condition as it is more intensive than the interventions used in those trials. For secondary outcomes, power is estimated to be 80% for detecting 12-week differences in mean change scores between groups of 9 units on the PCL-5, 6 units on the BDI, and 8 units on the BAI, both of which are smaller than the differences observed in a prior study with a similar sample (Peck et al., 2018). The estimated mean differences corresponding to 80% power using α=.05 for detecting group differences on ASI subscales are Employment=.119, Psych=.113, Family/Social=.083, Alcohol=.048, Medical=.179, Legal=.065, and Drug=.083.

Risks/Benefits: Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.

Risks include breach of confidentiality, emotional discomfort or frustration associated with the intake or follow-up assessments, and emotional distress during PET. Breach of confidentiality: Study data include medical, psychiatric and trauma histories and biological measures of illicit drug use. When study procedures are administered remotely, the risk for a breach of confidentiality is increased relative to in-person; however, the likelihood of a breach of confidentiality is low as we will take precautions to minimize this risk as described below under Adequacy of Protection against Risk.
Emotional discomfort or frustration associated with the intake or follow-up assessments: Intake and follow-up assessments will include questions about participants' medical, psychiatric, and trauma histories, urine tests of drug use, and questionnaires about mood and trauma symptoms. Answering these personal questions could make participants uncomfortable.
Emotional distress during PET: Participants may experience subjective distress during treatment while completing imaginal and in-vivo exposure exercises. This increase in subjective distress is temporary and as described below under Protection against Risk, we will include procedures for reducing and managing subjective levels of distress as part of the treatment protocol.

Protection Against Risk: (1) All study data will be confidential. The following steps will be taken to minimize risks to confidentiality: (a) a UVM-supported platform (Zoom) will be used any time that study procedures are conducted remotely to provide the highest level of privacy and security for the participant; (b) assessment data and treatment record forms will be kept in locked cabinets at the UVM research office; (c) participant identity will be disguised using ID numbers keyed to a master list; (d) session recordings of therapy sessions will be transferred to the secure UVM College of Medicine server; (e) data will be entered directly onto computer files that will be password protected; and (f) computer files will carry only participant numbers for case identification. All project staff will be trained in the importance of confidentiality. When the results of the study are published, data that might reveal the identity of a participant will be disguised.

(2) Patients are free not to participate in this study or to withdraw from it at any time. Participants who are determined to be ineligible based on exclusion criteria or who do not consent to participation in the study will be offered clinically appropriate treatment referrals outside the study. If patients decide not to participate in this study or to withdraw from this study, their decision will not prejudice their future medical care at UVM or UVM Medical Center. The investigator also retains the right to terminate patients' participation in the study if in their judgment continued participation would put them in physical or psychological danger. Additional details on our data and safety monitoring of the proposed research to ensure the safety of subjects is provided in the below section entitled "Data and Safety Monitoring Plan".

(3) Participants' reactions to study assessment and treatment will be closely monitored and negative reactions will be addressed therapeutically. To avoid or reduce mild to moderate emotional discomfort or frustration associated with psychiatric interviews and questionnaires, participants will be allowed breaks as needed during the intake and follow-up assessments. Additionally, intake assessments can be spaced over multiple visits, if needed.

(4) Prior to beginning PET, informed consent will be obtained from eligible participants to reduce the possible risks of mild to moderate anxiety when exposed to anxiety-provoking images and situations in treatment sessions, at home or completing homework exercises. Each participant will be given a rationale for PET and advised of the treatment procedure and the temporary effects that the procedure might have. Participants will be required to give consent prior to every exposure exercise or task. PET has well-documented efficacy for reducing PTSD symptom severity (Foa et al., 1999, 2005, 2008; Powers et al., 2010). While a small proportion of individuals fail to benefit from PET, very few report adverse effects. The exposure exercises will be individually and gradually titrated such that in-vivo exposure exercises start with real-life trauma reminders that elicit moderate anxiety and progress to more anxiety-provoking stimuli.

(5) Participants in each condition will be informed by study staff that they may call between sessions should they experience a crisis or are distressed enough to need psychological support. If a therapist becomes concerned about a participant's psychological welfare, contact will be made with the PI who will arrange for psychological evaluation. Although unlikely, if substantial emotional reactions develop that require additional interventions, participants will be withdrawn from the study and referred to public health treatment providers to receive these services. Such identification can be made by research therapists in consultation with the PI.

(6) In cases where danger to self or others is identified, the participant will be withdrawn from the study and clinically appropriate emergency service procedures will be implemented. In cases where a participant is determined to be a danger to self or others, the PI or qualified study staff member will assess the individual's level of risk and work with the participant to develop a safety plan. Study staff will also provide the participant with relevant educational material, contact information for national and local crisis services, and referrals to local counseling services. In cases where a participant is determined to be at imminent risk for harm to self or others, the PI will make referrals for more intensive psychiatric services and arrange for transportation to these facilities when necessary.

(7) Risks associated with OAT as usual may include non-reduction of PTSD symptoms.

Potential Benefits to Participants and Others

Participants may benefit by experiencing reductions in PTSD symptoms during their study participation, including reductions in substance use problems as well as the wide range of medical, psychiatric and psychosocial consequences associated with PTSD. They may also benefit from the financial compensation provided as part of the proposed study. The present study stands to provide scientific benefits by expanding our empirical knowledge related to the mechanisms through which OAT and PET promote reductions in PTSD symptomatology in a highly vulnerable clinical population. Furthermore, by providing PET to individuals with concurrent PTSD and OUD, the proposed research also stands to benefit public health in general by reducing the personal and societal costs associated with PTSD (e.g., medical, psychiatric, and substance use treatment utilization and costs, suicidality, poor physical health and decreased quality of life) in patients with OUD. Overall, the individual participant, the medical and scientific communities, and society in general may benefit by our efforts to determine whether OAT alone may attenuate PTSD symptomatology even in the absence of intensive cognitive-behavioral therapy. As such, the risks to which individuals may be exposed as a function of their research participation are reasonable in relation to the anticipated benefits.

Importance of the Knowledge to be Gained

The proposed project has the potential to produce important new scientific and clinically-relevant information related to the mechanisms through which OAT and PET promote reductions in PTSD symptomatology in a highly vulnerable clinical population. Thus, knowledge gained from this research may significantly improve quality of life, psychiatric distress and psychosocial functioning in this vulnerable population, as well as public health more generally. Consequently, the risk/benefit ratio is favorable. The risks to which individuals are exposed as a consequence of their research participation are generally no more than that associated with continuing opioid treatment as usual. In contrast, the potential and probable benefits to be derived by society in general and by individuals with concurrent PTSD and OUD as a group are considerable. In summary, conducting this research seems well justified.

Therapeutic Alternatives: List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.

☐ **Not Applicable**

Patients are free not to participate in this study or to withdraw from it at any time. Participants who decide not participate in the study will be offered clinically appropriate treatment referrals outside the study.

Data Safety and Monitoring: The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/UVM Medical Center process for review of adverse events should be included in the DSMP.

Patient eligibility and status. All intake data collection will be conducted by a trained bachelor's-level RA or doctoral- or master's-level research therapist using specialized forms and procedures. Intake information will be reviewed by the PI, who will determine participant eligibility. Only trained and IRB-approved research staff will complete informed consent with eligible and willing participants. The status of all active participants will be reviewed at weekly meetings between the PI and research staff.

Rigorous data management/Quality assurance. The majority of study data collection will be conducted using self-report questionnaires. All assessments will be administered by trained research staff. Randomly selected data will be checked by the RAs for completeness and to ensure quality (i.e., no appearance of rote answers, etc.). All subject data will be maintained in secure filing cabinets behind locked doors in order to protect confidential subject information. Safe places will include locked filing cabinets or locked rooms that will be accessible only to study personnel. Participant identity will be disguised using ID numbers keyed to a master list. Moreover, all data that are entered into spreadsheets and databases, in preparation for data analyses, will be entered twice. That is, two separate individuals will enter the data into databases, and a comparison between data entries will be conducted to detect data entry errors. All discrepancies in data entry will be checked against the raw data source, and the correct data entry will be used. All data that are entered into spreadsheets and databases will be password protected and coded by subject ID number and not by subject name. Additionally, all entered data will be backed up on a secure project server at least weekly. The biostatistician and PI will consult regularly to discuss ongoing data management and any problems that arise.

Auditing procedures. Review of any problems related to quality of data collection, transmission or analyses and of any AEs and SAEs that occurred during the past week will occur at weekly research staff meetings.

Define criteria to be used for decision making regarding continuation, modification, or termination of the entire study (not individual participation) (i.e. "stopping rules).

We do not anticipate early trial termination and thus do not have any a priori early stopping criteria.

What will be the frequency of the review? Please note that the frequency of reviews should be commensurate with the risk of the study. At a minimum, a review of the data should be conducted annually at time of continuing review. **Forward copies of the data and safety monitoring reports to the 1) IRB, 2) CRC (if applicable), and/or 3) UVMCC (if applicable).**

☐	Monthly	☒	Annually
☐	Quarterly	☐	Other (e.g. by dosing level, no. of subjects enrolled):
☐	Bi-annually		

Will the sponsor be conducting data monitoring visits for this study?

☐ Yes ☒ No ☐ NA

If yes, how often?

Adverse Event, Unanticipated Problem (UAP), Reportable New Information (RNI): Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/UVM Medical Center process for review of adverse events and UAPs to subjects or others should be included in the DSMP.

AEs and SAEs will be assessed at each clinic visit by a trained RA or research therapist. Any SAE will be brought to the attention of the PI as soon as possible and not longer than 24 hrs. Any SAE, whether or not related to study intervention, will be reported to the IRB's CHRBSS using the UVM Adverse Event Reporting Document within 5 days of the event. The CHRBSS will determine whether additional reporting requirements are needed. Any SAEs will also be summarized in the yearly IRB continuing review, including a review of frequency and severity.

Withdrawal Procedures: Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).

OAT+PET and OAT+PET+ participants who miss four consecutive weeks of treatment no longer be eligible to continue in PET but will be eligible to complete follow-up assessments. Furthermore, continued enrollment in standard buprenorphine or methadone maintenance treatment is necessary for patients to continue in PET. Patients who drop out of buprenorphine or methadone maintenance treatment will no longer be eligible for the study and their participation will be terminated. Patients are free not to participate in this study or to withdraw from it at any time. If they decide not to participate in the study, we will be glad to discuss with them other clinically appropriate treatment referrals for PTSD that may be available in Vermont. If patients decide not to participate in this study or to withdraw from this study, their decision will not prejudice their future medical care.

Sources of Materials: Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.

Research materials will include questionnaires, structured clinical interviews, and urine samples for analyzing recent drug use. All data will be collected for research purposes only. All data collection will be conducted by a trained bachelor's-level RA or doctoral- or masters-level research therapist with special training on all forms and procedures. All information will be reviewed by the PI, who will determine participant eligibility and complete informed consent with eligible and willing participants. Subject data will be maintained in secure filing cabinets behind locked doors in order to protect confidential subject information. Safe places will include locked filing cabinets or locked rooms that will be accessible only to study personnel. Participant identity will be disguised using ID numbers keyed to a master list and data will be entered directly onto computer files that will be password protected. Computer files will carry only participant numbers for case identification. Session recordings of therapy sessions will be transferred to the secure UVM College of Medicine server. Subject data and subject identifiers will only be accessible to approved research staff who will be trained in the importance of confidentiality.

DRUG INFORMATION

Investigators are encouraged to consult the UVM Medical Center Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) [X] **Not applicable**

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source.

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

Storage and stability – for both intact and mixed products.

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Is it FDA approved: (include FDA IND Number)

1. in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.
2. for the route of administration specified? If no, provide justification for route and describe the method to accomplish.
3. for the intended action?

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: Provide rationale for subject selection in terms of the scientific objectives and proposed study design.

Participants will be adults who are maintained on buprenorphine or methadone and have a current diagnosis of PTSD.

Vulnerable Populations: Explain the rationale for involvement of subjects (e.g., cognitively impaired, Non-English speaking, prisoners, students). Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).

X **Not applicable**

Inclusion/Exclusion Criteria: Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.

Participants must be >18 years old and be currently maintained on a stable methadone or buprenorphine dose for ≥1 month prior to the study. They must also endorse >1 traumatic event, meet current DSM-V PTSD criteria (American Psychiatric Association, 2013), and be willing to have therapy sessions audio recorded for the purpose of completing weekly homework assignments and have clear memory for the traumatic event. Individuals with an acute psychotic disorder, bipolar disorder with an active manic episode (but not simply the presence of bipolar disorder), imminent risk for suicide, a medical condition that may interfere with consent or participation (e.g., organic brain syndrome, dementia, head injury, neuropathy, etc.) will be excluded, as well those who demonstrate illiteracy in English.

Inclusion of Minorities and Women: Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.

The study will include minorities and women. We will do all that we can to assure that women and minorities are represented in the research, including using a wide range of recruitment sources to ensure that information regarding this project reaches as diverse of a population as possible (e.g., flyers posted in multiple local neighborhoods, advertisements in the widely-distributed primary local newspaper as well as alternative local papers).

Inclusion of Children: Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study. Provide target accrual for this population. Identify whether children are wards of the state. **If children are excluded** then provide appropriate justification.

Children will not be eligible for this study.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

N/A

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

X **Not applicable**

Will the SONA psychology Pool be utilized? *Include documentation indicating permission to use this recruiting tool* Yes [ ] No [X]

FINANCIAL CONSIDERATIONS

Describe all potential research related expenses to subjects:

There are no expenses to the subject for any aspect of the study.

Compensation for participation: Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.

☐ **Not applicable**

All participants will receive $60 for completing the initial intake assessment and $150 for completing follow-up assessments at 4-, 8-, and 12-weeks post-randomization. In addition, OAT+PET^{+} participants will earn vouchers that have monetary value for attending scheduled PET appointments. Vouchers will be given to participants immediately following completion of each session. No cash will be provided to patients; rather, subjects will be able to submit vouchers to a research assistant in exchange for gift cards that they can use for purchase of retail items and services in the local community. The initial session will be worth $20. Each consecutive attended session will increase the voucher amount by $5 such that the 2nd consecutive session will be worth $25, the 3rd $30 and so on (Table 1).

To support completion of the full 12-week PET protocol, we will incorporate additional strategically-placed bonuses into the reinforcement schedule with the goal of maximizing the percentage of subjects who complete the full 12-session protocol. Bonuses have been a mainstay of our voucher-based interventions with other challenging populations (Alessi et al., 2004; Dunn et al., 2008, 2010; Higgins et al., 1991; Roll et al., 1996, Roll & Higgins, 2000; Sigmon et al., 2016). First, to support consistent (vs. sporadic) attendance, participants will receive a $50 bonus for every two consecutive sessions attended (Table 1). Second, to support completion of the full PET protocol, participants will receive a $100 bonus upon completion of Session 12.

Missed sessions will earn no vouchers and will reset the voucher values for the next attended session back to the initial $20 value. Two consecutive attended PET sessions following a reset will return the voucher value back to the value immediately prior to the missed appointment. In prior studies, we demonstrated that this reset mechanism helps to maintain the momentum of behavioral change (Roll et al., 1996; Roll & Higgins, 2000). Overall, participants who are randomized to the OAT+PET^{+} group and who attend every PE session as scheduled can earn a maximum of $920 for session participation combined across both regular and bonus incentive schedules.

Collaborating Institutions

Will this research be conducted in collaboration with other sites at other locations? Yes ☐ No ☒

If so, complete the following for all collaborating institutions:

Institution Name	Describe Involvement	Is there an IRB? If yes, attach approval or explanation	Are other permissions required? If yes, attach approval or explanation

INFORMED CONSENT

a. Type of Consent

i. Are you obtaining Written Consent? ☒ Yes ☐ No

If yes, will there be more than one consent document? ☒ Yes ☐ No

If yes, how many consent documents and for what populations.

Consistent with our prior IRB-approved studies, we will utilize both a Screening and Study consent. This procedure is effective in limiting the number of individuals who are enrolled into the actual randomized trial who are determined not to be eligible during the initial intake assessment visit.

ii. Are you requesting a Waiver of Informed Consent? [ ] Yes [X] No

This request means that you will not be obtaining verbal nor written consent. **If yes**, complete the form Request for a Waiver of Informed Consent/Authorization/Documentation in UVMClick.

iii. Are you requesting an Alteration of Informed Consent Procedures? [ ] Yes [X] No

This is a request to alter an individual's informed consent or elements of informed consent. Deception in research would be one example when consent would be altered. See Policies and Procedures Manual for more information about when a subject's consent may be altered. **If yes**, complete the smart form Request for a Waiver of Informed Consent/ Authorization/ Documentation in UVMClick.

iv. Are you requesting a Waiver of Documentation of Informed Consent? [ ] Yes [X] No
This request means you are obtaining verbal or implied consent without obtaining the subject's signature on a consent form. See manual for the criteria required to obtain this type of waiver.

If yes, complete the form Request for a Waiver of Informed Consent/Authorization/Documentation in UVMClick.

v. Do you intend to obtain consent from a legally authorized representative? [ ] Yes [X] No
If yes, describe the process.

vi. Are you requesting a short form consent process for non-English speaking subjects? [ ] Yes [X] No
If yes, please describe. Guidance available in the Policies and Procedures Manual.

b. Consent Process

i. Once a prospective subject is identified, who initiates the informed consent discussion and answers questions presented by the subject or the subject's family?

The PI (Dr. Peck) or trained, IRB-approved research staff will initiate the informed consent discussion, answer questions, and explain all study procedures.

ii. Where (in what setting) is the informed consent process initiated? How much time is the subject given to decide?

Informed consent will be initiated in a private office in the UHC building. Participants will be given unlimited time to decide if they wish to participate.

iii. Is the principal investigator present for the initial and subsequent informed consent discussions with the subject?

The PI (Dr. Peck) and/or trained, IRB-approved research staff will be present and the PI will be continuously available to answer questions and explain all study procedures at any time.

iv. What other method of documentation is used to record the informed consent process, in addition to the executed consent form? See an example of documentation of the informed consent **process** under consent templates on our forms page.

N/A

Information Withheld From Subjects: Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.

[X] **Not applicable**

Research Data Management Plan: The Research Data Management and Security Plan form must be completed. The form, along with guidance, can be found in our forms library and must be submitted with your initial application.