REMOTE OBSERVED DOSING TO IMPROVE SUBOXONE COMPLIANCE IN CLINICAL PRACTICE

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Study Product *Remote Observed Medication Dosing (Adherence)*

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Study Summary

Title	REMOTE OBSERVED DOSING TO IMPROVE SUBOXONE COMPLIANCE IN CLINICAL PRACTICE
Short Title	RODISC
IRB Number	
Protocol Number	830028 (JIT)
Methodology	Two-Group RCT examining remote observed dosing. All participants receive Suboxone.
Study Duration	*13 weeks*
Study Center(s)	*University of Pennsylvania*
Objectives	To test the preliminary efficacy of using remote adherence monitoring in buprenorphine (Suboxone®) treatment for OUD
Number of Subjects	*40 subjects*
Main Inclusion and Exclusion Criteria	Opioid use disorder. Men and women over 18 years of age. Subjects must have current DSM 5 diagnosis of opioid use disorder. Subjects must be in good health and psychiatrically stable. They must have no other substance use disorder except tobacco use disorder or cannabis use disorder. Comorbid alcohol use disorder will be accepted if alcohol use disorder is not severe enough to require a medical alcohol detoxification. Subjects must not have received buprenorphine maintenance treatment within the past 3 months and must not have a current diagnosis of chronic pain requiring opioids.
Intervention	2 Group RCT: Group 1 (control): Attention match group that mirrors current clinical care Group 2 (treatment): Remote observed dosing of Suboxone

Statistical Methodology	Buprenorphine adherence will be measured using two-times-weekly creatinine normalized quantitative urine levels for buprenorphine and norbuprenorphine. Rates of illicit opiate use will be compared between the groups using combinations of urine drug screens(UDS) and TLFB self-reports obtained at each visit. At each office visit, subjects will complete standard questionnaires on mood, health behaviors, risky behaviors, and craving, and report all drug and alcohol use that has occurred since their last office visit. Submission of videos will be recorded (date and time) and assessed daily for compliance (i.e., taking the medication as prescribed).
Data and Safety Monitoring Plan	Data will be collected by trained study staff with standardized forms using only a study number and initials to identify the participant. A code that links the participant to the study will be kept confidential by the study team in a password protected secure database. The clinical research coordinator and fellow staff members will be responsible for collecting and checking all clinical data. This includes ensuring that all fields are completed appropriately, that the clinical database is complete and accurate and all corrections are done according to GCPs. Any inconsistencies/deviations will be documented and reviewed by the PI. All data collection is HIPAA compliant. The CSA supports the appropriate privacy of all clinical and research data collected as part of any study. We follow Penn's policy in the use and disclosure of protected health information in research in a manner that respects the patient's privacy in accordance with the "Privacy Rule" promulgated under the Health Insurance Portability and Accountability Act (HIPAA) and other applicable laws. All staff receive appropriate HIPAA training. All participants sign a combined Informed Consent and HIPAA-authorization form, receive a copy of this form, and receive a notice of Penn's privacy practice. HIPAA signed forms are retained in locked file cabinets with participants' source documents. Data analysis will be conducted by the Center statistician, Dr. Kevin G. Lynch, with assistance from the PI.

Background and Study Rationale

This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including the following regulations as they apply 45 CFR 46, 21 CFR Parts 50, 54, 56 All episodes of noncompliance will be documented.

1 Introduction

Opioid Use Disorder is a major public health problem, with high relapse rates and a strong association with negative health consequences. Suboxone (buprenorphine + naloxone) is an efficacious medication that is typically administered in an office-based setting; however, compliance rates are near 50% and diversion is a significant problem. This project proposes to develop and test the use of remote compliance monitoring of Suboxone to improve medication adherence and treatment outcomes.

1.1 Background and Relevant Literature

Opioid use disorder (OUD) is a significant public health problem. About 2 million Americans meet criteria for opioid use disorder involving prescription pain relievers and an additional 591,000 Americans meet criteria for a heroin use disorder (Center for Behavioral Health Statistics and Quality 2016). The rise in prescription opioid use in the US has resulted in a dramatic increase in heroin use, as prescription opioid users switch to heroin when their access to prescription opioids becomes limited (Peavy et al. 2012; Cicero, Ellis, and Surratt 2012; Cicero et al. 2014, 50). Opioids (including prescription opioids and heroin) killed more than 33,000 people in 2015, more than any year on record (CDC 2016). Nearly half of all opioid overdose deaths involve a prescription opioid.(Rudd et al. 2016) In addition to opioid overdose deaths, opioid use is associated with a number of medical problems, especially when used intravenously. Needle sharing and sexual practices place heroin users at high risk for human immunodeficiency virus infection and hepatitis c as well as other infectious diseases (Chen et al. 2015; Richard S. Garfein et al. 1996). Heroin use is associated with high utilization of emergency services (McGeary and French 2000).

Effective treatments for OUD are available but underutilized. From 2004-2013 only 21% of patients with an OUD received any treatment (Saloner and Karthikeyan 2015). This is despite the fact that there are currently 3 efficacious medications available to treat this disorder: methadone, naltrexone (Vivitrol®), and buprenorphine (Suboxone®). Methadone maintenance treatment (MMT) has been available the longest of the three and has been shown to a very efficacious treatment (Ball and Ross 1991) As an opiate agonist, methadone is able to alleviate opiate withdrawal symptoms, reduce opiate craving and, at higher doses, reduce the ability of illicit opiates to cause intoxication (Ward et al. 2009). However, there are a several aspects of MMT that are less attractive. For example, MMT occurs exclusively in the context of an Opiate Treatment Program (OTP), where dosing occurs daily at set times. Such programs require a large time investment from participants, as they must attend the clinic daily within set dosing hours. Another common problem with MMT relates to the associated side effects that can diminish patient compliance including weight gain and cognitive impairment (Curran et al. 2001; Mendelson et al. 1996; Nolan and Scagnelli 2007; Pirastu et al. 2006; Prosser et al. 2006). Lastly, federal regulations limit access to MMT making it logistically impractical for many patients (Johnson et al. 2000; Substance Abuse and Mental Health Administration 2015).

Buprenorphine, a partial agonist that exerts significant actions at the mu opioid receptor, has also been shown to be effective for the treatment of OUD (Johnson et al. 1995; Liebson et al. 1988; Johnson, Jaffe, and Fudala 1992). It offers agonist substitution that alleviates opiate withdrawal and reduces opiate cravings—thereby reducing opiate use (Gowing, Ali, and White 2009; Greenwald et al. 2007; W Ling and Wesson 2003). Buprenorphine has a higher affinity for the mu opiate receptor than all available full opiate agonists offering antagonist blockade that prevents patients from experiencing a high from illicit opiates (Greenwald et al. 2007; W. K. Bickel et al. 1988; Warren K. Bickel and Amass 1995). Because it is a partial agonist and not prone to overdose, it is considered to be safe enough to dispense out of a clinician's office as opposed to an OTP (Center for Substance Abuse Treatment 2004). The availability of buprenorphine treatment outside of an OTP has significantly expanded the availability of effective treatment for OUD and is associated with reducing disparities related to treatment access (Bonhomme et al. 2012; Kumari et al. 2016; Stanton 2006).

While initial studies reported little evidence of buprenorphine diversion (Stanton 2006), more recent studies have indicated buprenorphine is prone to diversion and poor adherence that can significantly diminish its safety and efficacy (Kumari et al. 2016; Tkacz et al. 2012). In these US clinical trials, adequate adherence to buprenorphine has been shown to occur in fewer than

50% of subjects who are prescribed the medication. In a trial involving 50 African American subjects with opioid use disorder participating in office based buprenorphine treatment, it was found that only 48% of the subjects were adherent to the medication as defined as having 80% or more of their visits associated with a positive UDS for buprenorphine (Kumari et al. 2016). In another trial involving 703 subjects with opioid use disorder only 41% of the subjects took buprenorphine 80% of the days it was prescribed (Tkacz et al. 2012). Finally in an examination of medical and pharmacy claims data over a year, only 32% of patients participating in office based buprenorphine treatment took buprenorphine on 80% or more days (Tkacz et al. 2014).

Poor adherence to buprenorphine treatment has been associated with a number of negative outcomes including poor treatment retention of patients participating in office based treatment (Matson et al. 2014). Compared to patients with good adherence, poorly adherent patients in office based buprenorphine treatment were ten times more likely to relapse to opioid use (Tkacz et al. 2012).

The growth in cell phone use creates an unprecedented opportunity to improve medication adherence (Krishna, Boren, and Balas 2009; Lester et al. 2010; Horvath et al. 2012; Granholm et al. 2011; Pop-Eleches et al. 2011). The use of Remote Observed Dosing (ROD) allows us to reach underserved, at-risk populations (Hoffman et al. 2010). In a study with cannabis dependent patients using ROD that was directly observed (DOT) over Skype for three weeks, every morning 20 participants were video called by staff who observed consumption of the study medication. Adherence was confirmed 96% of the time and was also assessed with weekly face-to-face visits, pill counts, and plasma drug levels (DeWorsop et al. 2016).

The ROD protocol we are proposing in this study is very similar to protocols used in studies with pediatric patients receiving iron chelation therapy and adult patients receiving anti-tuberculosis treatment that allows the user to video record dosing (Leonard et al. 2017; R. S. Garfein et al. 2015). Leonard and colleagues conducted a pilot study to examine the feasibility of using a smartphone app to improve compliance to iron chelation. Self-report adherence rates to chelation therapy are around 71%-76% and are as low as 43% based on pharmacy refill rates (Leonard et al. 2017). The protocol these researchers used involved: 1) patient recording daily videos of at-home medication administration and 2) provider feedback through cell phone messaging. The mobile ROD protocol was feasibly implemented in a clinic setting and reported high levels of compliance, disease knowledge retention, and acceptance among patients. In another pilot study with adult patients in Mexico and the US who were receiving anti-tuberculosis treatment, ROD was used to monitor compliance (R. S. Garfein et al. 2015). This protocol involved patients using a smartphone to record videos of themselves taking the medication and uploading the video to a secure website to document compliance. The research staff sent text message reminders—one before the doses were due and one after missed doses. Garfein and colleagues reported that adherence was similar in Mexico (96%) as in the US (93%) and ROD was preferred over observed in office dosing. In addition, ROD patients felt the technique was more confidential; never or rarely experienced problems recording the videos and 100% would recommend ROD to others (R. S. Garfein et al. 2015).

To address this need we recently completed a feasibility study of remote observed Suboxone® dosing to determine whether we could enroll and retain participants in such a study (**UPENN Protocol # 816651**). The observed dosing protocol we used was similar to the ones used to examine the feasibility of directly observed therapy (DOT) (DeMaio et al. 2001; DeWorsop et al. 2016). In our feasibility study, 10 participants were enrolled. Each participant received 12 weeks of Suboxone® during the study. Participants attended weekly in-office sessions where they took an observed dose of Suboxone® and then took the remaining weekday doses (M-F) while on a

video Skype call with study staff. Data from that study reveal low rates of continued opioid use while on Suboxone® and high rates of Skype-observed doses. All urines tested during the study were buprenorphine positive, demonstrating excellent adherence with the treatment. In addition, self-reports of opiate use corresponded to urine drug screen results, and only one participant continued to test positive for opioids intermittently during the study. ***Participants successfully completed 100% of required in-office visits, and 90% of scheduled Skype calls. Perhaps more important, participants did not find the daily Skype calls to be burdensome.***

However, the pilot study did not have a control group and because the clinic was only open Monday-Friday, we did not observe dosing on the weekends. While this is true for many physician offices and community based treatment providers, it is problematic because weekends are often a high risk time for drug users. It is important to observe dosing 7 days a week in order to ensure optimum adherence and avoid diversion. It is equally important to determine if ROD improves buprenorphine adherence compared to an attention-matched control group.

Dr. Curtis has developed a protocol that uses a ***smartphone to video record buprenorphine dosing and automatically sends this recording through HIPAA compliant means to clinical staff who can then review it at a convenient time and location***. Her protocol also uses SMS text messaging to communicate with patients. To address the feasibility of patients with an OUD using this technology, Dr. Curtis conducted a pilot study with 71 patients in OUD treatment locally regarding the feasibility and usability of such a technology. The preliminary data indicated:

- While 95% of patients had a cell phone, the majority of them (76%) had “pay as you go” plans with limited data capabilities. In addition, 71% reported changing their cell phone regularly.
- 87% reported sending and receiving SMS text messages daily, 60% used the video option on their phones to send videos, 54% watched videos online, and 53% used an “instant message app”.
- 78% reported they would take part in a text messaging program to help prevent relapse and 75% reported they would be receptive to a cell-phone based OUD intervention.

These findings suggest using the proposed platform to monitor buprenorphine dosing is both feasible and would be welcomed by patients undergoing opioid treatment.

2 Study Objectives

ROD has the potential to 1) improve adherence, 2) reduce the risk of diversion, and 3) increase access to buprenorphine treatment.

2.1 Primary Objective

- The overarching aim of this behavioral intervention is to test the preliminary efficacy of using remote adherence monitoring in buprenorphine (Suboxone®) treatment for OUD. For the ROD group, we will calculate the within-patient proportion of study days on which video captured adherence, as per protocol. We will use these data to compare observed adherence rates in this group to rates reported in prior studies and to the attention control group.

2.2 Secondary Objectives (if applicable)

- Rates of illicit opiate use will be compared between the groups using combinations of urine drug screens (UDS) and TLFB self-reports obtained at each visit.

3 Investigational Plan

Forty patients with OUD, who are not currently prescribed buprenorphine, will be recruited through the University of Pennsylvania's Center for the Studies of Addiction (CSA), an outpatient substance abuse treatment facility. Potential participants will be screened for physical and psychological appropriateness for inclusion in the study using the CSA standard intake procedures. This includes a psychosocial diagnostic evaluation, a medical exam, urine and blood tests, and an EKG (see Measures for full description of screening assessments). Participants who are appropriate for the trial will be inducted onto Suboxone® using standard office based induction as described in the ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use (Kampman and Jarvis 2015).

All patients will receive buprenorphine (Suboxone®; up to 24 mg daily) and will be randomly assigned to one of two groups. The experimental group (n=20) will receive daily remote observed dosing (ROD) via a secured video platform that records dosing using study-provided smartphones (approximately 5 minutes each session). ROD videos will be monitored daily for compliance. The attention control group (AC, n=20) dosing will not be observed. All subjects will attend 2 weekly study visits (3 study visits during the induction phase in Week 2). Study visits starting in Week 3, after the Induction phase, will consist of counseling in the form of weekly Medication Management (MM); buprenorphine distribution with medication management;and a urine screen. Study visit 4 will consist of a urine screen and phone management task (downloading study related videos) for those randomized to the Remote Observed Dosing Group.

3.1 General Design

Participants will be randomized into one of two study groups. Both groups will receive standard buprenorphine maintenance treatment. Participants will attend study visits twice weekly for 12 weeks and a close-out visit in week 13. One group will be assigned to Remote Observed Dosing (ROD) and will have all of their Suboxone® doses remotely observed using procedures described below. The attention control (AC) group will not have their dosing observed but will send a text message confirming they have taken their study medication to the study team daily matching contact with the study team.

3.2 Allocation to Interventional Group

Participants will be randomized into one of two study groups based on proportion of use of prescription opiates and heroin, gender, and prior Suboxone® treatment.

3.3 Study Measures

We will administer several standard assessments during the course of the study (shown below). At each office visit, subjects will complete standard questionnaires on mood, health behaviors, risky behaviors, and craving, and report all drug and alcohol use that has occurred since their last office visit:

Addiction Severity Index (McLellan et al. 1992). The ASI is a 45-minute interview which yields composite scores, ranging from 0 to 1, of problem severity over the past 30 days in 7 areas: medical, employment, drug use, alcohol use, legal, family/social, and psychiatric. Studies

have shown moderate to excellent interrater and test-retest reliability. The ASI was used to characterize baseline demographic and drug use variables for each subject. The composite scores will be used as secondary outcome measures. The ASI will be administered at baseline week 5, week 9 and at the end of study.

Adverse events. Adverse events are queried and documented at each visit and recorded in the CRF.

Clinical Global Impression Scale (Guy 1976). The CGI is a brief clinical rating of severity of illness (at time of interview) and global improvement (from admission) using a 7-point Likert scale. The CGI is done by an observer and the subject to assess clinical progress, global improvement and to assess the severity of the subject's illness at regular contacts over the course of the study. The CGI is done once during baseline by the observer and participant, at week 9 and at the end of the study.

Columbia Suicide Severity Rating Scale (Chappell et al. 2012). This is a 5-item scale with additional questions that may be asked based on the participant's responses to the core items. This questionnaire will assess both lifetime and recent suicidal ideation and behavior, including both passive and active thoughts/plans. It is extensively used across clinical practices, hospitals, research institutions and schools to address potential thoughts of suicide expressed by the client. This questionnaire will be administered at baseline, and once a week through the trial. The CSSRS is a form that has been included in all pharmacotherapy trials as a safety measure.(U.S. Department of Health and Human Services n.d.) *Note: This data will not be analyzed but will be included to help ensure the safety of the participants.*

Concomitant medications will be queried and recorded at each participant visit.

Hamilton Depression Rating Scale (Hamilton 1967). The Ham-D is a 20-minute, 24-item interview that measures the severity of depression and changes in depressive symptoms. The Ham-D is administered at baseline, week 9 and at the end of the study.

Locator Form. The locator form asks about addresses and phone numbers where the participant might be contacted, as well as names and addresses of other individuals who might know the participant's whereabouts. The information is used to locate participants who do not respond to a calls and weekly text messages.

Obsessive Compulsive Drug Use Scale (Franken, Hendriks, and van den Brink 2002). Adapted from the Obsessive Compulsive Drinking Scale(Anton, Moak, and Latham 1995) (OCDS), measures craving for heroin on a 12-item likert scale. Our version replaces heroin with opioids more generally. This will be administered at baseline and weekly throughout the trial.

Risk Assessment Battery (Metzger et al. 1993). The RAB is a 38 item self-report questionnaire which assesses high risk behavior for exposure to the HIV virus. The RAB yields drug, sex and total risk scores and will be administered at baseline and at the end of the trial.

Systems Usability Scale (Grindrod, Li, and Gates 2014). The SUS is a 10 item self-reported validated measure of learnability and user satisfaction that we will use to evaluate the remote medication monitoring protocol. It uses a 5-point Likert scale to provide a quantitative measure of the usability of the ROD protocol and provides an overall score between 0 and 100. This scale will be administered at the end of the study.

Timeline Follow Back Interview (Sobell and Sobell 1995). The TLFB is a 15-30 minute, semi-structured interview adapted by our laboratory to collect information about daily drug, alcohol, and nicotine use. The TLFB will be given by trained research staff at baseline to cover 3 months immediately preceding treatment entry and will be updated at each research visit to determine any time spent in a controlled environment and cocaine, nicotine, and other drug use during the

period since the last visit. The composite of these assessments are additive over the course of the study so that we will have continuous data.

Video Compliance. Submission of videos will be recorded (date and time) and assessed daily for compliance (i.e., taking the medication as prescribed). In addition, videos will be saved off the micro-SD cards at each office visit.

Laboratory Measurements (in alphabetical order)

Blood chemistry, Complete Blood Count (CBC), and Urinalysis are obtained to assess for adverse events. Enzyme levels will be obtained once at baseline and end of the study.

Pregnancy Testing. Urine pregnancy tests will be obtained from all women at baseline, week 5, week 9, and end of study.

Urine Drug Screen and Urine Buprenorphine and Norbuprenorphine Screen. Quantitative urine buprenorphine and norbuprenorphine levels (using gas chromatography) with urine creatinine used as a control for urinary concentration will be assessed twice weekly throughout the trial. Urinary buprenorphine levels have been used extensively to establish buprenorphine adherence (Fox, Tetlow, and Allen 2006; Vincent et al. 1999). Quantitative levels of methadone have been used successfully to establish methadone compliance in a methadone maintenance program (Preston et al. 2003). Our toxicology consultant will assist us in interpreting urine creatinine controlled quantitative buprenorphine levels to establish medication adherence. Data from this trial will be used in optimizing the use of quantitative urine buprenorphine and norbuprenorphine levels in the subsequent efficacy trial. Qualitative (emit) urine toxicology for other drugs (benzodiazepines, barbiturates, opiates, marijuana, methadone, and amphetamine) is done at baseline and weekly throughout the trial.

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

For the ROD group, we will calculate the within-patient proportion of study days on which video captured adherence, as per protocol.

Secondary Study Endpoints

We will use a combination of self-report and (nor)buprenorphine levels to classify patents in the AC group as adherent or non-adherent for each study day to compare their rates of adherence to the (video-verified) rates in the ROD group. These comparisons will give a direct estimate of the improvement in adherence likely to be observed between the proposed method and standard methods.

Rates of illicit opiate use will be compared between the groups using combinations of urine drug screens (UDS) and TLFB self-reports obtained at each visit.

4 Study Population and Duration of Participation

This study will involve 40 individuals with Opioid Use Disorder (OUD) who will receive three months (12 weeks) of buprenorphine (Suboxone®) (standard dose will be up to 24 mgs/day, adjusted as necessary on an individual basis). Suboxone® is a form of buprenorphine with naloxone added to reduce the potential for buprenorphine abuse.

4.1 Total Number of Subjects and Sites

Recruitment will end when approximately 40 subjects are enrolled at the University of Pennsylvania. It is estimate that we will need to approach approximately 160 participants. Of these potential participants, we anticipate 80 will undergo screening to recruit 40 participants.

4.2 Inclusion Criteria

Inclusion Criteria (prior to induction):

- Voluntarily provide written informed consent prior to the conduct of any study-related procedure
- Male, female, or transgender
- 18 – 45 years of age
- Meet DSM 5 criteria for opioid use disorder moderate to severe
- Women of childbearing potential must use a reliable means of contraception

4.3 Exclusion Criteria

Exclusion Criteria (prior to induction):

- Current diagnosis of AIDS
- Participation in buprenorphine maintenance treatment within the past 3 months
- Presence of AST and/or ALT equal to or > 3X upper limit of normal
- Total bilirubin and/or creatinine equal to or > 1.5X upper limit of normal
- Current diagnosis of chronic pain requiring opioids
- Pregnant or lactating women
- Previous hypersensitivity or allergy to buprenorphine
- Current use of agents metabolized through CYP 3A4 such as azole antifungals (e.g. ketoconazole), macrolide antibiotics (e.g. erythromycin), and protease inhibitors (e.g. ritonavir, indinavir, saquinavir)
- Meet DSM - 5 criteria for current use disorder for any psychoactive substances other than opioids, marijuana, cocaine or nicotine (e.g. alcohol, sedatives)
- Current use of benzodiazepines
- Significant medical or psychiatric symptoms or dementia which in the opinion of the investigators would preclude compliance with the protocol, adequate cooperation in the study, or obtaining informed consent
- Concurrent medical conditions (such as severe respiratory insufficiency) that may prevent the patient from safely participating in the study; and/or any pending legal action that could prohibit participation and/or compliance in study procedures

4.4 Subject Recruitment

The project will be conducted at the Center for the Study of Addiction at the University of Pennsylvania. The CSA has a community-based (non-veteran) outpatient addiction treatment-research program that is part of the University of Pennsylvania (CSA, Dr. Henry Kranzler, Director). The CSA offers outpatient addiction treatment for individuals from the greater Philadelphia area who are seeking treatment for their addiction and who qualify for one of our grant-sponsored treatment studies on alcohol, cocaine, dual cocaine-alcohol, opioid or nicotine dependence. Patient recruitment is ongoing and accomplished through community,

professional, and self-referrals from the greater metropolitan Philadelphia area. We will also recruit through placing flyers at Penn Medicine and Penn Medicine outpatient clinics. All patients enrolled at the CSA receive medical monitoring and high-quality treatment-at no cost. Female-focused recruitment strategies including direct appeals to female-medical specialties such as OB-GYN offices, has increased our ability to recruit women with OUD. In addition to Dr. Kampman's office based-buprenorphine practice, The University of Pennsylvania Health System supports office based buprenorphine treatment at the Charles O'Brien Center for Addiction Treatment and at nearby Penn Presbyterian Medical Center.

4.5 Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study

5 Study Procedures

See Measures for Description of Study Assessments
See Table 1 for Assessment Schedule

Regular evaluation visits. Subjects will have appointments with study staff two times weekly throughout the 12-week medication phase of the trial. A telephone reminder call and/or text message will be used to enhance attendance. Urine drug screens (UDS) for buprenorphine and norbuprenorphine will be obtained at each visit, along with concomitant medications, adverse events, and time line follow back (TLFB). The Columbia Suicide Severity Rating Scale (CSSRS) will be obtained at baseline and weekly. Other measures completed routinely but not weekly are listed in Table 1. A description and schedule of assessments is provided in the study measures section of the protocol. Each patient will meet weekly with the clinician who will assess clinical status, dispense study medications and monitor adverse events and concomitant medications.

After the completion of Week 13, or at the termination for patients who discontinue from the trial prematurely, we will conduct the following procedures: physical exam, electrocardiogram, monitor adverse events and concomitant medications, obtain blood samples for chemistry, CBC, obtain a urinalysis (and a pregnancy test for women), and complete other measures (See Table 1). The Systems Usability Scale will be conducted at the end of study visit. Safety follow up visit will be conducted one month after the completion of the medication phase.

Psychosocial Treatment. Subjects will participate in weekly Medication Management (MM), an intervention developed as part of NIAAA's Project COMBINE study, that provides advice and support from medical practitioners concomitantly with dispensing medications, safety checking and compliance (Pettinati et al., 2004). The main goal of MM is to increase the likelihood that patients will reduce their opioid use. The initial MM session is an hour; subsequent sessions are 15-30 minutes.

5.1 Screening

The University of Pennsylvania Center for the Study of Addictions, CSA, is home of the Treatment Research Center (TRC) (Dr. Henry Kranzler, Director) at 3535 Market Street, Philadelphia, PA 19104 will be the primary recruitment site. Subjects have been steadily recruited from the community for addiction treatment-research studies at the TRC. Subject

recruitment is ongoing and accomplished through community, professional, and self-referrals from the greater metropolitan Philadelphia area. Most of the TRC callers seeking treatment who are approved for intake (via center IRB-approved phone pre-screen) come in to consent to the General Screening Consent (Protocol #701074) for an intake appointment to review general medical and psychosocial criteria prior to consenting to a specific study. All participants enrolled at the TRC receive medical monitoring and high-quality treatment-at no cost. The TRC recruits through ads in local papers, radio ads, flyers at approved locations in the area, information at health fairs, online social media platforms, and other recruitment methods we have had success with in prior trials. Uniform screening procedures will be used. A standardized telephone interview is followed by an appointment for those who meet general study criteria. Participants who are ineligible for our studies, or participants who cannot be accommodated in one of our studies are instead referred to the outpatient clinic of nearby Presbyterian Hospital, which is a major part of the University of Pennsylvania Health System or to their insurance provider for treatment options.

After signing a screening consent, persons will be screened to verify that they meet all inclusion/exclusion criteria. A medical history, physical and laboratory examination will be conducted. The research clinician will offer eligible patients participation in the study. The study staff member obtaining informed consent will ensure that the patient understands the risks/potential benefits of the study prior to signing the consent form. Individuals will not be enrolled in the study until they successfully pass a “quiz” about the content of the informed consent.

Contacting Subjects: Subjects are informed during the informed consent process that contact information provided to the research staff may be used at a later date to contact them by phone or mail. Reasons for contact include but are not limited to: missed appointments, appointment reminders, requests for follow-up visits, notifications of medical testing results, or other clinical reasons. Subjects are instructed to notify study staff if they no longer wish to be contacted. Procedure for contacting subjects include but are not limited to: three attempts to reach the subject by phone by study staff, the Emergency Contact provided by the subject will be called by a clinical staff member, and an IRB approved letter asking the subject to come to the center and/or call the study team.

5.2 Study Intervention

5.2.1 Visit 1

- Medical Exam and EKG, CBC and blood chemistry Urinalysis (UA), Risk Assessment Battery
- Pregnancy Test (women), Addiction Severity Index (ASI)
- Urine Toxicology and Urine Buprenorphine and Norbuprenorphine Screen, Timeline Follow back (TLFB)
- Clinical Global Impression Scale (CGI), Hamilton Depression Rating Scale (HAM-D)
- Columbia Suicide Severity Rating Scale (C-SSRS), Obsessive Compulsive Drug Use Scale (OCDUS)
- Concomitant medications

5.2.2 Visits 2-4 (Suboxone Induction)

Participants who are appropriate for the trial will be inducted onto Suboxone® using standard office based induction as described in the ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use (Kampman, Kyle and Jarvis, Margaret 2015).

- Concomitant medications
- Medical Management, Pill Distribution
- Adverse Events
- Visit 4: Randomization & Distribution of Smartphone w/ intervention training

5.2.3 Visits 5-28

Patients will be seen twice weekly. For each in-office visit, patients will provide a urine sample that will be tested for drugs of abuse and for quantitative buprenorphine and norbuprenorphine levels. At each office visit, patients will also complete questionnaires about craving and depression. They will be asked about other medications they are using, about their drug and alcohol use since their last visit, and about any side effects they may be experiencing. Dosage adjustments will be made as needed at the discretion of their clinician. Subjects will also participate in weekly, manualized Medication Management. After induction, all patients will receive open-label Suboxone® for 12 weeks. Patients in both groups will receive a weeks' worth of Suboxone® at each medication management visit. After the 12 weeks of Suboxone®, subjects will be referred to on-going treatment options in the community.

5.2.4 End of Study Visit

After the completion of Week 14, or at the termination for patients who discontinue from the trial prematurely, we will conduct the following procedures: physical exam, vital signs and weight, electrocardiogram, monitor adverse events and concomitant medications, obtain blood samples for CBC, blood chemistry, obtain a urinalysis (and a pregnancy test for women), Urine drug screen and urine buprenorphine and norbuprenorphine levels, CGI, Timeline folllowback, and system usability screen (SUS). At the completion of the trial patients will be referred to MAT in the community, or if they decline they will receive a tapering dose of suboxone for one week.

5.3 Unscheduled Visits

Unscheduled visits will be accommodated based on staff availability.

5.4 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, AEs, or due to worsening of opioid use disorder. The Investigator may also withdraw subjects who violate the study plan, to protect the subject for reasons related to safety or for administrative reasons. It will be documented whether or not each subject completes the study. Subjects who withdraw early will have one final visit to collect final evaluations and assess adverse events.

5.4.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who withdraw consent to participate in the study will be seen for one final study visit. During this visit, they will be asked for permission to have the study team look into their survival status via publically available means.

5.5 Early Termination Visits

After the completion of Week 14, or at the termination for patients who discontinue from the trial prematurely, we will conduct the following procedures: physical exam, vital signs and weight, electrocardiogram, monitor adverse events and concomitant medications, obtain blood samples for CBC, blood chemistry, obtain a urinalysis (and a pregnancy test for women), Urine drug screen and urine buprenorphine and norbuprenorphine levels, CGI, Timeline folllowback, and system usability screen (SUS). At the completion of the trial patients will be referred to MAT in the community, or if they decline they will receive a tapering dose of Suboxone for one week.

5.6 Efficacy Evaluations (only if applicable)

For the ROD group, we will calculate the within-patient proportion of study days on which video captured adherence, as per protocol.

We will use a combination of self-report and (nor)buprenorphine levels to classify patents in the AC group as adherent or non-adherent for each study day to compare their rates of adherence to the (video-verified) rates in the ROD group. These comparisons will give a direct estimate of the improvement in adherence likely to be observed between the proposed method and standard methods.

Rates of illicit opiate use will be compared between the groups using combinations of urine drug screens (UDS) and TLFB self-reports obtained at each visit.

5.7 Pharmacokinetic Evaluation

Patients will provide a urine sample at each office visit that will test for quantitative buprenorphine and norbuprenorphine levels.

5.8 Genetic Testing

Not applicable

5.9 Safety Evaluation (only if applicable)

Adverse events will be monitored at each visit. Concomitant medications will be queried and recorded at each visit. Safety laboratory measures include, complete blood count (CBC), blood chemistries, urinalysis, urine pregnancy tests (for women), EKG.

6 Statistical Plan

6.1 Sample Size and Power Determination

One target of the study is to estimate the proportion of participants in the ROD group who adhere with their medication schedule for, say, 80% or more of their treatment days. If 90% of the 20 participants adhere, then our data will yield a 95% confidence interval of (68%, 98%) for the proportion adhering; if 95% are adherent, then our confidence interval will be (72%, 99%).

For the longitudinal comparisons of quantitative (nor)buprenorphine levels, transformed so that a linear model is appropriate, we use the methods of Hedeker and collegues. For an alpha level of 0.05, and assuming a within subject correlation of 0.4, and dropout of 10%, the sample size provides 80% power for a standardized linear group by time effect of d=0.65. Thus, the study is powered for medium to large effects in quantitative buprenorphine levels.

6.2 Statistical Methods

For the ROD group, we will calculate the within-patient proportion of study days on which video captured adherence, as per protocol. We will use these data to compare observed adherence rates in this group to rates reported in prior studies.[36,38,39] The primary comparison between the groups will use the creatinine normalized weekly quantitative urine levels for buprenorphine and norbuprenorphine. Exploratory analyses include the following: We will use a combination of self-report and (nor)buprenorphine levels to classify patents in the AC group as adherent or non-adherent for each study day, and use mixed effects logistic regression models to compare their rates of adherence to the (video-verified) rates in the ROD group. Rates of illicit opiate use will be compared between the groups using combinations of urine drug screens(UDS) and TLFB self-reports obtained at each visit. The ASI, CGI, and HAM-D scales are obtained monthly. To assess usability and acceptability of the ROD protocol and text messaging application, Dr. Curtis will conduct semi-structured interviews and analyze data from the Systems UsabilityScale (SUS) at the final office visit.

6.3 Control of Bias and Confounding (if applicable, typically observational study or if randomization is not taking place)

Subjects will be randomly assigned to the two groups

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

6.3.2 Analysis of Primary Outcome of Interest

The primary comparison between the groups will use the creatinine normalized weekly quantitative urine levels for buprenorphine and norbuprenorphine. For each response, we anticipate that a response transformation, such as the log transform, will yield responses appropriate for group comparisons based on linear mixed effects models, but we will consider generalized linear mixed effects models if necessary.88 Comparisons of BIC statistics across different covariance structures will be used to select the best model for within subject correlations – typically a model with random intercept and ar(1) residual correlations provides a good fit. The main explanatory variable will be a binary indicator for group (ROD vs AC). Time will be regarded as a continuous scale, and linear, quadratic or spline trends will be used as necessary, with group by time interactions examined for significance. Our primary analyses will examine the two sets of responses (buprenorphine and norbuprenorphine) separately, but we will also consider bivariate mixed effects models with cross-correlation structure to assess strength of dependence and concordance between the two sets of measures. These analyses will be performed using PROC GENMOD in SAS.

6.3.3 Pharmacokinetic Analysis (only if applicable)

Not Applicable

6.3.4 Interim Analysis (only if applicable)

Efficacy analyses will be conducted at the trial end. There are no plans for interim analyses.

7 Safety and Adverse Events

7.1 Definitions

7.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2 Serious Adverse Event

Study definition of serious adverse event. Potential definition that may be used if applicable:

Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- required intervention to prevent permanent impairment or damage
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

7.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported.

7.3 Relationship of AE to Study

The PI or medical director will review each adverse event and determine if it is definitely related, probably related, possibly related, unlikely, or unrelated to study procedures.

7.4 Reporting of Adverse Events and Unanticipated Problems

The Investigator will promptly notify the Penn IRB of all on-site unanticipated, Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the HS-ERA and in accordance with the Penn IRB timeline of 10 working days. The Investigator will notify the study sponsor and the DSMB as outlined in the sections below.

7.4.1 Follow-up Report

If an AE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator will ensure that all SAEs are followed until either resolved or stable.

When additional clinical information becomes available, a follow-up and/or final SAE report will be filed with the UPENN IRB, NIDA, the DSMB, and the FDA

7.4.2 Investigator reporting: notifying the study sponsor (if applicable)

A serious adverse event will be reported to the study sponsor within 24 hours of the event. All SAEs will be submitted to the NIDA Medical Monitor within 24 hours. The NIDA Program Official (PO) and the NIDA Project Scientist (PS) will be notified within 3 business days of learning of the SAE using the online SAETRS system. In addition, all written documentation for all SAEs and unexpected AEs will be provided to the NIDA Medical Monitor within three (3) days of reporting the event. The investigator will keep a copy of an SAE report form on file at the study site.

7.4.3 Data and Safety Monitoring Plan

The data and safety monitoring plan is comprised of the following:

- Principal Investigator- Brenda Curtis
- Study Medical Director- Kyle Kampman
- NIDA Medical Monitor
- Sponsor- NIDA
- Penn Independent Monitor
- Data Safety and Monitoring Board (DSMB)

Please see the attached Data and Safety Monitoring Plan for further details.

7.4.3.1 Data Safety Monitoring Board (if applicable)

A safety monitoring board has been established at the Center for the Studies of Addiction with the following purpose (according to NIDA guidelines): to assure that the safety of study subjects is protected while the scientific goals of the ongoing studies are being met. Specifically, the DSMB is charged with monitoring the safety of participants and the quality of the data, as well as the appropriate termination of studies either when significant benefits or risks have been uncovered or when it appears that a clinical trial cannot be concluded successfully. The board is chaired by James McKay Ph.D. a faculty member within the Department of Psychiatry at the University of Pennsylvania. Other members of the board include Kevin Lynch, Ph.D. (senior statistician), David Metzger, Ph.D., Deborah Dunbar, MSN, CRNP and Cynthia Clark Ph.D. CRNP who are faculty members or staff of the University of Pennsylvania School of Medicine.

When the current study is reviewed, Dr. Curtis will open the meeting with a report on the trial status, followed by a closed session under the direction of Daniel Langleben, MD who will stand in for Dr. McKay who is in conflict for this project. In addition, Ian Barnett, PhD (biostatistician) will stand in for Kevin Lynch, PhD who is in conflict for this project. Issues related to recruitment, subject safety and efficacy, whether the primary study question is being answered, conflict of interest, confidentiality, and ongoing study review (including AEs, SAEs, and regulatory issues) are assessed. Following each DSMB meeting, The designated member standing in for the Chair will make recommendations to Dr. Curtis, and a final report (edited by all Board members not in conflict with this project) will be prepared and submitted to NIDA, the Penn IRB, and (if required) the FDA according to each bodies reporting requirements.

The board meets every six months (unless more frequent meeting are deemed necessary). Safety data will be reviewed by the Data Safety Monitoring Board every six months. A Data Safety Monitoring Board report will be issued to the NIDA project officer with the annual progress report.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

The study has a Confidentiality Certificate.

8.2 Data Collection and Management

Data will be collected by trained study staff with standardized forms using only a study number and initials to identify the participant. A code that links the participant to the study will be kept confidential by the study team in a password protected secure database. The clinical research coordinator and fellow staff members will be responsible for collecting and checking all clinical data. This includes ensuring that all fields are completed appropriately, that the clinical database is complete and accurate and all corrections are done according to GCPs. Any inconsistencies/deviations will be documented and reviewed by the PI.

All data collection is HIPAA compliant. The CSA supports the appropriate privacy of all clinical and research data collected as part of any study. We follow Penn's policy in the use and disclosure of protected health information in research in a manner that respects the patient's privacy in accordance with the "Privacy Rule" promulgated under the Health Insurance Portability and Accountability Act (HIPAA) and other applicable laws. All staff receive appropriate HIPAA training. All participants sign a Combined Informed Consent and HIPAA-authorization form, receive a copy of this form, and receive a notice of Penn's privacy practice. Combined Informed Consent and HIPAA Authorization signed forms are retained in locked file cabinets with participants' source documents.

A computerized data entry and management system will be developed during the initial project months by the Center's data management unit (DMU). All data will be entered into this web-based entry system by the research staff or study participants (self-assessments only).

A closed and password protected data entry system has been designed so that only the responsible data entry person and the DMU supervisor can enter and/or edit data and this can be done only be using the programs and/or utilities available on the menu system. Data and user stamping are used to create an audit trail. Range checks, review screens, and various error trapping routines are built into the system as quality control procedures. All possible relevant information on the forms is pre-coded and field-validated. All specific instructions and choices are provided for all data forms. All errors on source documents must be initialed and dated. The DMU director will be responsible for working with the project staff to ensure the

integrity of the data entry process. The investigator or study research staff can request the data at any point during the study so that audits of the study's current data input can be conducted and the data's integrity assessed.

8.3 Records Retention

After entry of all data in the Case Report Forms, these source documents will be kept on location until study closeout at which point they may be moved to a secure long-term storage facility.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

One primary monitor will be assigned for this trial and will be responsible to complete the monitoring process. The monitor will be a Research Coordinator who is independent from the trial and the study team. A CV for the monitor will be obtained and updated annually. The CV will be kept on file in the Sponsor section of the Regulatory Binder to document the qualifications of the monitor. To train the independent Monitor, the Principal Investigator and the Research Coordinator actively overseeing this trial will schedule a monitoring training session to discuss the protocol, case report forms, the informed consent, and the monitoring plan. In addition a monitoring manual will be created, which includes the complete protocol with the approved informed consent form, approved CRF, and this monitoring plan.

Enrollment will be complete when 40 subjects are enrolled into the trial. Enrollment for this study means when a participant is found to be eligible and is started on the study medication. Approximately 2 subjects will be enrolled per month. After the study initiation visit, further monitoring visits will be conducted periodically throughout the study as described below. (Note: The specific data to be reviewed at each visit is indicated in section 7.3.2)

- The first independent monitoring visit will occur when the first two subjects have completed the study.
- The second independent monitoring visit will occur when 25% of the subjects have been enrolled.
- A third independent monitoring visit will be conducted when approximately 50% of the subjects have been enrolled.
- A fourth independent monitoring visit will be conducted after 100% of the subjects have been enrolled. This visit may be conducted after the subjects have completed the study and can also serve as the close-out monitoring visit

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Please see DSMP for additional info.

10 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to the Penn Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

10.1 Risks

The potential risks of this study include adverse reactions to the study medications, potential adverse interactions between the study medication and opiates, discomfort due to the interview process, risk of breach of confidentiality, and the small risk incurred by venipuncture.

Buprenorphine: Buprenorphine is a safe and well-tolerated medication FDA approved for the treatment of opiate dependence

Common side effects are categorized below:

Adverse events commonly observed with the sublingual administration of buprenorphine sublingual film are

- oral hypoesthesia
- glossodynia
- oral mucosal erythema
- headache
- nausea
- vomiting
- hyperhidrosis
- constipation
- signs and symptoms of withdrawal
- insomnia
- pain
- peripheral edema

To help minimize these risks subjects are asked about AEs at each study visit. Any reported AEs are assessed by the Nurse Practitioner or Medical Director and followed until resolution.

10.2 Benefits

Subjects will benefit from receiving Suboxone for their Opiate Use Disorder. They will benefit from close medical and psychiatric attention over and above that which they will receive in an intensive outpatient treatment program and the potential personal improvements in health resulting from a diminished desire for- and reduced-use or abstinence from opioid. The indirect benefits are the potential benefits to society to include decreased opioid use with a resultant decrease in opioid morbidity and mortality, as well as a reduction in the overall societal cost of opioid dependence.

10.3 Risk Benefit Assessment

The risks of participating in the study are outweighed by the potential benefits of participating in the study.

10.4 Informed Consent Process / HIPAA Authorization

Most of the TRC callers seeking treatment who are approved for intake (via center IRB-approved phone pre-screen) come in to consent to the General Screening Consent (Protocol #701074) for an intake appointment to review general medical and psychosocial criteria prior to consenting to a specific study

All subjects for this study will be provided a combined informed consent/HIPAA Authorization form describing this study providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The subject, or legally acceptable surrogate, must sign the consent form, and the investigator-designated research professional obtaining the consent. Subjects will be consented by the study Principal Investigator, or appropriate designee, in a private room we have selected in which to perform consent. Potential subjects will review the consent form in detail with the person designated to consent (either PI or CRC or Research Tech) and have the ability to take the consent home for further review. Subjects will be provided the opportunity to ask all of their questions prior to signing the consent form. Subjects will not be enrolled in the study until they successfully pass a “quiz” about the content of the informed consent.

10.4.1 Alterations to Typical Consent Process (only include if applicable)

Not applicable

10.4.1.1 Waiver of Consent (In some cases for screening/portions of that study that qualify as minimal risk, a waiver of documentation of consent may be permissible IRB SOP)

Not applicable

10.4.1.2 Waiver of Written Documentation of Consent

Not applicable

10.4.1.3 Waiver of HIPAA Authorization

Not applicable

11 Study Finances

11.1 Funding Source

This study is financed through a grant from the National Institutes of Health/ National Institute on Drug Abuse (NIDA).

11.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11.3 Subject Stipends or Payments

Participants will be reimbursed $15 for the time and effort needed to complete the baseline assessment. For each in-office visit, participants will be reimbursed $20 for their participation including travel ($5). The total possible compensation for a subject who complete all visits is $555. As required by Perelman School of Medicine all reimbursements will be done with ClinCards which can be used as to obtain cash and as debit or credit cards.

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13 Appendices

Table 1: Assessment Schedule

Assessment	Baseline (V1)	Week 2 (V2-V4)	Weeks 3-14 (V5-V28)	End of Study (V29)
Medical Exam and EKG, CBC and blood chemistry, Urinalysis (UA), Risk Assessment Battery	1X			1X
Pregnancy Test (women), Addiction Severity Index (ASI)	1X		2X, weeks 5 and 9	1X
Urine Toxicology and Urine Buprenorphine and Norbuprenorphine Screen, Timeline Follow back (TLFB)	1X		24X	1X
Clinical Global Impression Scale (CGI), Hamilton Depression Rating Scale (HAM-D)	1X		1X, week 9	1X
Columbia Suicide Severity Rating Scale (C-SSRS), Obsessive Compulsive Drug Use Scale (OCDUS)	1X		12X	
Systems Usability Scale (SUS)				1X
Concomitant Medications	1X	3X	24X	1X
Medical Management, Pill Distribution		3X	12X	
Adverse Events		3X	24X	1X
Video Compliance/Attention Control (7 days per week, weeks 3-14)			84X	

Table 2: Study Schedule

Study Phase	Study Week	Visit Number
Baseline	1	1
Induction Phase	2	2
	2	3
	2	4
Medication Phase	3	5
	3	6
	4	7
	4	8
	5	9
	5	10
	6	11
	6	12
	7	13
	7	14
	8	15
	8	16
	9	17
	9	18
	10	19
	10	20
	11	21
	11	22
	12	23
	12	24
	13	25
	13	26
	14	27
	14	28
EOS	15	29