Contingency Management to Enhance Office-Based Buprenorphine Treatment

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JHM IRB - eForm A – Protocol

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1. Abstract

Office-based buprenorphine could be an effective way to expand treatment for opioid use disorder, and thereby combat the opioid epidemic. However, office-based buprenorphine has three main limitations: 1) Many patients discontinue buprenorphine treatment prematurely, 2) some patients divert buprenorphine for illicit use, and 3) many patients continue to use illicit opioids during buprenorphine treatment. Contingency Management interventions, which provide incentives to patients when they meet therapeutic goals, could address these limitations that may serve as barriers to scaling office-based buprenorphine treatment to levels needed to combat the opioid epidemic. This project will compare the effectiveness of two Contingency Management interventions and Usual Care in promoting adherence to office-based buprenorphine treatment and reducing illicit opioid use among adults with opioid use disorder. In this 3-group randomized controlled trial, adults with opioid use disorder who are receiving office-based buprenorphine treatment will be invited to complete a 1-week induction period and then will be randomly assigned to one of two Contingency Management groups–a Buprenorphine Adherence and Opiate Abstinence group and a Buprenorphine Adherence Only group–or a Usual Care Control group. Buprenorphine Adherence and Opiate Abstinence and Buprenorphine Adherence Only participants will receive incentives for daily buprenorphine use. Buprenorphine Adherence and Opiate Abstinence participants also will receive incentives for providing opiate-negative saliva samples. Daily buprenorphine use and opiate abstinence will both be remotely verified using smartphone-enabled video directly observed therapy (Video DOT) provided by emocha Mobile Health, Inc. The incentives will be integrated into the Video DOT platform and delivered remotely to reloadable credit cards. Participants will be assessed every month during a 3-month intervention period and every 3 months during a 9-month follow-up period. The primary outcome measures will be a) opiate abstinence and b) buprenorphine adherence during the 3-month intervention as assessed by urinalysis results every month during the intervention. If the proposed intervention is effective, it could improve patients' access to and success in office-based buprenorphine treatment.

2. Objectives (include all primary and secondary objectives)

Primary Aims

- Determine effectiveness of Contingency Management compared to Usual Care in promoting buprenorphine adherence and opiate abstinence as assessed by urine drug screens during the intervention.

Secondary Aims

- Determine effectiveness of Contingency Management compared to Usual Care in: a) reducing buprenorphine diversion, b) promoting retention in buprenorphine treatment, c) reducing opioid overdose and risk of overdose, d) improving psychosocial functioning and quality of life, e) promoting patient treatment satisfaction, and f) maintaining any effects after the intervention period ends.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Opioid use has increased to epidemic levels in the United States and is a major cause of morbidity and mortality nationwide.[1-4] In 2016 alone, more than 42,000 people died from an overdose involving

opioids. This equates to approximately 116 opioid-related overdose deaths per day.[5,6] The opioid epidemic also has been associated with substantial increases in the prevalence of infectious diseases, such as Hepatitis C and HIV, which will similarly have public health and financial repercussions for decades to come. Opioid use disorder is associated with the highest level of disease burden of all illicit drugs,[7] and contributes to excess healthcare utilization, loss of work productivity, crime, and incarceration. The total cost of the opioid epidemic in 2015 was estimated to be over $500 billion annually. Improving access to and enhancing evidence-based treatment for opioid use disorder is an essential component of an effective response to the opioid epidemic.

Buprenorphine to Treat Opioid Use Disorder

Buprenorphine is the most accessible form of evidence-based opioid treatment in the United States and could serve the vast majority of adults with opioid use disorder.[8,9] Maintenance treatment with buprenorphine can decrease opioid use and reduce risk of opioid overdose, and is superior to non-medication-based approaches.[10] Due to its partial agonist properties, buprenorphine has limited respiratory depressant effects and low toxicity even at high doses.[11] Buprenorphine is often given in a formulation with naloxone that provides some protection against misuse. Importantly, buprenorphine can be prescribed in office-based treatment settings. Office-based buprenorphine permits patients to receive medication by prescription to be taken at home, thereby avoiding the requirement for, and associated stigma of, daily attendance at a federally regulated opioid treatment program. As of 2016, physicians who have an addiction specialty board certification or who have completed an 8-hour course, and nurse practitioners and physician's assistants who have completed an extended course, may receive a waiver to prescribe buprenorphine. Consequently, office-based buprenorphine could be an effective way to expand treatment for opioid use disorder and thereby combat the opioid epidemic. However, office-based buprenorphine has three main limitations (described below). These evidence gaps must be addressed to facilitate the safe and effective expansion of buprenorphine treatment.

Retention of patients in buprenorphine treatment. Many patients enrolled in office-based buprenorphine treatment do not remain in treatment (for systematic reviews, see[10,12]). In a recent multi-site, randomized controlled trial conducted by the Clinical Trials Network,[13] only 43% of participants remained in buprenorphine treatment over the 24-week trial. Rates of retention were similar in an earlier multi-site study with opioid-dependent adults, in which 46% of participants remained in buprenorphine treatment over a 24-week trial.[14] Retention in buprenorphine treatment is important because it is associated with better treatment outcomes, including reduced opioid use, improved social functioning and quality of life, and reduced risk for all-cause and overdose mortality.[15,16] Mortality increases significantly in the period after treatment stops.[17]

Buprenorphine diversion. Once approved to serve as a buprenorphine provider, medical professionals can prescribe many doses of buprenorphine per prescription, often in 30-day supplies.[18] Because office-based buprenorphine providers are not required to observe daily buprenorphine dosing (as is done in methadone maintenance programs), buprenorphine doses can be diverted easily. Diversion increases the availability of illicit buprenorphine on the street, diminishes the effectiveness of office-based buprenorphine treatment, and increases the risk that buprenorphine providers may be contributing to problems associated with buprenorphine diversion. The risk of diversion may limit the expansion of office-based buprenorphine treatment as physicians may be reluctant to prescribe buprenorphine because of its potential to be diverted. Many eligible medical professionals do not apply for the waiver to become buprenorphine providers, and many providers do not prescribe to capacity.[19-22] In surveys examining barriers to prescribing buprenorphine, physicians have raised concerns about illicit diversion of buprenorphine.[23-25] Indeed, diversion of buprenorphine is a serious and growing concern.[24,26] A recent large-scale, national survey reported that misuse of buprenorphine has increased substantially, and that over one-third of the buprenorphine misusers in the sample had used by the intravenous route.[26]

Continued use of illicit opioids during buprenorphine treatment. Even at clinically effective doses, some patients continue to use illicit opioids during buprenorphine treatment (for systematic reviews and meta-analyses, see[10,27,28]). In one of the largest, multi-site clinical trials conducted with patients with opioid use disorder, less than half of patients receiving buprenorphine treatment were abstinent from opioids during a 12-week maintenance period.[29] In the multi-site trial conducted by the Clinical Trials Network, 57% of participants receiving buprenorphine treatment relapsed during the 24-week trial. [13] Additional supports may be needed to promote long-term remission and prevent relapse to opioid use.

Contingency Management Interventions

Research over the past 40 years on the use of contingency management in the treatment of substance use disorders suggests that contingency management could be very effective in addressing the limitations of office-based buprenorphine and the current evidence gaps. Contingency Management interventions provide incentives (e.g., through vouchers or reloadable credit cards) to substance abuse patients when they meet therapeutic goals.

Theoretical underpinnings of contingency management interventions. Contingency management interventions are rooted in research that suggests the drug use is operant behavior that is maintained and modifiable by its consequences.[30] That research shows that immediate consequences exert greater influence over behavior than delayed consequences.[31] The benefits of health behaviors like medication adherence or drug abstinence are often delayed, which may explain why these behaviors do not always maintain without special interventions. Incentive interventions are designed to bridge the gap between health behaviors and their naturally occurring but delayed health benefits. Specifically, incentive interventions provide immediate incentives for health behaviors and increase their frequency.

Contingency management in the treatment of drug addiction. Contingency management has been highly effective in promoting abstinence from most commonly abused drugs.[32] Reviews and meta-analyses suggest that contingency management interventions, also called incentive interventions, may be the most effective psychosocial addiction treatments.[33-37] Silverman has demonstrated that voucher incentives can increase abstinence from opiates in injection drug users in methadone treatment;[38,39] and that increasing voucher values can initiate abstinence in treatment refractory patients.[40,41] Holtyn and Silverman have shown that incentives can increase opiate and cocaine abstinence in out-of-treatment opioid users.[42,43] As with other treatments, some patients relapse to drug use after an incentive intervention ends. To address relapse, Silverman has pioneered the use of incentives as a maintenance intervention, and showed that incentives can maintain drug abstinence over time[44] for as long as one,[45] three,[46] and four[47] years.

Contingency management in promoting medication adherence. Contingency management also is effective in promoting adherence to opioid use disorder medications.[48] Early studies showed that voucher incentives could promote adherence to oral naltrexone in recently detoxified, opioid-dependent adults.[49,50] In a series of studies, Silverman showed that employment incentives can promote use of extended-release[51,52] and oral[53] naltrexone in heroin-dependent adults. Holtyn and Silverman have successfully enrolled out-of-treatment injection drug users into medication-assisted treatment and used incentives to promote abstinence from opiates and cocaine.[42,43]

Remotely-delivered contingency management. Technological advances have allowed for the development and dissemination of an efficient way to remotely deliver contingency management interventions. One approach used an internet-based method to deliver a contingency management intervention for smoking cessation. The procedure required patients to remotely video record collection of breath samples with a carbon monoxide monitor, and delivered incentives through a web-based platform.[54] This intervention has been shown effective in promoting smoking cessation,[54-57] including in a nationwide study of smokers from around the US.[58] To facilitate dissemination, another approach used smartphones to

implement contingency management interventions for cigarette smoking,[59,60] alcohol use disorder,[61] and cannabis use disorder.[62]

The Proposed Plan

This project seeks to enhance office-based buprenorphine treatment by promoting buprenorphine adherence and reducing illicit opioid use among adults with opioid use disorder. A randomized controlled clinical trial is planned over 4 years. Participants will be randomly assigned to one of two Contingency Management groups–a "Buprenorphine Adherence and Opiate Abstinence" group and a "Buprenorphine Adherence Only" group–or a "Usual Care" group. Buprenorphine Adherence and Opiate Abstinence and Buprenorphine Adherence Only participants will receive incentives for daily buprenorphine use. Buprenorphine Adherence and Opiate Abstinence participants also will receive incentives for providing opiate-negative saliva samples. The incentive system will be based on extensive research on Contingency Management interventions and will be similar to incentive systems that we have shown to be extremely effective in promoting drug abstinence and medication adherence. Incentive earnings will be delivered remotely to reloadable credit cards. Daily buprenorphine use and opiate abstinence will both be verified using smartphone-enabled, commercially available video directly observed therapy (Video DOT).

Commercially Available Video Directly Observed Therapy (Video DOT)

We will use the commercially available Video DOT platform offered by emocha Mobile Health, Inc to allow for the entire intervention to be delivered remotely via mobile technology and to facilitate easy dissemination of the proposed interventions (see Figure 1 below). The fundamental component of Video DOT is asynchronous, video-based directly observed therapy in which patients can record and submit videos of themselves that are then viewable on a secure, web portal for treatment staff and providers to view. Encrypted videos and data are transmitted to a secure, cloud-based server within seconds and subsequently deleted from the patient's mobile device. Staff and providers are then able to review videos (at any future time) to confirm engagement in a target behavior (e.g., medication adherence). Incentive capabilities are integrated into the Video DOT platform. Asynchronous, Video DOT makes it possible for care and treatment to take place at times that are convenient for both the patient and provider.

Single IRB descriptor

Johns Hopkins Medicine is serving as the single IRB for this study. It is the preference of Johns Hopkins Medicine IRB to use the SMART IRB reliance agreement as the basis of reliance. The SMART IRB master reliance agreement was created in 2016 to harmonize and streamline the IRB review process for multisite studies. It enables reliance on a study-by-study basis, clearly defines roles and responsibilities of relying institutions and reviewing IRBs, and eliminates the need to sign reliance agreements for each study [e.g., a non-SMART IRB agreement]. 900+ institutions have already signed onto this agreement and are actively using it as the basis of reliance for multisite projects. Sites that will rely on JHM IRB are still responsible for conducting a local context review prior to the start of research at their site and for following any local and

Patient-facing mobile application
Patients record and submit videos of themselves, monitor incentive earnings, and receive reminders

HIPAA-compliant, cloud-based server
Receives and stores encrypted data

Provider-facing web portal
Providers or staff view and assess patient videos to verify treatment, view progress, deliver incentives, and view analytics

Figure 1

institutionally required policies as it applies to research at their site [e.g., reporting of unanticipated problems].

4.	Study Procedures
a.	Study design, including the sequence and timing of study procedures
	(distinguish research procedures from those that are part of routine care).

Study Participants

Potential participants will learn of the study by posted, mailed, and internet-posted notices, newspaper advertisements, and word-of-mouth referral, as well as physician referrals from study co-investigators (co-Is Fingerhood and Buresh) and/or clinicians not on the study team. All interested individuals will first complete a brief screening interview to ensure general eligibility prior to a full-screening interview. Individuals who appear eligible based on the brief screening will be invited to complete the informed consent process and full-screening interview.

Standard Treatment Services

All participants will receive office-based buprenorphine at their treatment programs. All participants will be referred to services, as needed, by our staff including referrals for mental health services, housing, job-skills training, food assistance, and entitlement services.

Induction Period

To increase the chance that we engage participants, during an initial 7-day period, participants will be offered access to the study smartphone app and incentives. We have used similar induction procedures in our prior studies to successfully engage participants. Participants will have the smartphone app installed on their smartphones and will be taught how to use the app. Participants will then be asked to use the application to record a video of themselves for 7 days. Each video will be uploaded into a web portal, which can be securely accessed by our research staff, and will be reviewed by our research staff. Participants will be able to earn $10 per day over the 7-day period for submitting a video of themselves each day. Participants who use the smartphone application to record and submit videos on 6 or more days during the 7-day induction period will be randomly assigned to a study group (as described in detail below).

Experimental Design

Participants (N=375) will be randomly assigned to one of two Contingency Management groups–a Buprenorphine Adherence and Opiate Abstinence group and a Buprenorphine Adherence Only group–or a Usual Care (Control) group. A computerized urn randomization procedure will be used to randomize participants and to balance groups on three characteristics that may influence outcome: (1) opioid use severity (used illicit opioids ≥15 days out of the past 30 days, Y/N), (2) cocaine use (cocaine-positive urine, Y/N), and (3) age (greater than rolling median, Y/N). Participants will be stratified by opioid use, cocaine use, and age because each has been associated with buprenorphine treatment outcomes.[65-67] Participants will be assessed every month during the 3-month intervention and every 3 months during a 9-month follow-up period. We will teach participants the details of their study group with instructions and quizzes.

General Contingency Management Procedures

Both Contingency Management groups (Buprenorphine Adherence and Opiate Abstinence and Buprenorphine Adherence Only participants) will receive incentives for daily buprenorphine use. Buprenorphine Adherence and Opiate Abstinence participants also will receive incentives for providing opiate-negative saliva samples. Both of the Contingency Management interventions will have the following

features:

Video Directly Observed Therapy (Video DOT). We will use the Video DOT platform offered by emocha Mobile Health, Inc to allow for both Contingency Management interventions to be delivered remotely via mobile technology. Participants in the Contingency Management groups will have the Video DOT application installed on their personal smartphones and will receive training on how to use the application. Participants in both Contingency Management groups (Buprenorphine Adherence and Opiate Abstinence and Buprenorphine Adherence Only) will use Video DOT to record a video of the buprenorphine self-administration process. Buprenorphine Adherence and Opiate Abstinence participants also will use Video DOT to record a video of themselves completing the saliva drug-testing process. Each video will be uploaded into the provider-facing web portal, which can be securely accessed by research staff. Staff can verify each video to confirm that the video shows the correct person and that the buprenorphine dose was administered appropriately and, if applicable, that the saliva sample was opiate negative.

Reminders. During the initial training, study staff will ask participants to select at what time they will submit their video(s) each day. The selected time will be programed into the application by study staff. Then, the Video DOT platform will send an automatic reminder to participants who have not yet submitted videos by their selected time.

Immediate feedback. If participants submit a video within the allowed window (i.e., before midnight), the last screen of the application will be a message confirming that the video was submitted.

Validation of video of buprenorphine administration and saliva testing. By 4:00 PM on the day after a participant submits a video, or Monday if the participant submitted the video on Friday or Saturday, a staff member will review the videos. The validation process will occur on a staff computer using the provider-facing web portal. First, the program will display a previously obtained photo of the participant alongside the video to confirm that the correct person provided the video. The staff member will confirm that the person in the video matches the photo of the participant. If the person in the video matches the photo of the participant, the staff member will view the video to determine if the participant correctly administered his/her buprenorphine dose, or to determine if the participant provided a valid, opiate-negative saliva sample, if applicable. Participants will be able to visualize their earnings over time on a dashboard within the application.

Contesting the validation decision. Participants will be able to contest the validation decision of a staff monitor. Participants will be taught how to contest the validation decision during the in-person training and can see the decisions made on their video submissions from the application. All contested videos will be viewed by an independent staff member that was not involved in the original video validation.

Reloadable Credit Cards. At the start of enrollment, each participant will be given a reloadable credit card. Any incentive earnings will be added to the card. Each card can then be used as a regular credit card to make purchases at most businesses. We currently use this reloadable credit card system in our ongoing incentive programs, and it has proven very efficient and highly acceptable to participants.

Usual Care Control Group

Participants assigned to the Usual Care group will receive routine office-based buprenorphine treatment at their treatment programs. The primary rationale for selecting this control group is to maximize clinical applicability and generality of study results by evaluating office-based buprenorphine treatment as it is typically delivered. The issue this study addresses is what clinical benefit is achieved by adding two different intensities of Contingency Management to office-based buprenorphine. Our Usual Care group will

determine the percentage of the study population that will adhere to buprenorphine treatment and maintain opiate abstinence under routine conditions.

Buprenorphine Adherence Only Group

Participants assigned to the Buprenorphine Adherence Only group will receive financial incentives for promoting daily buprenorphine use for 3 months. Participants will be able to earn $10 per day for taking their buprenorphine dose and submitting a valid video recording of administration before midnight. If a participant fails to submit a video or if a submitted video is deemed invalid, the participant will not receive the scheduled incentive that day and the daily incentive value will be decreased to $3 per day. Then, the amount earned per day will increase to $10 per day after the participant submits a valid video of buprenorphine administration every day for seven days.

Buprenorphine Adherence and Opiate Abstinence Group

Similar to the Buprenorphine Adherence Only group, this group will receive financial incentives for promoting daily buprenorphine use using the procedures described above. However, to reduce or eliminate the opiate use that we expect will persist in participants in the Buprenorphine Adherence Only group, this group also will receive financial incentives for opiate abstinence. Participants will be asked to provide saliva samples according to a random, and then progressively more intermittent drug-testing schedule. Participants will receive an in-app notification each day stating whether or not it is a mandatory collection day. Initially, participants will be required to provide three saliva samples per week, on average. After 30 days in which all mandatory samples meet the abstinence criteria, participants will be required to provide two saliva samples per week, on average. After an additional 30 days in which all mandatory samples meet the abstinence criteria, participants will be required to provide one saliva sample per week, on average.

Participants will be able to earn $10 per day for every day since the last sample for providing an opiate-negative saliva sample and submitting a valid video recording of testing before midnight on mandatory sample collection days. If a participant fails to submit a video or if the participant tests positive for opiates, the participant will not receive the scheduled incentive amount and the maximum incentive value will be decreased to $3 per day. In addition, the schedule will switch to the most frequent testing schedule that was employed at the beginning of treatment. Then, the amount earned per day will increase to $10 per day after the participant provides an opiate-negative saliva sample over seven days.

Participants will be asked to complete saliva drug testing in a private location (such as the participant's home). We will give the participants Oral Fluid Drug Screen Devices. Participants will be asked to record a video using the smartphone app while performing the saliva drug test. To perform the test, the participant will remove the Oral Fluid Drug Screen Device from a sealed pouch to expose a collection pad. Participants will be asked to rub the inside of their mouths with the collection pad until it collects a sufficient amount of saliva (indicated by a colored line on the front panel of the collection pad). Participants will be asked to insert the collection pad into the screening device and to record the front panel of the Drug Screen Device for about 10 minutes.

Our staff will review these participant videos on the secure, web-portal to confirm that the saliva drug testing process was conducted appropriately (e.g., the test was conducted by the correct participant, the front panel of the Drug Screen Device contained control lines, etc) and to confirm if the saliva drug test was negative or positive for opiates (based on the presence or absence of a red, horizontal line next to the opiate test region). In the web-portal, we will indicate whether the participant did or did not earn the daily incentive for an opiate-negative saliva test. The Drug Screen Device can detect 6 drugs: methamphetamine,

THC, cocaine, amphetamine, opiates, and phencyclidine. We will enter the results of saliva drug testing for these 6 drugs into REDCap.

Intake and Outcome Assessments

Assessments will be conducted at intake, every month during the 3-month intervention period, and at 6, 9, and 12 months after randomization. Participants will be paid $50 for completing each of the intake and monthly assessments, and $100 for completing the follow-up assessments. These assessments will be collected using REDCap. Whenever possible, assessments will be conducted remotely via phone or web-conferencing.

Intake Only Assessment Instruments

DSM-5 Checklist for Opioid Use Disorder. The DSM-5 checklist for opioid use disorder is a structured assessment that will be used to determine if participants have opioid use disorder.

Non-Study Medical and Other Services – NSMOS-BL. This assessment will be used to collect information on medical services participants may have received in the 3 months prior to study intake.

Intake and Major Assessment Instruments

Urine and saliva toxicology testing. Urine and saliva samples will be collected and tested for opioids and other drugs. Toxicology testing may be conducted by sending a testing kit to participants through the mail. Participants would then be asked to complete the toxicology tests (urine and saliva) and provide a video showing the results of the tests using the study smartphone app.

Time-line follow-back (TLFB). Participants will be asked whether or not they are in treatment for their opioid use disorder, including treatment other than buprenorphine (e.g., methadone maintenance). For participants who report being in buprenorphine treatment, the TLFB procedure will be used to elicit participants' self-reported taking of their buprenorphine dose each day. Pharmacy and/or clinic records (with participant permission) may be used to confirm self-reported data.

Opioid Overdose Risk Assessment. An opioid overdose risk assessment will be used to assess the rate at which participants report engaging in behaviors that may put them at risk for an opioid overdose.

The Addiction Severity Index – Lite (ASI-Lite). The ASI-Lite is a structured interview designed to assess problem severity in areas commonly affected by drug and alcohol use (medical, legal, employment, family/social, and psychiatric) with good reliability and validity.

Smartphone Form. This questionnaire will document participants' access to and willingness to use a smartphone during the study.

Treatment Acceptability Questionnaire. To assess the acceptability of our intervention, we will administer a Treatment Acceptability Questionnaire to participants who are exposed to our smartphone incentive intervention at the end of the 3-month intervention period.

Client Satisfaction Questionnaire (CSQ-8). To assess patient treatment satisfaction, we will use the CSQ-8, a brief (8-item) validated instrument that has been used widely across health services.

Short Form (SF-36). We will assess self-reported quality of life using the 36-item short-form survey instrument.

Non-Study Medical and Other Services – NSMOS-FU. This assessment will be used to collect

information on medical services participants may have received during the intervention.

Northern Michigan University

This protocol is a multi-site study (See Section 1, Question 9). The Center for Learning and Health, Johns Hopkins University School of Medicine will serve as the lead/coordinating center for this multi-site study (See Section 1, Question 9) and JHM IRB will serve as the single IRB of record for this protocol (See Section 1, Question 10).

Northern Michigan University will serve as the second site in this study. Northern Michigan University will assist in overseeing the entire project, providing PCORI with needed information and documents, managing the Data Safety Monitoring Committee, managing the Study Advisory Committee, preparing the data for analyses, preparing reports required for PCORI, and preparing and submitting manuscripts for publication and presentation. Dr. Forrest Toegel is a co-investigator on this project and will serve as the PI for Northern Michigan University. Forrest Toegel is an Assistant Professor at Northern Michigan University. Under Dr. Toegel's supervision, research assistants will work with research staff at Johns Hopkins University School of Medicine to prepare the study data for analyses, and summarize and graph data for reports, publication, and presentation.

b. Study duration and number of study visits required of research participants.

Study participation will include a 3-month intervention evaluation period and a 9-month follow-up period for a total study duration of 12 months. Outcome assessments will be conducted at intake, every month during the 3-month intervention period, and at 6, 9, and 12 months after randomization.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Participants will not be blinded as to their study condition because participants in the incentive intervention cannot be blind to that intervention.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A

e. Justification for inclusion of a placebo or non-treatment group.

N/A

f. Definition of treatment failure or participant removal criteria.

Participants will be removed from the study if they threaten the safety of staff or other research participants, or of any other persons on the Johns Hopkins Bayview Campus.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Throughout the study, participants will be given referrals to services they might need (e.g., drug counseling, housing, medical, or employment services). Participants will continue to receive buprenorphine treatment as long as that treatment is available in the program they attend.

5. Inclusion/Exclusion Criteria

Applicants will be invited to participate in this study if they: a) are ≥ 18 years old, b) meet DSM-5 criteria for opioid use disorder, c) are enrolled in buprenorphine treatment, and d) use the smartphone

application to record and submit videos on 6 or more days during the 7-day induction period. Applicants will be excluded if they: a) have current suicidal/homicidal ideation, or b) are unwilling or unable to use a smartphone.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

N/A

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

We will compare the three study groups on primary and secondary outcome measures.

a. Primary outcome variable.

Buprenorphine Adherence. We will assess the percentage of participants with buprenorphine-positive urine samples at the monthly assessments during the 3-month intervention evaluation period (Yes/No at each assessment).
Opiate Abstinence. We will assess the percentage of participants with opiate-negative urine samples (excluding buprenorphine and methadone if self-report confirms that the participant is enrolled in buprenorphine or methadone treatment) at the monthly assessments during the 3-month intervention evaluation period (Yes/No at each assessment).

b. Secondary outcome variables.

Buprenorphine Diversion. We will assess the number of days participants report diverting their daily buprenorphine dose (selling or giving their buprenorphine dose to someone else) during the 28 days prior to each of the monthly assessments during the 3-month intervention evaluation period (based on TLFB).
Retention in Buprenorphine Treatment. We will assess the last day that participants reported taking buprenorphine during the 3-month intervention evaluation period (based on TLFB).
Overdose risk. We will assess the rates at which participants report engaging in overdose risk behaviors at the monthly assessments during the 3-month intervention evaluation period (based on total scores from the opioid overdose risk assessment).
Psychosocial Functioning. We will assess patient-reported psychosocial functioning during the 3-month intervention evaluation period (based on the ASI-Lite).
Quality of Life. We will assess patient-reported quality of life during the 3-month intervention evaluation period (based on scores from the SF-36).
Patient Treatment Satisfaction. We will assess patient-reported treatment satisfaction during the 3-month intervention evaluation period (based on scores on the CSQ-8).
Post-Intervention Effects. We will assess the outcomes described above every 3 months during a 9-

month follow-up after the intervention ends.

c. Statistical plan including sample size justification and interim data analysis.

Statistical Analyses

We will analyze measures assessed repeatedly over time with a longitudinal logistic regression model. Within-person correlated outcomes will be handled using generalized estimating equations (GEE; Zeger, Liang, & Albert, 1988). Measures assessed once will be analyzed using logistic regression. The magnitude of effects will be expressed using odds ratios with 95% confidence intervals. Retention in buprenorphine treatment during the intervention period will be analyzed with a Cox proportional hazards model. We will adjust the intent-to-treat analyses for covariates used for stratification (Pocock, Assmann, Enos, & Kasten, 2002).

Primary outcome analyses. We will fit a longitudinal logistic regression model logit $(Y_{ij}) = \beta_0 + \beta_1 tx_1 + \beta_1 tx_2 + \beta_{3\text{-}4} x_{2\text{-}4} + \varepsilon_{ij}$, where Y_{ij} is evidence of buprenorphine adherence or opiate abstinence for the ith person at the jth timepoint (3 visits over 12 weeks), β_1 is the covariate of interest representing the expected increase in log odds of evidence of buprenorphine adherence or opiate abstinence as a function of assignment to the treatment group, and $\beta_{2\text{-}4}$ are the coefficients for the 3 randomization covariates. We also will fit models with time and time by treatment interactions to look at change over time in buprenorphine adherence and opiate abstinence in each study group.

Secondary outcome analyses. We will fit longitudinal logistic regression models for the secondary measures. We will assess effects during the 3 months by fitting analogous models as described above for each outcome, including fitting models to look at change over time in each study group. Retention in buprenorphine treatment will be analyzed using a Cox proportional hazards model.

Missing data. We expect to collect ≥85% of the study assessments. Our primary approach to handle missing data will be to impute missing values as the adverse outcome (e.g., buprenorphine-negative urine sample). Model parameter estimates from this approach will be compared to a method without imputation. If these methods yield differing results, conclusions will need to be tentative, but results from both approaches will be reported in publications. To investigate sensitivity to missing values, participants with and without missing values will be compared by covariates and group assignment. If rates are higher than expected, we may use mixed effects models rather than GEE estimation, as the former has less strict assumptions regarding missing data (missing at random, rather than missing completely at random).

Power Analyses

We used Liu and Liang[84] to determine the number of participants required to detect a difference of 15% between groups using the three monthly assessments during the 3-month intervention period with 80% power and adjusting for missing data (15% missing). Based on these analyses, we will randomize a total of 375 participants (125 per group).

Buprenorphine adherence. We expect a fairly large difference in buprenorphine adherence between the two Contingency Management groups and the Usual Care group. Specifically, we expect that each Contingency Management group will provide urine samples positive for buprenorphine on 85% of the assessments, whereas we expect that the Usual Care group will provide urine samples positive for buprenorphine on 45% of the assessments. Thus, we expect to obtain a 40% difference in buprenorphine adherence between each of the Contingency Management groups and the Usual Care group.

Opiate abstinence. We expect large differences in opiate abstinence between each of the two Contingency Management groups and the Usual Care group, but a relatively small difference in opiate abstinence between the two Contingency Management groups. The Power Analysis was designed to allow

us to detect the smallest difference in opiate abstinence between groups: the difference between the Buprenorphine Adherence Only (expected 68% opiate negative) and the Buprenorphine Adherence and Opiate Abstinence (expected 83% opiate negative) groups; to detect this difference, we would need 106 participants.

Total sample size. Based on the analyses described above, we would need 106 participants per group to detect effects between the pairs of groups for the planned comparisons. After adjusting for the anticipated rates of missing data (15% missing), we need to randomize 125 participants to each of the three groups to ensure that we have sufficient sample sizes (125 participants x 0.85 collected assessments = 106 participants per group). Thus, we will randomize a total of 375 participants.

d. Early stopping rules.

The study investigators and a Data Monitoring Committee (DMC) will provide data and safety monitoring of the proposed trial. To monitor adverse events, all staff members who have regular contact with study participants are instructed on the need to report to an investigator any indication that an adverse event has occurred. When the staff members and investigators learn of an adverse event, they will investigate until they have determined as many of the relevant details of the adverse event as possible. To provide consistent monitoring of adverse events across groups, participants will be asked about all categories of adverse events at each routine assessment visit conducted throughout the study. At least one investigator will review each adverse event as it occurs. The DMC will review a summary of adverse events annually. This frequency of review will be increased if the adverse events occur at a higher rate than anticipated. The protocol can be stopped based on recommendations of the investigators or DMC who are reviewing the adverse events in the study. We will ask the investigators and DMC to recommend that the trial be stopped if a review of the adverse events suggests to any of the investigators or DMC members that the number of related adverse events is unacceptably high. The investigators or DMC will be allowed to request statistical analyses to compare the groups on the rates of different adverse events or to have the adverse event data summarized in other ways that they deem appropriate.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

This study involves the development and evaluation of a behavioral intervention to promote adherence to an FDA-approved medication (buprenorphine) for opioid use disorder. The study poses little risk to participants and offers the potential of substantial benefit. There is essentially no risk above those of normal daily living associated with the incentives, or with the data collection procedures in this study.

b. Steps taken to minimize the risks.

To protect confidentiality, all research participants are identified by participant identification codes (Participant IDs) consisting of their initials and sequentially-assigned participant numbers on most forms and data files, and not by their names. All research data are stored in locked areas accessible only to research staff and are not left unattended. Documents with confidential information are shredded before being discarded. Confidential information is never given to anyone outside of the research program without the explicit written permission of the research participant. Only selected designated staff members are approved to give confidential information out after obtaining explicit written permission from the participant. All research staff are trained in these procedures. We collect only general information about participant activities, legal and illegal. We do not collect information about specific illegal acts. Finally and importantly, the study smartphone app that will be used to provide monitoring and incentives has features that promote compliance with HIPAA.

To protect against suicide risk, participants will be routinely screened for suicidal ideation using the question "In the past 30 days, have you experienced serious thoughts of suicide?" on the ASI-Lite at each study assessment. If a participant shows any indication that he/she might be at risk for suicide at any point during the study, a staff member will remain with an at-risk participant until an appropriate healthcare professional takes responsibility for the participant. The staff member will immediately notify the study clinician and the Principal Investigator upon learning of the suicide risk. The participant will be seen by the study clinician, who will assess the risk of suicide and determine the appropriate course of action. If a participant indicates that he/she is at risk for suicide over the phone, staff will call 911 and stay on the phone with the participant until the police arrive. Our research team is trained to implement and has experience implementing these procedures.

To protect against overdose risks, all participants will be offered referrals to the Baltimore City Health Department's Staying Alive Program, which teaches drug users how to avoid opioid overdoses and how to respond in the event of an opioid overdose emergency. At each study assessment, we will provide participants with the Center for Disease Control and Prevention's pamphlet on preventing an opioid overdose (https://www.cdc.gov/drugoverdose/pdf/patients/Preventing-an-Opioid-Overdose-Tip-Card-a.pdf), which includes overdose risk factors, signs and symptoms, and bystander response to overdose.

c. Plan for reporting unanticipated problems or study deviations.

Unanticipated problems or study deviations will be reported based on the guidelines of the Johns Hopkins University School of Medicine IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

There are risks that the confidential information we collect could be revealed to people not involved in the research such as a friend, relative, or an outside organization. This could be embarrassing to the participant if the participant wanted to keep participation in the study secret. We do not collect information about specific illegal acts. Thus, the risks associated with the assessments are not greater than the risks associated with routine psychological examinations or tests.

e. Financial risks to the participants.

There are no financial risks above those of normal daily living. Each participant is responsible for ensuring that the earnings are reported properly to relevant government or private agencies and for determining whether or not the earnings will affect any benefits they might receive from those agencies.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Participants in the experimental groups will receive access to our customized mobile-health application that could improve buprenorphine treatment. If the proposed intervention is an effective means of promoting buprenorphine treatment engagement and adherence, it could reduce the substantial morbidity, mortality, and societal healthcare costs associated with opioid use disorder.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

All incentives in this study will be provided by giving participants reloadable credits and adding incentives to the card when earned. We have been using these reloadable credit cards in our ongoing research and they have proved attractive to participants and convenient for staff to manage.

Incentives for participating in the 7-day induction period. Participants will be invited to participate in a 7-day induction period. Participants may earn up to $70 for participating in the induction period.

Incentives for completing study group instructions. Participants will be paid $50 for completing study instructions that will teach them about the details of their study group.

Incentives for completing routine assessments for both groups. Outcome assessments will be conducted at intake, every month during the 3-month intervention period, and at 6, 9, and 12 months after randomization. Participants will be paid $50 for completing each of the intake and monthly assessments, and $100 for completing each of the follow-up assessments. In total, participants can earn $500 for completing these assessments.

Participant referral fees. Participants will have the optional opportunity to earn incentives for referring people who are interested in the study. If a referral attends the initial screening and completes the necessary assessments, the participant who referred the person will receive up to $20. If a referred person enrolls in the main study, the participant who referred the person will receive up to $40 for the referral.

Contingency management for facilitating buprenorphine adherence. Participants in the Buprenorphine Adherence and Opiate Abstinence group and the Buprenorphine Adherence Only group will be able to earn $10 per day for taking their buprenorphine dose and submitting a valid video recording of administration before midnight. Over the entire 3-month study period, participants in these groups could earn $910 for adhering to buprenorphine treatment.

Contingency management for opiate abstinence. Participants in the Buprenorphine Adherence and Opiate Abstinence group will be able to earn $10 per day for providing opiate-negative saliva samples and submitting a valid video recording of saliva drug testing. Over the entire 3-month study period, participants in this group could earn $910 for providing opiate-negative saliva samples.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no costs to participants for any services or treatment provided in this study.