Official Title: Buprenorphine Treatment Engagement and Overdose Prevention

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1. Abstract

The United States is experiencing an epidemic of opioid-related overdose deaths. Office-based buprenorphine treatment could expand access to treatment to the many opioid users who are not in treatment and who are at great risk for opioid overdose. However, office-based buprenorphine has two limitations that we will address in this application: 1) Patients prescribed buprenorphine by office-based providers can divert the buprenorphine for illicit use. 2) Many people in need of buprenorphine treatment do not initiate and remain in office-based buprenorphine treatment. We will use Video DOT and incentives to enhance office-based buprenorphine treatment. Video DOT is an innovative, mobile health platform that patients can use to record and submit videos of themselves taking medication that are then viewable on a secure, web portal for providers to confirm medication adherence. Video DOT could facilitate adherence to buprenorphine treatment and safeguard against diversion. The addition of incentives could engage out-of-treatment opioid users into treatment and increase treatment retention. Incentive interventions, which provide incentives to patients when they meet therapeutic goals, have been highly effective in promoting a wide range of health behaviors and have firm theoretical and empirical foundations. Incentive interventions can promote treatment engagement in individuals with substance use disorders, including out-of-treatment opioid users. We propose to develop and pilot test a novel combination of Video DOT and incentives to promote buprenorphine treatment engagement and adherence in out-of-treatment opioid users. The Video DOT+ intervention will provide an incentive for linking to buprenorphine treatment and facilitate retention in treatment by providing incentives for maintaining daily buprenorphine use as verified by the Video DOT system. The incentives will be integrated into the Video DOT platform and delivered remotely to reloadable credit cards to allow for the entire intervention to be delivered via mobile technology and to facilitate easy dissemination of the Video DOT+ system. Two randomized pilot studies are planned over 3 years. In both studies, out-of-treatment opioid users (N=105) will be referred to buprenorphine treatment and randomly assigned to a Usual Care (Control) group or Video DOT+ group. Video DOT+ participants will receive the Video DOT+ intervention being developed and evaluated in this project. We will assess participants every 4 weeks throughout a 24-week intervention period and at 12 weeks after the intervention ends. The primary outcome measure will be buprenorphine treatment adherence during the 24-week intervention. Secondary measures will include buprenorphine treatment engagement (linkage and retention), opioid use, risk of opioid overdose, and post-intervention effects. The project will allow for the development and preliminary evaluation of a novel intervention to promote buprenorphine treatment engagement and adherence in out-of-treatment opioid users.

2. Objectives (include all primary and secondary objectives)

Study 1 and Study 2 have the same primary and secondary objectives:

Primary Aim

- Buprenorphine treatment adherence. Assess efficacy of Video DOT+ in promoting buprenorphine

treatment adherence as assessed by urine drug screens.

Secondary Aims

- Buprenorphine treatment engagement. Assess efficacy of Video DOT+ in promoting linkage to and retention in buprenorphine treatment.
- Opioid use and overdose risk. Assess efficacy of Video DOT+ in reducing opioid use and overdose risk.
- Post-intervention effects. Assess efficacy of Video DOT+ in promoting buprenorphine treatment engagement and adherence, and reducing opioid use and overdose risk after the intervention 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 has been associated with a dramatic increase in overdose deaths (Wheeler et al., 2015; Wilkerson et al., 2016). 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 (Centers for Disease Control and Prevention, 2016), and recent data suggests that the opioid overdose epidemic is worsening (Ahmad et al., 2018).

Maryland–where we will conduct this research–is among the top five states with the highest rates of opioid overdose deaths (Seth, Scholl, Rudd, and Bacon, 2018). As shown in Figure 1, the number of people who have died from an opioid overdose in Maryland has increased dramatically since 2009. Between 2015 and 2016, the number of opioid-related deaths increased by 70%, the largest single-year increase ever recorded (Maryland Department of Health and Mental Hygiene, 2017).

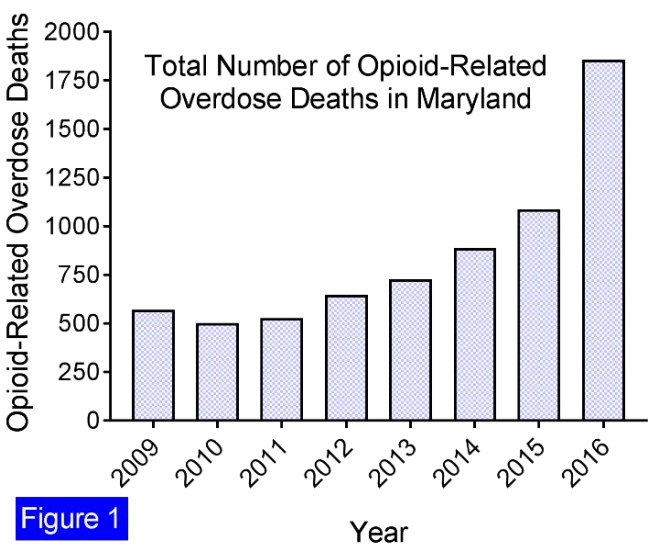


Figure 1

The dramatic increase in overdose deaths in Maryland has predominantly been attributed to heroin and the synthetic opioid fentanyl. Between 2015 and 2016 the number of deaths involving heroin and fentanyl increased by 62% and 229%, respectively. The number of prescription-opioid related deaths increased by 19%; many of these deaths occurred in combination with heroin and/or fentanyl (Maryland Department of Health and Mental Hygiene, 2017).

Buprenorphine to Treat Opioid Use Disorder and Reduce Opioid Overdose

A key driver of the overdose epidemic in Maryland and nationwide is untreated opioid use disorder. The mu-opioid receptor full agonist (methadone), partial agonist (buprenorphine), and antagonist (naltrexone) are FDA-approved pharmacotherapies for the treatment of opioid use disorder. Treatment with these pharmacotherapies can decrease opioid use and reduce risk of opioid overdose, and are superior to non-medication-based approaches (Jarvis, Holtyn, et al., 2018; Krupitsky et al., 2011; Mattick, Breen, Kimber, and Davoli, 2009; 2014). However, methadone is highly regulated and can only be dispensed in federally approved opioid treatment programs (Connery, 2015). While naltrexone can be prescribed in office-based treatment settings, it precipitates withdrawal in opioid-dependent individuals so it can only be initiated in patients who have stopped opioid use for several days. As a result, many individuals do not initiate treatment with naltrexone (Jarvis et al., 2018; Lee et al., 2017). Nearly 80% of the 2.1 million

Americans with an opioid use disorder are not in treatment (Center for Behavioral Health Statistics and Quality, 2017; Wu, Zhu, & Swartz, 2016). Consequently, improving access to evidence-based treatment is an essential component of an effective response to the overdose epidemic.

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 (Jones, Campopiano, Baldwin, and McCance-Katz, 2015; Morgan, Schackman, Leff, Linas, and Walley, 2018). Unlike methadone, buprenorphine can be prescribed in office-based treatment settings (provided a buprenorphine prescribing waiver is obtained). Office-based buprenorphine permits patients to receive medication by prescription to be taken at home, thereby avoiding the requirement for daily attendance at methadone maintenance programs. Due to its partial agonist properties, buprenorphine has limited respiratory depressant effects and low toxicity even at high doses (Lange, Fudala, Dax, and Johnson, 1990). At clinically effective doses, buprenorphine can protect against opioid overdose because of its strong affinity for the mu-opioid receptor. Furthermore, buprenorphine is often given in a formulation with naloxone that provides some protection against misuse.

Office-based buprenorphine treatment could be expanded substantially to treat many Americans with an opioid use disorder who are not in treatment. 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. Once approved to serve as a buprenorphine provider, medical professionals can prescribe many doses of buprenorphine per prescription, often in 30-day supplies (Schuckit, 2016).

Buprenorphine diversion. Because office-based buprenorphine providers can prescribe 30-day supplies of buprenorphine at a time and are not required to observe daily buprenorphine dosing (as is done in methadone maintenance treatment 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 also may limit the expansion of office-based buprenorphine treatment. Many eligible medical professionals do not apply for the waiver to become buprenorphine providers, and many providers do not prescribe to capacity (DeFlavio et al., 2015; Huhn and Dunn, 2017; Kundsen, 2015; Sharma et al., 2017). In surveys examining barriers to prescribing buprenorphine, physicians have raised concerns about illicit diversion of buprenorphine (Andrilla et al., 2017; Johanson et al., 2012; Schuman-Olivier et al., 2013). Indeed, diversion of buprenorphine is a serious and growing concern (Cicero et al., 2014; Johanson et al., 2012). 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; respondents reported that they had injected buprenorphine/naloxone tablets and film after using methods that they believed separated the buprenorphine from naloxone (Cicero et al., 2014).

Retention of patients in buprenorphine treatment. Although buprenorphine can reduce opioid use and protect against opioid overdose, many patients enrolled in office-based buprenorphine treatment do not remain in treatment (for systematic reviews, see Mattick et al., 2014; Timko et al., 2016). In a recent multi-site, randomized controlled trial conducted by the Clinical Trials Network (Lee et al., 2017), 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 (Hser et al., 2014).

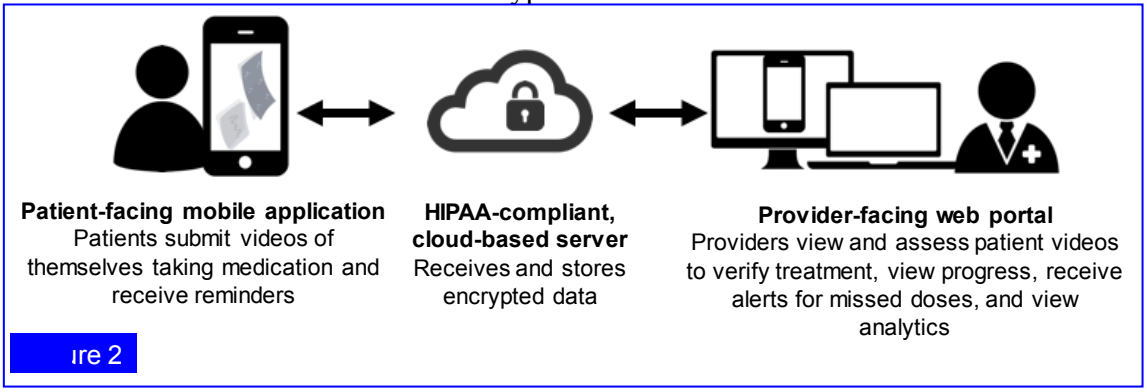
Addressing the limitations of office-based buprenorphine treatment. Office-based buprenorphine could be an ideal pharmacotherapy in the movement to expand access to treatment for opioid use disorder and thereby combat the opioid overdose epidemic, but it has two limitations that we plan to address in this

application: 1) Buprenorphine that is prescribed by office-based providers can be easily diverted for illicit use. 2) Many people in dire need of buprenorphine treatment do not initiate and remain in office-based buprenorphine treatment.

Reducing Diversion through Video-Based Directly Observed Therapy (Video DOT)

Methadone maintenance programs minimize the risk of diversion by directly observing dosing in the methadone clinics. While effective in minimizing diversion, directly observed dosing is costly to both the providers and patients, and may be limited in scalability and long-term effectiveness. Office-based prescription of buprenorphine reduces the cost of administering opioid treatment medications for both the providers and patients and offers a means of dramatically increasing our capacity to treat people with opioid use disorder. Fortunately, mobile technology can facilitate directly observed dosing for buprenorphine treatment at a relatively low cost and thereby reduce the risk of diversion.

emocha Mobile Health, Inc (emocha) has developed an innovative mobile health platform for facilitating medication adherence called Video DOT (see Figure 2 below). The fundamental component of Video DOT is asynchronous, video-based directly observed therapy in which patients can record and submit videos of themselves taking medication that are then viewable on a secure, web portal for treatment staff and providers to confirm medication adherence. 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 adherence. Thus, Video DOT provides a novel and efficient way to remotely and objectively confirm medication adherence as well as safeguard against diversion. All data is encrypted on the phone, both in transmission and on the server. Videos are deleted automatically upon uploading, ensuring privacy and confidentiality. emocha developed and validated their Video DOT system for promoting medication adherence in the treatment of tuberculosis and hepatitis C virus and currently offers their Video DOT system commercially to interested consumers. emocha has adapted its system to provide Video DOT for buprenorphine treatment and is pilot testing their Video DOT system in buprenorphine treatment patients (R44 DA044053). In collaboration with emocha, we will use their Video DOT system to ensure regular adherence to office-based buprenorphine treatment.



ıre 2

Using Incentives to Increase Retention in Buprenorphine Treatment

Many patients enrolled in office-based buprenorphine treatment do not remain in treatment (Mattick et al., 2014; Timko et al., 2016). In recent studies, less than half of the patients enrolled in office-based buprenorphine treatment remained in treatment for 24 weeks (Lee et al., 2017; Hser et al., 2014). However, discontinuing buprenorphine treatment can increase the risk of opioid overdose (Sordo et al., 2017). To increase retention in buprenorphine treatment, we will offer patients behavioral economic incentives for taking scheduled doses of buprenorphine as verified by emocha's Video DOT system.

Theoretical underpinnings of incentive interventions. Research over the past 40 years on the use of behavioral economic incentives in the treatment of substance use disorders and other health problems

suggests that incentives could be very effective in promoting engagement and retention in buprenorphine treatment. That research shows that immediate consequences exert greater influence over behavior than delayed consequences (Bickel et al. 2014). 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 thereby increase their frequency.

Incentive interventions in the treatment of drug addiction. Incentive interventions have been highly effective in promoting abstinence from most commonly abused drugs, among other targets (Higgins, Silverman, and Heil, 2008). Reviews and meta-analyses suggest that incentive interventions, also called contingency management interventions, may be the most effective psychosocial addiction treatments (Castells et al., 2009; Dutra et al., 2008; Knapp et al., 2007; Lussier et al., 2006; Pilling et al., 2007). Silverman (Co-Investigator on this project) showed that voucher incentives can increase abstinence from cocaine (Silverman et al., 1996; 1998) and opiates (Robles et al., 2002; Silverman, Wong, et al., 1996) in injection drug users in methadone treatment; and that increasing voucher values can initiate abstinence in refractory patients (Dallery et al., 2001; Silverman et al., 1999). Holtyn (Principal Investigator) and Silverman (Co-Investigator) have shown that incentives can increase cocaine and opiate abstinence in out-of-treatment opioid users (Holtyn et al., 2014a, b). 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 could maintain drug abstinence over time (Silverman et al., 2012) for as long as one (DeFulio et al., 2009), three (Silverman et al., 2002), and four (Aklin et al., 2014) years.

Incentive interventions in promoting medication adherence. Particularly important to this application, incentive interventions have been effective in promoting adherence to pharmacotherapies in the treatment of opioid use disorder (DeFulio and Silverman, 2012). Early studies showed that voucher incentives could promote short-term adherence to oral naltrexone treatment in recently detoxified, opioid-dependent adults (Carroll et al., 2001; Preston, Silverman, et al., 1999). In a series of studies, our team demonstrated that employment-based incentives can promote long-term use of extended-release (DeFulio et al., 2012; Everly et al., 2011) and oral (Dunn et al., 2013) naltrexone in heroin-dependent adults.

The Target Population: Out-Of-Treatment Adults with Opioid Use Disorder

Out-of-treatment adults with opioid use disorder are at high risk for opioid overdose (Degenhardt et al., 2009, 2011; Kimber et al., 2015; Sordo et al., 2017) and could benefit from expanded access and effective treatment with buprenorphine. The use of emocha's Video DOT system and incentives to provide buprenorphine treatment to out-of-treatment opioid users could ensure that this critical population maintains adherence to buprenorphine treatment and could minimize the risk of buprenorphine diversion. While emocha has begun to apply their Video DOT technology to the provision of buprenorphine treatment (under an SBIR grant from the National Institute on Drug Abuse, R44 DA044053; see above), they have focused their initial efforts on adults who are already in buprenorphine treatment and they have not incorporated incentives into the treatment. Out-of-treatment opioid users have been difficult to engage in treatment (Booth, Crowley, and Zhang, 1996), but behavioral interventions have shown some promise in engaging out-of-treatment opioid users in treatment (Booth, Kwiatkowski, and Stephens, 1998; Kidorf et al., 2009). Particularly relevant to this application, Holtyn (PI) and colleagues have successfully recruited and enrolled out-of-treatment injection drug users into methadone treatment and used behavioral economic incentives to promote abstinence from opiates and cocaine (Holtyn et al. 2014a; Holtyn et al. 2014b).

Scientific Premise: *Engaging out-of-treatment opioid users into buprenorphine treatment*

The United States is experiencing an epidemic of opioid-related overdose deaths. Office-based buprenorphine could expand access to buprenorphine treatment to the many opioid users who are not in treatment and who are at great risk for opioid overdose. However, office-based buprenorphine has two limitations that we plan to address in this application: 1) Patients prescribed buprenorphine by trained office-based medical professionals can easily divert the buprenorphine for illicit use. 2) Many people in dire need of buprenorphine treatment do not initiate and remain in office-based buprenorphine treatment. Video DOT is an innovative, patient-centered, mobile health platform that could facilitate adherence to buprenorphine treatment and safeguard against diversion. The addition of incentives could engage out-of-treatment opioid users into treatment and increase retention in treatment. We propose to develop and pilot a novel combination of Video DOT and incentives to promote buprenorphine treatment engagement and adherence in out-of-treatment opioid users.

The Proposed Plan

Our proposed intervention will combine the commercially available Video DOT platform offered by emocha Mobile Health Inc. with an empirically-based incentive system – a combination we are calling "Video DOT+". The incentive system will be based on extensive research on incentive interventions and will be similar to incentive systems that we have shown to be extremely effective in promoting medication adherence. The Video DOT+ intervention will provide incentivesfor linking to buprenorphine treatment; facilitate retention in buprenorphine treatment via emocha's Video DOT system and incentives for maintaining daily buprenorphine use; and add incentives remotely to reloadable credit cards. The incentives will be integrated into the commercially available platform offered by emocha to allow for the entire intervention to be delivered remotely via mobile technology and to facilitate easy dissemination of the Video DOT+ system. We will evaluate this system in out-of-treatment adults with opioid use disorder who are at high risk for opioid overdose and could benefit from expanded access to effective buprenorphine treatment.

Two randomized pilot studies are planned over 3 years. In both studies, out-of-treatment opioid users will be recruited through street outreach, at agencies that serve the target population (e.g., The Baltimore City Health Department), word-of-mouth referrals, and by posting fliers and information sheets with our toll-free number in Baltimore publications (e.g., the city paper) -- methods that we have used previously to recruit out-of-treatment opioid users. Participants in Study 1 will be referred to buprenorphine treatment and randomly assigned to a Usual Care (Control) group or a Video DOT+ group. Participants in Study 2 will be invited to participate in a 7-day induction period, and then randomly assigned to a Usual Care (Control) group or a Video DOT+ group. Video DOT+ participants will receive the Video DOT+ intervention being developed and evaluated in this project. We will assess participants every 4 weeks throughout a 24-week intervention period and at 12 weeks after the intervention ends. The long-term goal of this line of research is to develop and disseminate a sustainable and scalable intervention that can promote buprenorphine treatment engagement and adherence, and thereby combat the opioid overdose epidemic.

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 1 AND STUDY 2

Study Participants

Recruitment and screening. We will use the following recruitment procedures that we used successfully in our prior study with out-of-treatment opioid users (Holtyn et al., 2014): 1) We will inform

staff at programs that serve the target population about the study and encourage them to refer potential participants to us. 2) We will post IRB-approved flyers and distribute business cards and information sheets with our toll-free number in each of these programs and in Baltimore publications (e.g., the city paper). 3) As in our previous studies, participants will have the option to earn incentives for referring people who are interested in the study. All interested individuals will first complete a brief screening interview by telephone or in-person 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 in-person informed consent process and full-screening interview.

Standard Treatment Services

Referrals to buprenorphine treatment. All participants will be referred to receive office-based sublingual buprenorphine treatment either by their primary care provider or by one of our collaborating programs, based on participant preference. If the participant has a primary care provider and is interested in receiving buprenorphine from that provider, we will determine whether their provider is waivered to prescribe buprenorphine. We will use SAMHSA's online Buprenorphine Treatment Practitioner Locator, which assists in finding physicians authorized to treat opioid use disorder with buprenorphine by state (SAMHSA, 2018).

If the participant is unable to receive or uninterested in receiving buprenorphine treatment from their primary care provider, we will refer the participant to one of our collaborating programs (e.g., the Comprehensive Care Practice and REACH Health Services).

To facilitate access to buprenorphine, study physicians located at the Behavioral Pharmacology Research Unit (BPRU) on the Johns Hopkins Bayview Medical Campus may provide buprenorphine prescriptions to participants in this study.

Referrals to other treatment services. All participants will be referred to additional services, as needed, by our outreach staff including referrals for mental health services, housing, job-skills training, food assistance, and entitlement services.

STUDY 1

Computer-Based Education Program

Upon enrollment in Study 1, participants will be taught about the available medication-assisted treatments (buprenorphine, methadone, and naltrexone) for opioid use disorder as well as opioid overdose prevention and treatment strategies through a computer-based education program. All participants who are eligible for Study 1 will be invited to complete the computer-based program. After participants complete the computer-based program, they will be randomly assigned to a study group (as described in detail below).

Course Content. The content of the computer-based education program was developed using information from SAMHSA (Opioid Overdose Prevention TOOLKIT and Medications for Opioid Use Disorder). The computer-based program was divided into three courses that differ by topic area. Course 1 defines opioids and other key terms such as tolerance and withdrawal. Course 2 provides training on opioid overdose risks, prevention, and identification, and "do's and don'ts" of responding to an overdose. Course 3 provides training on the three FDA-approved medications for opioid use disorder (buprenorphine, methadone, and naltrexone), including when, where, and how these medications are typically taken.

Computer-Based Education Program. Each of the three courses are divided into 12 Modules consisting of Presentation and Mastery Units. Presentation Units were designed to introduce new material, while Mastery Units allow participants to practice answering questions about that material. Each Mastery Unit consists of a series of question screens with multiple-choice questions about the content in the previous Presentation Unit. Question screens may be presented in random order in a one-minute practice

trial (i.e., "timing"). Participants can earn $2.00 for completing each of the 12 Modules and $0.05 for each correct response during a timing. Thus, total earnings for participating in the computer-based training will depend on the speed and accuracy with which participants answer questions during the timings. In our prior computer-based training study, participants answered 15 questions correctly per minute in Mastery Units, on average (Subramanian et al., 2019). Based on this, we estimate that participants will earn up to about $33 for participating in the computer-based training (12 Mastery Units x 15 correct responses per Mastery Unit x $0.05 per correct response; 12 Modules x $2.00 for completing each Module).

Knowledge Tests. We will evaluate effectiveness of the computer-based education program by giving participants tests before and after they complete parts or all of the program. We may re-administer the test at the end of the main study to measure retention. A 50-item Knowledge Test (see Section 20, Supplemental Study Documents for a copy of the questions from the Knowledge Test) will be used to assess performance prior to and following training in each of the three courses – participants will complete the test four times. The test consists of multiple-choice questions with two to four response options. Participants will be able to earn $0.05 for each question they answer correctly on the test for a total of up to $10 across the four administrations. Participants will be provided with their test score (number of correct/incorrect responses and amount of incentives earned) after completing each administration of the test. Participants will not be provided with feedback on their responses to each question in the test.

Evaluation Strategy. We will use a multiple-probe design to evaluate learning in the education program. The program is divided into three courses and the Knowledge Test of content from all three courses will be delivered before and after participants complete each course. Each participant will complete the 50-item test described above four times (Test 1, Test 2, Test 3, and Test 4). Participants will be asked to complete Test 1 prior to taking Course 1, Test 2 after taking Course 1 and prior to taking Course 2, Test 3 after taking Course 2 and prior to taking Course 3, and Test 4 after taking Course 3. The expectation is that performance on each test will increase following completion of each course.

Experimental Design

Participants will be randomly assigned to a Usual Care Control or Video DOT+ group. A computerized urn randomization procedure (Wei & Lachin, 1988) will be used to randomize participants and to balance groups on two baseline characteristics that may influence outcome: (1) sex (male/female) and (2) intake urine sample positive for cocaine (Yes/No). Participants will be stratified based on sex and evidence of cocaine use because each has been associated with buprenorphine treatment outcomes (Marsch et al., 2005; Sullivan et al., 2010). While it might be desirable to stratify on other variables, increasing the number of variables is not practical given the sample size proposed for this study.

STUDY 2

Computer-Based Education Program

Upon enrollment in Study 2, participants will be taught how to use the Video DOT application through a computer-based education program. All participants who are eligible for Study 2 will be invited to complete the computer-based program. After participants complete the computer-based program, they will be invited to participate in a 7-day smartphone induction period (as described in detail below).

Course Content. The content of the computer-based program was developed using screenshots of the different sections of the study smartphone app. The program teaches participants the main functions of each setting in the app while using the screenshots as a visual aid.

Computer-Based Education Program. The course is divided into Modules consisting of Presentation and Mastery Units. Presentation Units were designed to introduce new material, while Mastery Units allow participants to practice answering questions about that material. Each Mastery Unit consists of a series of question screens with questions about the content in the previous Presentation Unit. Question

screens may be presented in random order in a one-minute practice trial (i.e., "timing"). Participants will be able to earn $30 for completing the computer-based education program.

Smartphone Induction

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 be asked to use the app 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 $20 per day over the 7-day period for submitting a video of themselves each day. Participants who use the smartphone app to record and submit videos on 6 or more days during the 7-day period will be randomly assigned to a study group (as described in detail below).

Experimental Design

Participants will be randomly assigned to a Usual Care Control or Video DOT+ group. A computerized urn randomization procedure (Wei & Lachin, 1988) will be used to randomize participants and to balance groups on two baseline characteristics that may influence outcome: (1) sex (male/female) and (2) intake urine sample positive for cocaine (Yes/No). Participants will be stratified based on sex and evidence of cocaine use because each has been associated with buprenorphine treatment outcomes (Marsch et al., 2005; Sullivan et al., 2010). While it might be desirable to stratify on other variables, increasing the number of variables is not practical given the sample size proposed for this study.

Buprenorphine Induction

Participants will be offered a supervised buprenorphine induction at the Behavioral Pharmacology Research Unit (BPRU) on the Johns Hopkins Bayview Medical Center Campus. Participants will receive incremental doses of buprenorphine throughout the day, up to a maximum of 24mg of buprenorphine on the induction day. The induction protocol will be conducted as clinically indicated, based upon medical team recommendations. To increase comfort during the induction, the medical team may administer the concomitant medications described in Section 6 (Drugs/Substances/Devices). Participants may then be maintained on buprenorphine as an outpatient for up to 3 weeks, or until they connect to a community buprenorphine treatment program, whichever occurs first. Participants who are maintained on buprenorphine as an outpatient will receive blister packages of sublingual buprenorphine for outpatient administration and may receive up to 24mg/day (beginning the day after induction) during this period. The highest potential dose (24mg) is below what can be administered for use on a daily basis (32mg). Participants will be required to visit the BPRU on a weekly basis to exchange blister packages.

STUDY 1 AND STUDY 2

Usual Care Control Group

Participants assigned to the Usual Care Control group will receive the standard treatment services described above, including referrals for buprenorphine treatment. This group will determine the percentage of the study population that will enter and adhere to buprenorphine treatment under routine conditions.

Video DOT+ Group

Participants assigned to the Video DOT+ group will receive the standard treatment services described above and the full intervention being evaluated in this study for 24 weeks.

Incentive for linkage to buprenorphine treatment. Participants will be able to earn $70 for participating in the supervised buprenorphine induction and $70 for documenting that they have an active

prescription for buprenorphine from a community provider. We selected this incentive value because it has been highly effective in linking individuals to treatment at community programs in our ongoing controlled trial (R01AI117065). This incentive value is also similar to the incentive value in a prior study ($50) shown to be effective at linking out-of-treatment opioid users to treatment (Kidorf et al., 2009).

Video DOT+ for facilitating sublingual buprenorphine adherence. Participants will have the Video DOT+ application installed on their personal smartphones/tablets and will receive in-person training by study staff, during which they will be taught how to use the application. The participant will use Video DOT+ to record a video of the buprenorphine administration 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. Participants will be able to earn daily incentives for taking their buprenorphine dose and submitting a valid video recording of administration before midnight. In Study 1, participants will be able to earn $10 per day and in Study 2, participants will be able to earn $20 per day. If for some reason participants are temporarily unable to access the smartphone application, we will allow them to validate the buprenorphine administration process via research staff direct (in-person) observation.

Immediate feedback. If the participant takes his/her buprenorphine dose and submits a video within the allowed window (i.e., before midnight), the last screen of the application will be a congratulatory message and they will receive an in-app notification once their submission has been assessed that visualizes their earnings for the day. Patients will be able to visualize their adherence and earnings over time on a dashboard within the application.

Validation of video of sublingual buprenorphine administration. A research team member will review the videos to confirm the participant took his/her buprenorphine dose appropriately. 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 sample. 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.

Buprenorphine dosing reminders. During the initial in-person training, study staff will ask participants to select at what time they will take their buprenorphine dose each day. The selected time will be programed into the application by study staff. Then, the Video DOT+ platform will send an automatic SMS reminder to participants who have not yet submitted videos by their selected time of the day. In those instances, the following message will be displayed: “Please remember to take your buprenorphine dose.”

Reset in the incentive magnitude for a missed video or invalid buprenorphine administration. If a participant fails to submit a video or if a submitted video is deemed invalid, the participant will not receive the scheduled incentive amount that day and the daily incentive value will be decreased to $1 per day. Then, the amount earned per day will increase to the maximum incentive value (Study 1: $10; Study 2: $20) after the participant submits a valid video of buprenorphine administration every day for seven days.

Reloadable credit card. At the start of enrollment, each participant will be given a reloadable credit card. After the staff member verifies that participants correctly ingested their buprenorphine dose, 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.

Contesting the validation decision. Participants will be able to contest the validation decision of a staff monitor via the Video DOT+ application. 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. If a participant believes that they submitted a valid video but the staff monitor marked the video as invalid, the participant can contest the result. All contested videos will be viewed by an independent staff member that was not involved in the original video validation.

Intake and Outcome Assessments

Assessments will be conducted at intake, every 4 weeks during the 24-week intervention period, and at a 12-week follow-up period. Participants will be paid $50 for completing each of the assessments. These assessments may be collected using Qualtrics or REDCap.

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.

Treatment Facilitators and Barriers Questionnaire. This questionnaire will assess participants' self-reported barriers and facilitators to accessing opioid use disorder treatment.

Intake and Major Assessment Instruments

Urine toxicology testing. Urine samples will be collected under observation and tested for opioids and other drugs.

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

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.

The Beck Depression Inventory (BDI). The BDI is a 21-item questionnaire designed to screen for severity of depression.

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 24-week intervention period.

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

Study participation for Study 1 and Study 2 will include a 24-week intervention evaluation period and a 12-week follow-up period for a total study duration of 36 weeks. Outcome assessments will be conducted at intake, every 4 weeks during the 24-week intervention period, and at a 12-week follow-up period.

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

Participants in Study 1 and Study 2 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 either 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 Study 1 and Study 2, 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

Study 1

Applicants will be invited to participate in this study if they: a) are ≥ 18 years old, b) meet DSM-5 criteria for current opioid use disorder, c) provide an opioid-positive urine sample, d) report not receiving any type of drug abuse treatment in the past 30 days, and e) are interested in receiving buprenorphine treatment. Applicants will be excluded if they: a) have current suicidal/homicidal ideation, b) are pregnant or nursing, or c) are unwilling or unable to use a smartphone.

Study 2

Applicants will be invited to participate in this study if they: a) are ≥ 18 years old, b) meet DSM-5 criteria for current opioid use disorder, c) provide an opioid-positive urine sample, d) report not receiving any type of drug abuse treatment in the past 30 days, and e) are interested in receiving buprenorphine treatment. Applicants will be excluded if they: a) have current suicidal/homicidal ideation, b) are pregnant or nursing, c) are unwilling or unable to use a smartphone, d) do not have access to a smartphone that can submit videos using the study smartphone app.

6. Drugs/ Substances/ Devices

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

Study 1

N/A

Study 2

Buprenorphine: Buprenorphine is FDA-approved for the treatment of opioid use disorder and it will be used according to that indication in this study. Participants will be offered a supervised buprenorphine induction as a part of this study. The buprenorphine induction will be open label and will follow standard clinical practice procedures. Participants will be inducted onto and maintained on buprenorphine for up to 3 weeks, or until they connect to a community buprenorphine treatment program, whichever occurs first. Participants who are maintained on buprenorphine as an outpatient will receive blister packages of sublingual buprenorphine for outpatient administration and may receive up to 24mg/day (beginning the day

after induction) during this period. The highest potential dose (24mg) is below what can be administered for use on a daily basis (32mg).

Concomitant Medications: Consistent with standard clinical practice treatment, some medications will be available to participants as needed during the supervised buprenorphine induction and at discharge from the induction. The following medications may be offered during the supervised buprenorphine induction: acetaminophen (500mg, 1-2 tablets every 6 hours as needed for pain), clonidine (0.1-0.2mg every 4 hours as needed), dicyclomine (10mg every 6 hours as needed for abdominal cramps), hydroxyzine (25mg, 1-2 tablets every 8 hours as needed for anxiety), ibuprofen (600mg every 6 hours as needed for myalgia), loperamide (2mg, 1-2 tablets every 4 hours as needed for diarrhea), methocarbamol (750mg, 1 tablet every 4 hours as needed for myalgia), and ondansetron (8mg every 6 hours as needed for nausea/vomiting). The following medications may be offered at discharge from the induction: clonidine (up to four 0.1mg tablets, 1 tablet to be taken every 6 hours as needed), hydroxyzine (25mg, 1-2 tablets as needed for anxiety), ibuprofen (up to four 600mg tablets, 1 tablet to be taken every 6 hours as needed for myalgia), ondansetron (8mg, 1 tablet as needed for nausea/vomiting), and trazodone (100mg, 1 tablet as needed for sleep). These concomitant medications will be available to reduce withdrawal symptom severity during the buprenorphine induction and at time of discharge from the supervised induction.

Concomitant medications will be administered as needed per clinical recommendation and overseen by the study clinician co-investigator(s) who are conducting the supervised buprenorphine induction. Not all medications will be dispensed. The provision of these additional supportive medications may be necessary to prevent treatment attrition.

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

Separate statistical analyses will be conducted for Study 1 and Study 2. We will compare the Usual Care Control and Video DOT+ groups on primary and secondary outcome measures. To preserve statistical power and minimize the likelihood of endorsing false conclusions, we identified one primary outcome measure and several secondary outcome measures, each associated with a *Specific Aim*.

a. Primary outcome variable.

Study 1 and Study 2 have the same primary outcome:

Specific aim. Assess efficacy of Video DOT+ in promoting buprenorphine treatment adherence as assessed by urine drug screens. We will assess the percentage of participants with buprenorphine-positive urine samples at the 4-week assessments during the 24-week intervention evaluation period (Yes/No at each assessment). *Hypothesis:* We expect that Video DOT+ participants will have more buprenorphine-positive urine samples during the 24-week intervention relative to the Usual Care Control participants.

b. Secondary outcome variables.

Study 1 and Study 2 have the same secondary outcomes:

Specific aim. Assess efficacy of Video DOT+ in promoting self-reported buprenorphine treatment

adherence. We will assess the number of days participants report taking their daily buprenorphine dose during the 30 days prior to each of the 4-week assessments during the 24-week intervention evaluation period (based on TLFB). *Hypothesis:* We expect that Video DOT+ participants will have more days of taking their buprenorphine dose as prescribed during the 24-week intervention relative to the Usual Care Control participants.

Specific aim. Assess efficacy of Video DOT+ in promoting linkage to buprenorphine treatment. We will assess the percentage of participants who link to buprenorphine treatment during the 24-week intervention evaluation period (Yes/No, based on self-report and medical records). *Hypothesis:* We expect that more Video DOT+ participants will link to buprenorphine treatment during the 24-week intervention relative to the Usual Care Control participants.

Specific aim. Assess efficacy of Video DOT+ in promoting retention in buprenorphine treatment. We will assess the total number of days participants are in buprenorphine treatment from the time of randomization until the last day of medication during the 24-week intervention evaluation period (based on self-report and medical records). *Hypothesis:* We expect that Video DOT+ participants will be retained in buprenorphine treatment for more days during the 24-week intervention relative to the Usual Care Control participants.

Specific aim. Assess efficacy of Video DOT+ in reducing opioid use. We will assess the percentage of participants with opioid-positive urine samples (excluding buprenorphine and methadone if self-report and medical records confirm that the participant is enrolled in buprenorphine or methadone treatment) at the 4-week assessments during the 24-week intervention evaluation period (Yes/No at each assessment). *Hypothesis:* We expect that Video DOT+ participants will have fewer opioid-positive urine samples during the 24-week intervention relative to the Usual Care Control participants.

Specific aim. Assess efficacy of Video DOT+ in reducing risk of opioid overdose. We will assess the rates at which participants report engaging in overdose risk behaviors at the 4-week assessments during the 24-week intervention evaluation period (based on total scores from the opioid overdose risk assessment). *Hypothesis:* We expect that Video DOT+ participants will engage in lower rates of opioid overdose risk behaviors during the 24-week intervention relative to Usual Care Control.

Specific aim. Assess efficacy of Video DOT+ in promoting buprenorphine treatment engagement and adherence, and reducing opioid use and risk of opioid overdose after the intervention ends. We will assess these outcomes at the 12-week follow-up after the intervention ends. *Hypothesis:* We expect that Video DOT+ participants will have better buprenorphine treatment outcomes relative to the Usual Care Control participants after the intervention ends.

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

Statistical Analyses

Separate statistical analyses will be conducted for Study 1 and Study 2, using the procedures described below.

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 24 weeks of 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). Tests will be two-sided and, because we have one primary outcome, alpha will be set at 0.05.

Primary outcome analyses. The primary outcome measure will be the percentage of participants with buprenorphine-positive urine samples at the 4-week assessments during the 24-week intervention

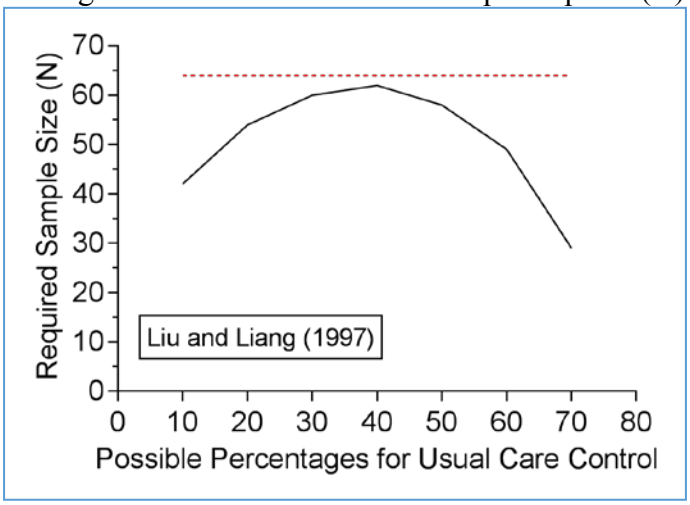
evaluation period (Y/N at each assessment). We will fit a longitudinal logistic regression model logit (Y_{ij}) = $\beta_0 + \beta_1 tx + \beta_{2\text{-}3} x_{2\text{-}3} + \varepsilon_{ij}$, where Y_{ij} is evidence of buprenorphine adherence for the ith person at the jth timepoint (6 visits over 24 weeks), β_1 is the covariate of interest representing the expected increase in log odds of evidence of buprenorphine adherence as a function of assignment to the treatment group, and $\beta_{2\text{-}3}$ are the coefficients for the 2 randomization covariates. We will fit models with time and time by treatment interactions secondarily. These models will allow us to look at change over time in buprenorphine adherence in each study arm.

Secondary outcome analyses. We will fit longitudinal logistic regression models, similar to those described for the primary outcome measure, for self-reported buprenorphine treatment adherence, opioid use, and opioid overdose risk behaviors. Linkage to buprenorphine treatment and post-intervention effects will be assessed by logistic regression. Retention in buprenorphine treatment during the 24 weeks of the intervention period will be analyzed with 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). If the data are missing not at random, then we will fit pattern mixture models as described by Hedeker and Gibbons (1997).

Power Analyses

We used Liu and Liang (1997) to determine the number of participants required to detect a difference between groups with 80% power. The adjacent figure shows the total number of participants (N) that would be required to detect a difference of 25% between the Usual Care Control and Video DOT+ groups with the six assessments during the 24-week intervention period. The figure shows different percentages for the Usual Care Control group because that value affects the sample size required. Twenty-five percent is smaller than the increase produced in our prior study of incentives to promote daily adherence to oral naltrexone in opioid-dependent adults (Dunn et al., 2013). It is also smaller than the incentive effects in promoting drug abstinence, medication adherence, and other health behaviors as shown in three different meta-analyses (Petry et al., 2012; Prendergast et al. 2006; Lussier et al., 2006). Based on this, we need to randomize 64 participants (horizontal dashed line) to detect a difference between the Usual Care Control and the Video DOT+ groups on the primary outcome measure.



d. Early stopping rules.

The PI (A. Holtyn, PhD) and two co-investigators at Johns Hopkins University School of Medicine (K. Silverman, PhD; M. Fingerhood, MD) will provide data and safety monitoring of the proposed studies. 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 studies. At least one investigator will review each adverse event as it occurs. All investigators will review a summary of adverse events at the time of the annual reports to the IRB. 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 who are reviewing the adverse events in the studies. We will ask the investigators to recommend that the trial be stopped if a review of the adverse events suggests to any of the investigators that the number of related adverse events is unacceptably high. The investigators 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 uptake of and adherence to an FDA-approved medication (sublingual buprenorphine) for opioid use disorder. Buprenorphine has very few contraindications, but is not recommended for use with the opioid antagonist naltrexone or other opioid agonists. It is rated in pregnancy category C, therefore all women who are pregnant or nursing will be excluded from study participation. Buprenorphine's side effects are minimal and rare (hyperhidrosis 14%, abdominal pain 11%, constipation 12%, nausea 15%, headache 37%, insomnia 14%) and overlap significantly with known opioid withdrawal symptoms (e.g., abdominal pain, nausea). It is expected that participants may experience some level of opioid withdrawal. Symptoms of opioid withdrawal include nausea, diarrhea or stomach cramping, muscle aches and pains, yawning, sweating, pupil dilation, minor increases in blood pressure, and runny nose/tearing eyes. To help to alleviate these symptoms, the study clinician co-investigator(s) who are conducting the supervised buprenorphine induction may offer participants the concomitant medications listed in Section 6.

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 proposed 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 Video DOT+ application that will be used to provide monitoring of adherence and incentives has features that promote compliance with HIPAA.

Buprenorphine has been approved for use by the FDA and our study will conform to the FDA guidelines. Participants will be referred to our collaborating primary care providers to receive buprenorphine treatment. In addition, the exclusion criteria were selected to minimize the risks associated with buprenorphine treatment. If a participant becomes pregnant while in the study, she will be referred for

medical treatment in an appropriate medical clinic (e.g., a specialty clinic for pregnant women who abuse drugs).

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. The legal risks are limited because we collect only general information about participant activities, legal and illegal. 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.

All participants will be offered referrals to buprenorphine treatment, which could help to reduce their opioid use and risk of opioid overdose death. Participants in the experimental group will receive access to our customized mobile-health application that could facilitate adherence to 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 untreated 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. Payment for participating in Study 1 and Study 2 are described in detail below.

Study 1

Incentives for taking and completing a computer-based education program. Participants will be invited to participate in a computer-based training program. Participants may earn up to $10 for completing the Knowledge Tests and may earn up to about $33 for participating in the computer-based training.

Incentives for completing routine assessments for both groups. Outcome assessments will be conducted at intake, every 4 weeks during the 24-week intervention period, and at a 12-week follow-up period. Participants will be paid $50 for completing each of the assessments.

Participant referral fees. As in our previous studies, 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 appointment 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 making the referral.

Incentive for linkage to buprenorphine treatment. Prior to earning incentives for buprenorphine treatment adherence, participants in the Video DOT+ group will be able to earn $70 for documenting that they have an active prescription for buprenorphine.

Video DOT+ for facilitating sublingual buprenorphine adherence. Participants in the Video DOT+ 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 24-week study period, participants in the Video DOT+ group could earn $1,680 for adhering to buprenorphine treatment.

Study 2

Incentives for taking and completing a computer-based education program. Participants will be invited to participate in a computer-based training program. Participants can earn $30 for completing the computer-based training.

Incentives for completing routine assessments for both groups. Outcome assessments will be conducted at intake, every 4 weeks during the 24-week intervention period, and at a 12-week follow-up period. Participants will be paid $50 for completing each of the assessments.

Participant referral fees. As in our previous studies, 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 appointment 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 making the referral.

Incentive for linkage to buprenorphine treatment. Participants can earn $70 for participating in the supervised buprenorphine induction and $70 if they obtain a buprenorphine prescription from a community program.

Video DOT+ for facilitating sublingual buprenorphine adherence. Participants in the Video DOT+ group will be able to earn $20 per day for taking their buprenorphine dose and submitting a valid video recording of administration before midnight. Over the entire 24-week study period, participants in the Video DOT+ group could earn $3,360 for adhering to buprenorphine treatment.

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.