Mobile Medication Adherence Platform for Buprenorphine-Naloxone (MAP4BUP) During Treatment of Opioid Use Disorder: Phase I MAP4BUP Study

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STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH) funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Washington State University Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Mobile Medication Adherence Platform for Buprenorphine-Naloxone (MAP4BUP) During Treatment of Opioid Use Disorder: Phase I MAP4BUP Study

Opioid misuse and abuse affect the health and the well-being of millions of Americans. On average, 130 Americans die every day from an opioid overdose in 2017, according to CDC data. Opioid agonist therapy, such as buprenorphine-naloxone (BUP/NAL), can reduce opioid overdose deaths, decrease opioid misuse, and improve quality of life. Unfortunately, poor medication adherence is a barrier to long term efficacy of this therapy. To assess compliance, we plan to substantially monitor adherence to inexpensive oral buprenorphine-naloxone with Pillsy, a Bluetooth-connected smart pill cap and pharmacy software platform. The technology platform was developed over the past three years using principles of behavioral science, modern design, and highly scalable wireless and mobile technologies.

We will build out and adapt our current Pillsy platform, then test it in a small-scale trial to assess feasibility, usability, and effectiveness. We propose, in Phase I, to conduct a study involving 30 subjects selected randomly among patients prescribed (BUP/NAL) for to opioid misuse to better understand their willingness to use Pillsy and identify areas of problematic compliance. Using the data obtained in Phase I and after meeting with the FDA, we will further refine the platform in Phase II. This will be a collaborative study between Washington State University, Pillsy and the clinical site Ideal Option.

The purpose of this randomized, controlled trial in Phase I is to determine whether the Pillsy intervention can improve adherence to BUP/NAL compared to services as usual (SAU). The primary endpoint will be adherence to MAT as determined through the medication possession ratio at the end of the trial. The hypothesis is that the Pillsy intervention will significantly improve adherence to medication-assisted treatment (MAT) compared with SAU.

Study Design

Narrative Study Description

The research coordinator (RC) will provide the Pillsy device and orient the participants in the use of the Pillsy app. Participants in both groups will also have full access to services normally provided by the prescribing office including blood testing and counseling services (i.e. SAU). All participants will receive the Pillsy cap (to track and time stamp pill bottle openings, closings, etc). The participants assigned to the Pillsy intervention, will also have a mobile phone reminder application. If the participant does not take their medicine at the correct time, a light on the smart pill cap will flash. If the bottle is not opened within 20 minutes, the Pillsy app sends an SMS text message to participant's phone. If the bottle is not opened within 60 minutes, the participant then receives an automated phone call. The participant may also receive brief motivational phrases or craving surveys that can be tailored to participant needs and preferences.

Pillsy also includes a Pillsy Helpers feature in which the participant can name friends and family members who will also receive a text message notification one hour after a missed dose. If the participant is struggling, his or her social support can attempt to contact the participant. The MAT prescriber may also be a Pillsy Helper. The MAT prescriber may be contacted when the participant has missed a dose if they are designated as a helper, giving the prescriber the opportunity to intervene. Providers may decide to call the imminently nonadherent participant to provide a brief, timely therapeutic intervention for which the provider can bill using the 99091 CPT code.

All data handling will conform to appropriate regulatory guidelines (HIPAA) and will be collected in such a way that it can be integrated into existing EMRs. The long-term goal is for this information to be available to one's prescriber and provider in real-time for monitoring.

Participants in SAU arm will receive a prescription for BUP/NAL tablets/sublingual films and any services normally provided by the prescribing office. Participants in SAU arm will receive an inactive Pillsy smart cap that will track openings but will not provide reminders or any other messaging.

Primary Endpoint

Adherence to BUP/NAL treatment assessed by medication possession ratio (pills taken/pills prescribed)

Secondary Endpoints

1. Participant engagement quantified through office visits and assessed via real time surveys
2. Usability and reminder feedback assessed through questionnaires
3. Participant self-report of adherence
4. Use of non-prescribed opioids

2. INTRODUCTION

2.1 STUDY RATIONALE

The United States is in the midst of an opioid epidemic. According to the Substance Abuse and Mental Health Services Administration (SAMHSA) 2016 estimates, 11.5 million people misuse their prescription opioids, 948,000 use heroin, and 2.1 million people meet diagnostic criteria for opioid use disorder (OUD). A documented 42,249 Americans died of opioid overdose in 2016, which is an average of 116 preventable deaths per day [1]. Opioid Agonist Therapy (OAT), such as buprenorphine/naloxone (BUP/NAL), can reduce opioid overdose deaths by at least 70%, decrease opioid misuse, and improve quality of life. Because of its proven efficacy, the National Institute on Drug Abuse (NIDA), the Substance Abuse and Mental Health Services Administration (SAMHSA), the American Society of Addiction Medicine (ASAM), and the American Academy of Addiction Psychiatry (AAAP) endorse the use of medication-assisted therapy in the treatment of OUD.

Poor medication adherence is one of the main barriers to long term efficacy of opioid agonist therapy (OAT). A year-long outpatient study of OAT in 225 treatment-seeking patients with opioid use disorder (OUD) [2] showed that treatment retention fell to under 50% by 12 weeks and only 25% of patients remained at one year. Novel depot formulations of efficacious drugs can improve adherence. However, in Ling's study, depot opioid agonists provided only a modest increase in adherence (13.8% compared to oral buprenorphine/naloxone BUP/NAL) despite the significant (565%) price increase compared to the generic drug.

To improve performance, we plan to substantially increase adherence to inexpensive oral BUP/NAL with Pillsy, a smart technology platform developed over the past three years using principles of behavioral science, modern design, and highly scalable wireless and mobile technologies. Pillsy acts like a digital medication coach, providing education and reminders using a mobile app, text messages, and automated phone calls. The platform is built around a Bluetooth-based smart pill bottle cap that automatically tracks doses, timing and sends intelligent reminders to create a unique feedback loop, which allows us to constantly optimize our incentive/reminder messages to meet user needs and increase adherence. Since its recent launch, the company has already over 1,000 clients. Pillsy can substantially increase adherence to OAT and decrease opioid-related morbidity and mortality. Since Pillsy only nominally increases the cost of oral BUP/NAL treatment and providers can bill for monitoring time (CPT code 99091), it is an attractive solution to patients, providers, and payers. However, there are few if any studies available that have systematically investigated this technology's impact on medication adherence in this population.

We will conduct a Phase I study involving 30 subjects selected randomly among patients prescribed (BUP/NAL) for to opioid misuse, to better understand their willingness to use Pillsy and identify areas of resistance.

3. OBJECTIVES AND ENDPOINTS.

1- Compare Pillsy delivered BUP/NAL adherence to conventional BUP/NAL therapy.
2- Evaluate non-prescribed opioid use and therapy retention between groups.
3- Understand participants' willingness to use Pillsy and identify areas of resistance.

4. STUDY POPULATION

Recruitment

Goal: Enroll 30 eligible adults: 15 control group services as usual (SAU); 15 Pillsy group (PLY).

4.1 INCLUSION CRITERIA

Participants will be **eligible for inclusion** if they meet all the following criteria:

• Subject can and has signed an Institutional Review Board (IRB) approved informed consent form (ICF).

• Age ≥18 and up.

• Self-reported that they have been diagnosed with an OUD and are in receipt of BUP/NAL for their OUD.

• Owns a working smartphone.

• Has been prescribed BUP/NAL and is a current patient at Ideal Option.

• Able to read and speak English.

• Can identify one study partner/caregiver who agrees to participate (i.e., as described above, this "helper" can be a friend of family member, a provider, etc.).

4.2 EXCLUSION CRITERIA

Participants will be **excluded** if they:

• Have known hypersensitivity or allergy to BUP and/or NAL.

• Are pregnant or lactating women, or women of childbearing potential who are not using any form of birth control.

• Require opioids for the treatment of chronic, non-acute pain.

• Are unable to provide voluntary informed consent.

• Have pending legal issues that could adversely affect the participant's freedom to participate.

• Cannot read or speak English.

4.3 SCREENING FAILURES

Participants who do not meet one or more criteria required for participation in the study during the screening procedures, are considered screen failures. These participants will still be assigned a screening number, but we will only collect the minimal information including demography and the reason for screen failure.

Participants who did not meet the criteria to participate in this trial because of pending legal issues may be rescreened if their legal situation is resolved. All keys study personnel will be trained according to the Collaborative Institutional Training Initiative (CITI) and receive protocol training before starting any recruitment.

4.4 STRATEGY FOR RECRUTEMENT

Study participants will be recruited from Ideal Option outpatient treatment centers (a drug addiction treatment center) in Spokane WA, that routinely prescribes OAT. In general, patients will have received referrals from emergency departments, hospital discharge staff for opioid overdose, or law enforcement. Patients may be given up to 30 days of BUP/NAL prior to this initial referral visit. At least 30 patients between 18 and 60 years of age will be randomized to receive PLY or SAU.

Potential subjects will be identified by the outpatient clinicians, nurse managers, medical assistants and referred to the study coordinator. Patients will also see flyers in the waiting room and can self-identify and request an appointment with the coordinator. The study coordinator will assess subject eligibility and obtain informed consent. The latest version of an approved informed consent form by Washington State University IRB will be used.

Subject Characteristics and Data Collection Procedure

Only subjects who qualify for BUP/NAL treatment for OAT will be approached. Subject characteristics that will be documented include age; sex; race; employment; history of psychiatric illness; opioid of choice; years of opioid use; history of overdose; other substance use (tobacco, alcohol, cocaine, or benzodiazepines); previous addiction treatment, history of opioid medication assisted therapy. With subject permission, we will collect pertinent medical history and retrospective clinical laboratory results from the last 30 days from the patient's referring medical team and going forward during their time while enrolled in the study. This data will be collected automatically at Ideal Option and will be downloaded and connected to the research data collected. REDCap (Research Electronic Data Capture) is a data platform that ensures subject privacy and data security. This is the platform that will be used to enter research data that is collected.

Screening and Consenting

As described above the medical assistant or other clinic staff will ask whether patients would like to participate in a clinical research trial. If the patient answers yes, the patient will be

referred for follow-up with a RC. The RC will contact the patient and assess the participant's appropriateness for the study in a screening interview. The RC will explain the clinical study in detail and will obtain informed consent. All potential participants will be given plenty of time to read the consent form. They will have time to ask questions and their questions will be answered to their satisfaction by the study RC, the Principal Investigator, or the Co-investigator.

After ensuring the potential subject has understood his/her role in the study, then he/she will be requested to sign and date the Institutional Review Board (IRB) approved Informed Consent Form (ICF), after which a screening number will be assigned. The consenting process should be conducted at the clinic's site and in a consistent manner for every potential participant.

The consent process for this study will include a video demonstration of handling of the Pillsy cap and how the Pillsy system works to aid in the subject's and study subject partner's understanding of this technology. If the participant meets inclusion/exclusion criteria, he/she will be randomly assigned to one of the two arms of the study.

Method of Assigning Subjects to Study Arms: Randomization

Subjects will be centrally registered and randomly assigned 1:1 to the PLY or SAU group. We will use permuted block randomization and stratify on 1) age, 2) sex, and 3) severity of OUD (mild, moderate, severe) based on DSM-5 criteria for diagnosis of opioid use disorder (Mild: 2-3 symptoms. Moderate: 4-5 symptoms. Severe: 6 or more symptoms).

5. STUDY ASSESSMENT AND PROCEDURES

This will be a collaborative study between Washington State University, Pillsy*, Inc*, and the clinical site Ideal Option (opioid and other substance use disorders treatment center).The overarching goal is to evaluate if the use of the Pillsy system will improve treatment adherence. The study coordinator will work closely with the medical assistant from the clinical site, conducting a scripted screening, by phone or in person, documenting substance use, addiction treatment history, medical and psychiatric history, medications and availability of social support. Only patients recently initiating BUP/NAL treatment will be approached to assess their eligibility for the study.

The clinical site will be responsible for the BUP/NAL prescription and treatment plan. Participants will receive their prescription medications through their normal pharmacy. Pillsy, though the RC will provide the Pillsy system which includes the smart bottle cap (Pillsy Cap), the mobile application (Pillsy App), and the SMS texting platform with a brief training on how to utilize the system. Pillsy Cap tracks when the bottle is opened or closed. Figure 1 (below) is a draft CONSORT diagram of participant flow through the study protocol.

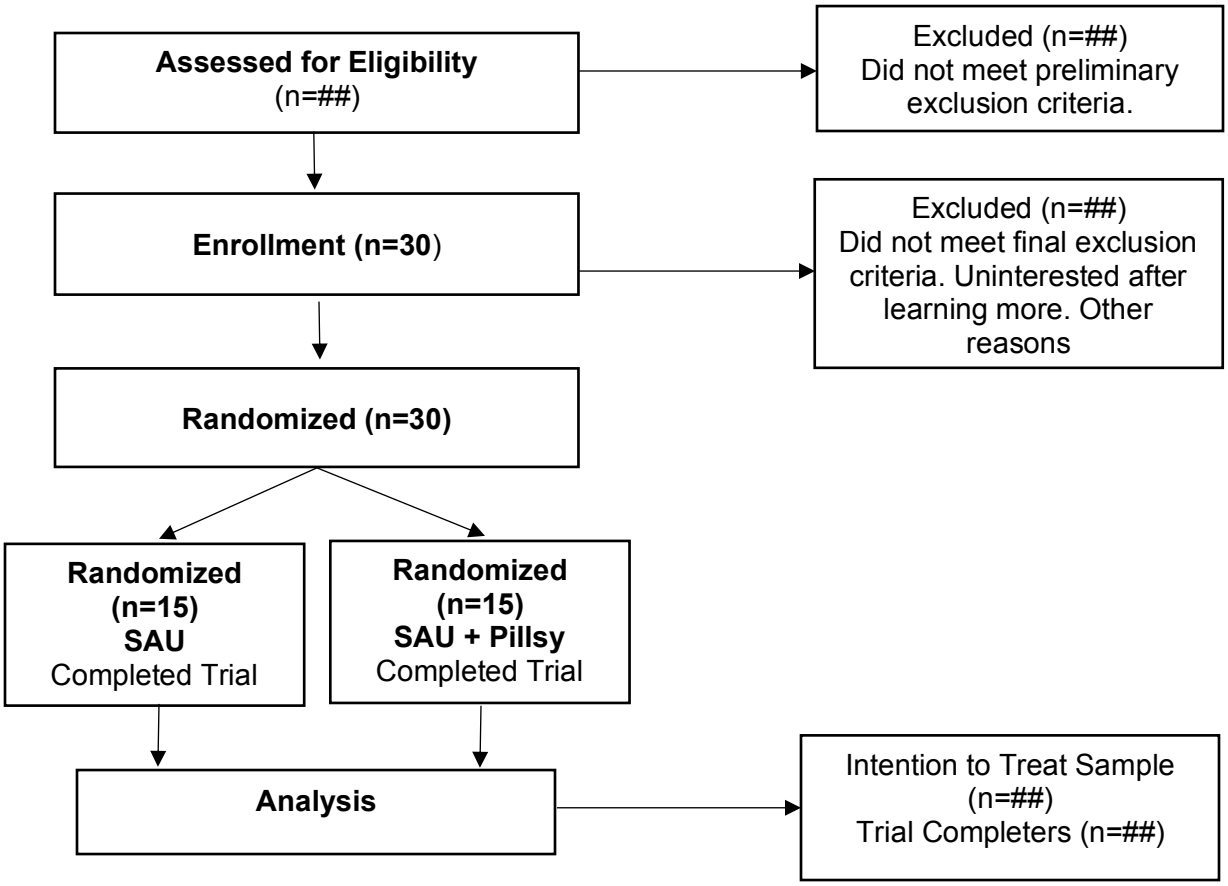

Figure 1. Overview of study Procedures and CONSORT Diagram for Participant Flow.

Intervention

Participants will be directed to preferably bring their pill bottle and medication in for their baseline visits. While it is possible for us to orient participants to the intervention before they have received their prescription or after even if they don't have the bottle, this lessens the training experience substantially and could decrease the utility of the cap and efficacy of the system. The RC will orient the participants in the use of the Pillsy app. The participants in both groups will also have full access to the services normally provided by the prescribing office including blood testing and counseling services. The Pillsy intervention consists of a Smart Pill Cap and a mobile phone application. All participants will receive the Pillsy cap (to track pill bottle openings), but only the active group will receive the Pillsy app with messaging and reminders. Please note this when reading the below, since the below is what the PLY group will receive, but not the SAU group.

If the patient does not take their medicine at the correct time, a light on the smart pill cap begins to flash. If the bottle is not opened within 20 minutes, the Pillsy application sends an SMS text reminder to the patient's phone. If the bottle is not opened within 60 minutes, the patient receives an automated phone call. The patient may also receive brief motivational phrases that can be tailored to patient needs and preferences. Pillsy also includes a "Pillsy Helpers" feature in which the patient can name friends and family members who will also receive a text message notification one hour after a missed dose. Thus, if the patient is struggling, his or her support system can attempt to contact the patient and offer motivation. Importantly, as proposed in the clinical trials detailed in this application, the MAT prescriber can also be a Pillsy Helper.

All data handling will conform to meet HIPAA requirements, including administrative, physical, and technical safeguards. Data will be encrypted in storage and in rest in REDCap with regularly schedule data deposits from Pillsy into REDCap.

Participants in the service as usual (SAU) arm will receive a prescription for BUP/NAL tablets/sublingual films and any services normally provided by the prescribing office. Participants in the SAU arm will receive an "inactive" Pillsy smart cap that will track openings but will not provide reminders or any other messaging.

Screening Visit

The RC will screen the patient to assess the participant's appropriateness for the study. If the prospective participant meets inclusion/exclusion criteria, the RC will explain the clinical study in detail and informed consent will be obtained. If eligible, the participant will be trained on how to use the Pillsy system (cap and app) if randomized to PLY group. No training will be needed for the SAU. While their cap will be activated to capture open and close times, that is the only data that will be collected on the cap. and randomized to one of the study groups.

Week 1 Assessment

Study participants will return to office as frequently as the prescriber sees fit in the course of addiction treatment. At 1 week +/- 1 day, the RC will count BUP/NAL tablets/sublingual films and compare to the prescribed number of pills for that period. Participants will complete questionnaires.

Week 6 Assessment

Study participants will return to office as frequently as the prescriber sees fit in the course of addiction treatment. At 6 weeks +/- 2 days, the RC will count BUP/NAL tablets/sublingual films and compare to the prescribed number of pills for that period. Participants will complete questionnaires.

Week 12 Assessment

Study participants will return to office as frequently as the prescriber sees fit in the course of addiction treatment. At 12 weeks +/- 3 days, or RC will count BUP/NAL tablets/sublingual films

and compare to the prescribed number of pills for that period. Participants will complete questionnaires.

Ongoing Assessments

Pillsy will continuously collect data on pill bottle openings, missed doses, text messages sent, automated phone calls made, etc. If there is a loss of contact, or the participant stops their engagement with the study, the RC will attempt to contact the participant (up to two (2) attempts) with an exit interview, by phone. If no answer, no message will be left. The coordinator will attempt to call again 2-3 business days later for a final attempt to describe reasons for withdrawal from the study.

Table 1. Schedule and Types of Assessments Performed: MAP4BUP Phase I.

	Screening/Baseline	**Week 1**	**Week 6**	**Week 12**
Informed consent	X			
Verify inclusion/exclusion criteria are met	X			
AUDIT	X			
Demographics	X			
Fagerström	X			
Addiction Severity Index – Lite	X			
Timeline Follow-Back of medication use and drug and alcohol use	X	X	X	X
*DSM-5 OUD Checklist**	X			
Pill/film count and self-report of prescriptions	X	X	X	X
Barratt Impulsiveness Scale (BIS) 8	X	X	X	X
Opioid Craving Scale	X	X	X	X
Healthy Days Core Module (CDC HRQOL-4)	X	X	X	X
Sleep Related Impairment	X	X	X	X
Sleep Disturbance	X	X	X	X
Pain Intensity	X	X	X	X
Pain Interference	X	X	X	X
*Standard counseling, prescribing, dose changes***	As needed, determined by prescribing provider and medical team.			
Pillsy System Usability Questionnaire		X		X
Adverse event monitoring	X	X	X	X
Reason for quitting	Administered once, triggered by predefined non-adherence to the treatment.			

*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Opioid Use Disorder (OUD) research checklist
**To be guided by the discretion and standard practices of the prescriber.

Laboratory Assessment

Ideal Option performs comprehensive histories and physical examinations as well as collecting samples for required laboratory tests. Ideal Option has private bathrooms and locations that are commonly used for collection of urine samples. Ideal Option collects and processes urine

samples as part of their day-to-day operations. Through a signed data use agreement, all of this data will be made available to Washington State University for combination with research data at the end of the study.

5.1 Assessment of Safety

Ideal Option has robust Diversion Control and Patient Safety policies in place to ensure that patients are taking their medication as prescribed. Providers are supplied with a variety of clinical tools to uphold patient safety while not disturbing the trust in the patient-provider relationship. Further, Ideal Option has a robust Nurse Care Team which provides support and continuing education to all its providers.

5.1.1 Adverse events (AE)

According to the code of federal regulation title 21 of the Food and Drug Administration (FDA), an Adverse event refers to any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related or not.

All AEs, whether volunteered, elicited, or noted on physical examination, will be recorded throughout the study (i.e., from signing of the ICF until completion).

All AEs will be collected in and recorded in REDCap.

Classification of an Adverse Event

Severity of event

Each AE will be assigned a category by the Investigator as follows:

Mild: An AE that is easily tolerated by the subject, requires minimal or no treatment and does not interfere with the participant's daily activities.

Moderate: An AE that results in a low level of inconvenience or concern by therapeutic measures. Moderate events may cause some interference with functioning. Intervention may be needed.

Severe: An AE that prevents normal everyday activities and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. If there is a change in severity of an AE, it must be recorded as a separate event.

Relationship of Event

The Investigator will make every effort to assess the relationship of the AE, if any, to the study intervention. The Investigator should use knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine

whether an AE is related to the study treatment. Causality should be assessed using the categories presented below:

Related: The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. “Reasonable possibility” means that there is evidence to suggest a causal relationship between the study intervention and the AE.

Not Related: There is no reasonable possibility that the administration of the study intervention caused the event. There is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Action Taken

The investigator will describe the action taken in the appropriate section in REDCap, as follows:

- None
- Study procedure or medication stopped
- Study medication temporarily interrupted
- Concomitant medication
- Other, specify

Reporting Adverse Events

All adverse events should be documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant CRF pages. The following information should be documented for each AE:

- Description of the symptom event
- Classification of ‘’serious’’ or ‘’not serious’’
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of the event (unknown, recovered, not yet recovered, recovered with sequelae, death)

5.1.2 Adverse Events or Serious Adverse Events (AEs or SAEs)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization, prolongation of existing hospitalization, a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, though life-threatening or require hospitalization may be considered serious when, based upon appropriate medical judgment, they jeopardize the ’s life or require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical

events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. SAEs are life-threatening adverse events or life-threatening suspected adverse reactions. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An SAE form must be completed as thoroughly as possible with all available details of the event, signed by the Investigator (or appropriately qualified designee), and emailed to Dr. Sara Parent (sara.parent@wsu.edu), the medical monitor within 24 hours of first becoming aware of the event. Also, SAEs will be reported to Jeff LeBrun at jeff@pillsy.com of Pillsy, Inc and, the Washington State University IRB within 24 hours of first becoming aware of the event.

Reporting of Serious Adverse Events

Any serious adverse event experienced by a participant after randomization will be reported (within 24 hours of the Investigator becoming aware of the event) to Pillsy, Inc and, the Washington State University IRB, whether considered study intervention related or not.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by Pillsy, Inc and should be provided as soon as possible.

5.1.3 Other Safety Considerations

Data and Safety Monitoring Plan

Patients receiving opioid use disorder treatment will receive care as usual. Half of the participants will also receive the Pillsy intervention. The Pillsy intervention is a smart pill cap, mobile application with text and other messaging capability. We will keep enrollment to the lowest numbers possible that still allow sufficient power to answer research questions.

The risk to patients from the digital intervention is negligible. All data is collected in a HIPAA-complaint manner. Private identifiable information will be encrypted and kept secure.

Study visits will be conducted in a manner to protect participant privacy. The consent process, administration of questionnaires, etc. will occur in a private area. To reduce the risk of unauthorized disclosure of confidential information all personal identifiers will be kept separate from participant files and a study specific research identification number (key) will be assigned to each participant. Data will be collected, entered and accessed by study personnel trained in issues of confidentiality related to human subject protection. The key will be kept separate and not in the same enclave component of the network. Data will be entered into a password-protected database that is encrypted and firewalled. The consent form states that all information provided by the participant will be kept private except in the case that this would immediately put the participant or someone else in danger. In that case the Investigator would release information to keep the participant or another person safe. The consent states that if

Investigator learn about abuse to a child or an elder, that information must be reported to the proper authorities.

As in all research of this nature, there is the possibility of discomfort or embarrassment related to questions dealing with opioid use and social stigma for engaging in these types of behaviors. Participants will be informed that they have the right to refuse to answer any question. If participants find any aspects of their involvement in the research study particularly distressing, they will be encouraged to discontinue participation.

The risk to patients from the digital intervention is negligible. The potential benefit of the intervention is improved adherence to opioid agonist/antagonist therapy specifically and medication-assisted therapy in general. This benefit may occur in the patients participating in the trial, and the data collected may extent to future users of the technology.

Medication-assisted therapy is our best hope for combatting the opioid crisis in the near term. Adherence to opioid agonist/antagonist therapy is critical. Pillsy is a technology that can improve adherence to opioid agonist/antagonist therapy and thereby could help curb the current opioid crisis. Since Pillsy is a digital intervention, no physical adverse events are anticipated. However, participants will be undergoing medication-assisted therapy during their clinical care. Patients will be monitored by their respective provider for drug-related adverse events as they would during clinical care. If a provider decides to stop BUP/NAL for any reason (including, but not limited to, a treatment-related adverse event), the participant will also be discontinued from the Pillsy intervention. RCs will attempt to gather subjective feedback about the Pillsy intervention from discontinued participants.

6. STATISTICAL CONSIDERATIONS

6.1 Sample Size

For this Phase I study we are planning to randomize 15% of the targeted N (200) of a full-scale Phase II study, resulting in a total of 30 subjects, 15 per arm. More than anything, this is designed as a “proof-of-concept” study to demonstrate that Pillsy can produce some amount of adherence improvement and is both feasible and useful to patients so we can plan a larger version of this study in Phase II.

Sample size calculations – Our choice of sample size for the Phase II trial (n=200) was based on power calculations for detecting a 20% increase in our primary outcome of increasing adherence to BUP/NAL while also considering treatment retention assessed by office visits and assuming a 25% attrition rate in our cohort. This translates to an OR of 2.4, which we would have 99% power to find based on 3 longitudinal assessments and assuming we are examining the between effect only. Using a more conservative estimate of a 10% change, we would still have 90% power to detect this effect (OR of 1.6).

6.2 Statistical Analyses

Results will be presented as means, medians, and ranges for continuous variables and as totals and percentages for categorical variables. All significance tests will be 2-tailed, and all

confidence intervals will be presented with 95% degree of confidence. Differences in the quantitative responses at the baseline assessment will be statistically analyzed using Student's t test for two groups. Repeated measures tests will be used for longitudinal data, e.g., generalized estimating equations, including our primary and secondary outcomes. When the null hypothesis is rejected by primary analysis, appropriate post hoc analyses will be used.

6.3 Datasets or Population Analyzed

The dataset will consist of all enrolled subjects. This excludes all patients who failed the screening for this study or those who were eligible but uninterested in study participation. The primary efficacy analysis will be done with an intention-to-treat sample per protocol.

6.4 Handling of Missing data

If data are missing, the absence of data will be handled in a manner consistent with current expert recommendations, some of which have been established by our own team.[3-6] Our approach emphasizes either maximum likelihood or multiple imputation. All participants who dropped out will be included in all analyses up to the time of withdrawal.

6.5 Safety Analysis

While we anticipate a very low rate of adverse events, the medical monitor will compare AEs and SAEs between the two arms. We will conduct this analysis to inform the Phase II clinical trial of this intervention.

7. QUALITY ASSURANCE AND QUALITY CONTROL

7.1 Audit and Inspection

Ideal Option in Spokane, Washington State University, Pillsy Inc and the study documentation, can be subject to quality assurance audit during the study. In addition, inspection may be conducted by regulatory authorities at their discretion.

7.2 Data Management and Coding

Washington State University will be responsible for activities with the data management of this study. This will include setting up a relevant database and data transfer mechanism, along with the appropriate validation of data and resolution of queries. Data generated within this study will be handled according to the relevant procedures outlined by Washington State University and in accordance with several other investigations conducted at Washington State University. Details follow.

7.3 Handling of Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviation will be handled in accordance with the Washington State University IRB (www.irb.wsu.edu). If a protocol deviation occurs, corrective actions will be implemented promptly.

8. ETHICS

Training Requirements

Human Subjects CITI Training

All Research staff will complete online training through The Collaborative Institutional Training Initiative (CITI) https://about.citiprogram.org/en/homepage/, a web-based training program on Human Research Subject protections, before starting the study training.

Study Training

All RCs and Research Associates or Research Assistants will complete all the following before interacting with participants:

Thoroughly read the protocol and guidelines on consenting and safety procedures found below. RC should be knowledgeable on all procedures and safety procedures. This includes HIPAA training. Documentation of course completion will be included in the study file.

Practice all study procedures & consenting with existing study personnel. All study staff should be able to answer common questions from participants.

Shadow and watch an approved RC complete an entire study visit: recruiting, consenting, and randomizing with a participant.

Receive approval by the Principal Investigator.

Informed Consent

General Guidance for Informed Consent

Human subjects research at Washington State University is coordinated through the Washington State University Institutional Review Board (IRB). The IRB is responsible for the review and approval of all research activities involving human subjects. The IRB is charged with protecting the rights and welfare of human subjects to ensure that all study participants are treated physically, psychologically and socially in such a way as to minimize embarrassment and stress and to avoid harm or other negative effects.

The process of obtaining informed consent is a basic ethical obligation and a required element of human subject research. The IRB will require that informed consent be documented using an electronic written consent form approved by the IRB and signed and dated by the subject. The participant will be given ample time to read the consent document before it is signed. Participants will be asked to type in their name and date for the consent electronically. A copy of the document will be made available to the person signing the form.

The informed consent form will be presented to allow potential participants to review facts about the study and what will be asked of them so that they can voluntarily choose whether to participate as a research subject.

Changes to the study protocol may result in the need for a new consent form. Only the approved and most recent consent form will be used. The consent form document will have an IRB stamp of approval, version number and date at the bottom each page.

Please note: Unless you have the PI's authorization, do not conduct the consenting process.

Consenting Process:

1. The consenting process will be conducted in a consistent manner for every potential participant.
2. If participant is eligible, the iPad that was used for screening will display the consent form. RA or RC will explain that this document will explain the details of the study they are being asked to take part in. Allow the participant plenty of time to read.
3. When the participant is done reading the consent, they will be asked if they have any questions about the study. All questions will be answered before the participant signs the informed consent document. The consent form will then be thoroughly reviewed to ensure that the participant understands what they are agreeing to. Participants will be asked to type in their name and date for the consent electronically, and actually sign their name electronically.
4. Eligibility for the study is determined by study procedures. Signing the consent does not ensure eligibility to participate. That said, it will be made clear to the prospective participant that participation will not impact their care.
5. The most key point to stress in the consenting process is that participation is voluntary. Moreover, continued involvement in the study is also voluntary. Participants can choose not to consent to the study or discontinue at any time for any reason. They can choose not to answer any questions that make them feel uncomfortable.
6. Show the participant where to type their name and date the consent form. The participant must date and initial the consent and be offered a paper copy of the consent to the participant for their records.
7. Remember that consenting is an ongoing process.

SUICIDAL & HOMICIDAL IDEATION/BEHAVIOR

If a person reveals SUICIDAL IDEATION (in the last 30 days) at any level or during the screening:

1. Staff will explain their concern for the subject and inform their supervisors.

2. All current (last 30 days) suicidal ideation and behavior concerns will be immediately reported to "911" or appropriate clinic staff so that their protocol can be initiated.

3. Document the conversation in the Adverse Event Log, including date and time you called.

ABUSE & NEGLECT

Always inform the participants if issues regarding abuse or neglect are raised. Such information must be reported to the appropriate local or state authorities.

GENERAL PERSONAL SAFETY

- When meeting with a new participant, staff will sit closer to the door
- Staff will not be allowed to meet with a participant alone in the clinic
- If a person becomes agitated, they will state “I am going to get help”
    - This will be stated confidently, and staff will then walk to the door and exit the office in the direction of the front desk or nearest safe location

CONFIDENTIALITY ISSUES

All information gathered during this study is confidential. Participants can talk to anyone about their participation in the study. Study staff will not talk to anyone who is not on the research team about their participation without written authorization from the participant, except in cases of safety. If a participant asks about another participant’s involvement research staff will respond saying: “Everything related to a person’s participation in the research is confidential.” Discussions regarding participant related information will occur in an office with a door closed. Treat every participant with respect before, during, and after interactions. Some participants may express feelings of frustration, confusion, or even laughter. Staff will be sensitive to the fact that our discussions of these feelings (e.g., complaining about a participant’s behavior) may be overheard by the participant or others. Always be respectful.

REFERENCES

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