PennState

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:
A Randomized Clinical Trial of Comprehensive Cognitive Behavioral Therapy (CBT) via reSET-O for a Hub and Spoke Medication Assisted Treatment (MAT) System of Care.

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1.0 Objectives

1.1 Study Objectives

The overall goal of this RCT is to conduct a patient-level community-based effectiveness trial of the comprehensive, mobile app-based cognitive-behavioral intervention reSET-O, to determine whether this intervention improves the adherence to and outcome of medication assisted treatment (MAT)for opioid use disorder (OUD) in the setting of a Hub and Spoke implementation system.

This RCT is part of an R21/R33 NIH grant. The R21 pilot trial is currently underway (IRB: 00009931) with some subjective positive observations in terms of subject participation and engagement with the app. The R21 trial has laid the ground work for the R33 to be conducted successfully.

The primary hypothesis is that a greater proportion of patients assigned to Treatment As Usual (TAU) + reSET-O, compared to those assigned to TAU alone, will complete 6 months of MAT.

The Pennsylvania Psychiatric Institute (PPI) is committed to providing a wide range of high quality behavioral health services, including an Opiate Treatment Program (OTP) established in October 2017. Through the Pennsylvania Coordinated Medication Assisted Treatment (PACMAT) system, PPI functions as the "Hub," herein referred to as the PPI Hub, offering medication assisted treatment (MAT) with methadone, dispensed and prescribed buprenorphine-naloxone (suboxone) and buprenorphine (Subutex). The PPI Hub also offers extended release naltrexone to a limited number of patients. The PPI Hub also offers counseling with individual and group settings to the level of intensive outpatient treatment using evidence-based Cor-12 and Matrix model programs for groups to start. Treatment continues either at the PPI Hub or at one of the outlying spokes, depending on geography and patient clinical needs. Whether at PPI Hub or spokes, patients are assigned a case manager who meets with them regularly and coordinates their care with the prescribing physician.

The study test article, reSET-O (Pear Therapeutics, Inc.), is a commercially available version of the web-based Therapeutic Education System (TES).

1.2 Primary Study Endpoints

The primary outcome measure will be retention in treatment on MAT for 6 months after initiation.

1.3 Secondary Study Endpoints

The secondary outcome measures will be opioid use and other substance use (urine and self-report), craving, and measures of quality of life including mental health symptoms and social functioning. Exploratory analyses will examine whether the effect of reSET-O on 6-month adherence is mediated by improvements in quality of life outcomes.

2.0 Background

2.1 Scientific Background and Gaps

Medication assisted treatment (MAT) is a cornerstone of an effective national response to the epidemic of opioid use disorder (OUD). A key goal of the SAMHSA-funded State Targeted Response (STR) grants is to make MAT widely available to patients with OUD throughout the U.S. by reducing systemic barriers and increasing local capacity. However, a major barrier to the effectiveness of MAT is patient adherence. Studies show that 50% or more of patients with OUD initiating MAT will drop out of treatment within the first 3 to 6 months. Dropout is associated with a high risk of relapse and overdose, and 6 months of treatment is considered a minimum needed for most patients to enter into long term abstinence and recovery.

2.2 Previous Data

The Opioid Epidemic and Medication Assisted Treatment (MAT)

The opioid epidemic has spread rapidly over the past decade, reaching virtually every region of the U.S. It is estimated that 2.4 million Americans are currently addicted to opioids, and the prognosis is poor, if left untreated, including mortality from opioid overdose (Hser et al., 2001). Different types of MAT such as buprenorphine-naloxone, buprenorphine, methadone, and extended-release naltrexone, may be remarkably effective if patients adhere to treatment, the challenge is adherence to treatment. Studies of buprenorphine-naloxone, specifically, typically show less than 50% of patients retained in treatment for 6 months (Hser et al., 2014; Lee et al., 2017), and dropout from treatment is associated with relapse (Weiss et al., 2011; 2015; Hser et al., 2016; 2017). Hence, to combat the opioid epidemic, it is critical that MAT become universally available, and that patients' adherence to MAT be improved.

The digitally delivered intervention to be tested in this proposed study, reSET-O, targets treatment adherence, keeping appointments, and adherence to medication, while utilizing techniques of cognitive behavioral therapy and skills to avoid drug use and address problems with cravings, mood, and relationships, in order to avoid relapse, and rebuild a healthy lifestyle to support long term recovery.

Barriers to Implementation of MAT and the Penn State Hub and Spoke System

Three evidence-based Medication Assisted Treatment (MAT) approaches for treatment of opioid use disorder are approved in the U.S., methadone, buprenorphine, and extended release injection naltrexone. Maintenance treatment with methadone, a full opioid agonist, has been available for treatment of opioid use disorder since the 1970s. Methadone can only be prescribed under special regulations that are burdensome to patients (e.g. daily attendance at clinic required initially). Buprenorphine, approved in the U.S. in 2002, is a partial opioid agonist with less abuse potential, similar effectiveness, and more widespread availability than methadone, since it can be prescribed by any licensed physician who completes a modest training requirement. However, the supply of physicians actively prescribing buprenorphine remains limited. New prescribers need to be trained and supported within a variety of available clinical settings. The SAMHSA Opioid STR grants awarded to the States beginning in 2017 provided additional funding for MAT and encouraged the use of implementation models to address the shortage of prescribers, case managers, and associated services. With STR funding to the State of Pennsylvania, the Penn State-Hershey Medical Center established a Hub and Spoke (described below), based at Pennsylvania Psychiatric Institute, which is modeled on the Vermont program (Brooklyn and Sigmon 2017). This Hub and Spoke offers methadone, buprenorphine and buprenorphine-naloxone. It is within this system that the study proposed here will unfold, so that the findings may generalize to other States and regions around the U.S. utilizing similar models that support expansion of MAT through specialty clinic Hubs and primary care Spokes. All three forms of MAT are subject to substantial rates of dropout from treatment, and dropout carries a high risk of relapse to opioid use. It is our hypothesis that reSET-O will reduce dropout and hence improve the effectiveness of MAT treatment.

Barriers to Implementation of MAT: The Importance of Behavioral Therapy

Another key systemic barrier that has been identified is lack of access to behavioral intervention and counseling to accompany MAT prescribing (Quest et al., 2012; Hutchinson et al., 2014; DeFlavio et al., 2015). Provision of counseling is a regulatory requirement for methadone, buprenorphine, and buprenorphine-naloxone treatment. Further, evidence suggests that counseling and behavioral treatments improve adherence to and effectiveness of MAT (McLellan et al., 1993), particularly contingency management approaches (Peirce et al., 2006; Nunes et al., 2006; Carroll and Weiss 2017). Primary care practices and other clinical settings new to treating addictions typically lack staff with expertise in relevant behavioral treatments. Even addiction treatment programs serving as "hubs" may struggle to deliver more than rudimentary counseling due to time constraints and lack of expertise in the latest evidence-based interventions. The intervention to be tested in this proposed study, reSET-O, is a comprehensive cognitive behavioral treatment, with a strong evidence-base to suggest that it can improve adherence and outcome of MAT treatment for opioid use disorder (OUD), compared to standard counseling. Since it is a mobile app, delivered through patients interacting with a smart phone, it does not require a large time commitment or behavioral health expertise of clinical staff. Thus, reSET-

O has the potential to address the need for behavioral treatment as part of STR efforts to rapidly expand MAT, while improving the effectiveness of MAT at ushering patients into stable recovery.

2.3 Study Rationale

The study proposed here would be the first randomized controlled clinical trial of a comprehensive cognitive behavioral therapy to increase the effectiveness of MAT for the treatment of OUD in the context of a regional Hub and Spoke system to expand access to MAT. Programs like the Penn State Hub and Spoke have been set up to serve rural and impoverished small urban communities that have become the epicenter of the opioid epidemic. The need to deliver evidence-based psychosocial treatment has been identified as one of the key barriers to implementing MAT in such primary care settings, where the time and expertise needed to deliver such interventions are scarce. A digitally delivered cognitive behavioral intervention such as reSET-O has the potential to fill this gap. Since reSET-O is a commercially available mobile app, if found effective in supporting MAT, it has the potential to be rapidly disseminated across the U.S. health system in support of the STR initiative.

The study of reSET-O proposed here would be the first test of a randomized control trial of comprehensive cognitive behavioral therapy (CBT) to increase the effectiveness of MAT for the treatment of OUD in the context of a regional effort to expand implementation of MAT. As a comprehensive CBT treatment, reSET-O focuses not only on drug use, craving, and medication adherence, but also on skills to help patients address common problem areas, such as relationships, mood and related problems, and social functioning, in order to rebuild a healthy lifestyle. It is also individualized in that patients can select and repeat therapy lessons relevant to their most pressing problem areas. Most evidence-based behavioral interventions are delivered by clinicians and require training and supervision of clinical staff to deliver the intervention correctly, and substantial time of clinical staff to actually deliver the intervention to patients at scale. Clinicians' time and expertise are resources that are in short supply in community-based efforts to expand implementation of MAT and have been identified as significant barriers to delivering MAT to date. If found effective in the trial proposed here, reSET-O has the potential to lead the field of MAT implementation toward a new paradigm where a behavioral intervention becomes a resource that can be down-loaded from the web and prescribed to patients, rather than an intervention that needs to be learned and painstakingly delivered by clinicians. This has the potential to promote widespread implementation of MAT both by reducing barriers to delivering behavioral therapy, and by improving adherence to MAT and overall treatment outcome. This effort may also in the long run encourage the development of other web-based behavioral interventions to support implementation of MAT.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

- 18 years of age or older
- Diagnosis of opioid use disorder (OUD) as determined through routine clinical care
- Recently starting outpatient treatment for OUD within the PACMAT Hub and Spoke System of Care.
- Initiating MAT with buprenorphine-naloxone (suboxone), buprenorphine (Subutex), or methadone. Since buprenorphine (Subutex) is an FDA approved MAT for pregnant women with OUD, pregnant women are eligible to participate in the research study, assuming they meet all other eligibility requirements.
- Ability to read, write, and comprehend English
- Providers who are engaged with the reSET-O app and talking to their patients who have agreed to participate in the study and also assigned to use the reSET-O app.

3.2 Exclusion Criteria

- Initiating maintenance treatment that does not include MAT or switching to a maintenance treatment that does not include MAT (i.e.: detoxification and counseling treatment only without MAT).
- Planning an outpatient detoxification
- Judged by the evaluating physician or allied clinician to need a higher level of care (i.e.: residential or inpatient treatment)
- Less than 18 years of age
- Unable to read, write, and comprehend English

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

There are a number of reasons for potential subject withdrawal from the research study. If funding for the research study ends, then all subjects will be withdrawn from the research study. If it appears as though their OUD diagnosis is becoming worse, then subject will be withdrawn from the research study. This information will also be outlined in the consent form.

3.3.2 Follow-up for withdrawn subjects

Withdrawn subjects will be categorized by why they withdrew (disease progression, etc.), and the timing of withdrawal at the 1, 3, and 6-month time points. Withdrawn subjects will not be replaced. Withdrawn subjects will have the opportunity to have a follow-up visit with the study doctor if there are any concerns regarding next steps and/or treatment.

4.0 Recruitment Methods

4.1 Identification of subjects

Patients will be identified at the PPI Hub clinic through the PACMAT Hub and Spokes system of care. Patients are categorized as either Hub or Bridge/Spoke patients, depending on if they routinely seek treatment at the PPI Hub or a Spoke site. The PACMAT Hub and Spokes system of care has a strong track record of recruiting patients with substance abuse disorders. These centers are already providing treatment for patients with opioid use disorder (OUD), making them a primary source of treatment and attracting a high volume of patients. Additionally, the PPI Hub has a valued partnership with the Recovery-Advocacy-Service-Empowerment (RASE) Project and Just for Today (JFT) Recovery Services that connect clients to the PPI Hub and Spokes in our continuum of care and provides Case Managers for patients receiving their MAT care at Spoke practices.

All patients entering treatment for OUD within the PACMAT Hub and Spoke system will be verbally introduced to the study by the treating clinician who is also a study team member. Patients who are interested in participating in the study will be taken to the research office in the clinic and will engage in a phone call/zoom session with a research assistant to begin the recruitment process (if the research assistant is working remotely). If the research assistant is on site, then they will escort the patient to the research room for in-person recruitment. Those interested in learning more about the study will be scheduled for an appointment to ask questions about the study, go through the consenting process. Complete baseline questionnaires, and be randomized. Recruitment appointments will be scheduled 7-21 days after the patient completes clinic intake and provides contact information to research staff. Research activities will occur remotely with the patient at the PPI Hub or in a place of the patient's choosing (i.e. patient's home). All in-person research activities will occur at the PPI clinic.

In addition, research staff will place project flyers and handouts in the PPI OTP waiting room and research rooms (submitted with this modification). Flyers and handouts will introduce the project and provide contact information (email and phone) for research staff. If patients reach out to research staff

directly, research staff will verify eligibility before discussing the project and beginning the consent process.

Providers at PPI will be engaged in the app. Providers at PPI continue to function in-house and through telehealth procedures. Providers will login to the clinician dashboard to discuss modules completed with patients (either virtually or in-person) who have agreed to participate and have also been assigned to use the app. Once the study is complete, these providers will also be asked to engage in an open-ended discussion about the research study and complete a brief survey regarding the feasibility and acceptability of the app intervention. This open-ended discussion and survey may be done remotely or in-person, depending on the status of the current COVID19 pandemic at the end of this study.

Providers will only use the clinician dashboard side of the app to review their patient-completed modules and discuss these modules with their appropriate patients. Providers will not use the app for their patients who do not wish to be in the research or who have decided to quit the research study. Providers will receive a running list from research staff of their patients who are enrolled in the study and assigned to the use the app. This will be updated and provided on a monthly basis.

4.2 Recruitment process

4.2.1 How potential subjects will be recruited.

New patients at the OTP at PPI are required to present in-person to the clinic. Potential patients will be recruited first by being verbally introduced to the study at their first intake clinical appointment by a treating clinician who is also a study team member. Patients coming to the PPI Hub clinic for treatment and who use or plan to use MAT will be identified through physician referral. The PPI Hub clinic currently has five part-time physicians and one full-time nurse practitioner. Patients who are interested in the study will be asked to talk with a research assistant via phone, zoom session, or in-person in a private room (within the clinic).

4.2.2 Where potential subjects will be recruited.

Patients will be recruited at the PPI Hub clinic, and RASE and Just for Today spoke sites in southern Central PA.

4.2.3 When potential subjects will be recruited.

Patients will be recruited during their routine clinical care appointments.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB.

[*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

Screening a patient medically/psychiatrically to determine appropriate type of MAT is a clinical decision that is part of routine care, so that the research study is not responsible for erecting criteria that MAT is safe and appropriate at the outset.

Eligibility criteria are broad with minimal exclusionary criteria in keeping with the goals of an effectiveness trial to select a fully representative sample of patients seeking treatment in real world community-based treatment settings. Inclusion criteria include being over 18 years of age, being fluent in English, being interested in participating in research about opioid use and having

started Methadone or Suboxone within the past 42 days. Exclusion criteria include not being fluent in English and staying at a treatment facility or program where the use of cell phones or a tablet device is prohibited.

5.0 Consent Process and Documentation

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☒ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement. *[Complete Section 5.5]***

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

Consent will occur 0-42 days after the intake appointment. Consenting will occur through a remote zoom session conversation (when the research assistant is working remotely) and in-person (when the research assistant is on site) while the prospective participant is at the PPI Hub. The baseline research appointment will be scheduled as a remote session during a time that is conducive for both the research staff and potential research subject. The subject and research coordinator will review the consent form over a zoom session or in-person. The subject will be offered either an electronic version of the consent form or a hard copy of the consent form to review on their own before the consent meeting and/or during the meeting. Subjects will be given time to review the consent form and all questions will be answered by the research coordinator. IRB approved hard copy consent forms will be stored in unlocked cabinets in research rooms where the zoom consenting session will take place, in which a research assistant may instruct the participant to retrieve if appropriate. The consent form may also be emailed or mailed to the subject (before the meeting or during). The subject will be allowed to take the consent form home for further review or to discuss with family, friends, or a provider actively involved in their care if they wish.

If participants are interested in participating in the study, they will have three different options for completing the consent process (depending on if the research assistant is working on-site or remotely):

1. Patients will be sent a REDcap link via personal email or text message on the PPI OTP clinic smartphone, a personal cell phone, or a personal tablet device. This REDcap link will ask for participant consent including the date and time, entry of their first and last name, as well as their signature as drawn through a computer mouse or finger. The individual obtaining consent will also complete a REDcap form indicating the date, time, and signature that the consent form was explained to the participant. REDcap has the ability to data-lock fields. As soon as the participant and consenter sign the REDcap consent form, the consenter will lock the data fields.

2. If there are technological challenges using the e-signature process or if the patient prefers to use a different option, the patient will have the option of signing a hard copy of the consent form. If the patient chooses this option, then research staff will also complete the "Phone Consent to Participate In a Research Study Signature Page." Once both forms have been collected, the baseline process (baseline surveys) can continue.
3. If research staff are on-site, research staff will provide the patient with a hard copy of the consent form and both the patient and research staff will sign the same consent form.

Upon obtaining consent, participants will be asked to complete a brief quiz with questions related to the consent form. It is estimated that this quiz will take 5-10 minutes to complete and is used to ensure the participant's understanding of the consent form and the research study overall. There is no penalty for incorrect answers to the consent quiz questions. For any consent quiz question that is answered incorrectly, the research staff conducting the consent appointment will review the respective areas to ensure the participant's understanding. A copy of the signed consent form will be emailed or mailed to the participant. If in person, a copy of the signed consent form will be handed to the patient. We may also email the signed consent form to the participant's PPI clinical provider, who is also a study team member, to print the form at the clinic and physically hand the form to the participant. Method of delivery of the signed consent form will be based on participant preference.

Providers engaging with the app as appropriate will be provided a summary of explanation for research to provide an overall synopsis of the study as well as their involvement. This summary of explanation will be emailed to all providers engaging with the app. Provider questions may be answered via email or over the phone.

We will ensure that the participant is completing the correct version of the consent by dating the consent database within the reSET-O project based on the IRB approval date. This will be noted/filed in the regulatory binder to ensure smooth quality assurance checks and monitoring. This way, there is no confusion as to which consent form database needs to be used, which will be particularly helpful once the consent IRB stamp of approval changes as a result of continuing reviews, modifications, etc.

If updated versions of the consent and/or addendums are required, we will generate new consent and/or addendum databases within the reSET-O project in REDcap. We will be sure to date the databases with the most recently approved IRB version to avoid confusion on which REDcap consent database should be used. Newly enrolled participants from that point would then complete the new, updated consent form. Established participants would then be contacted to complete an e-signature through REDcap for an addendum if necessary. The same steps above, as outlined for consent completion, will occur for addendum review and signature.

5.2.2 Coercion or Undue Influence during Consent

Prospective participants will have the opportunity to read the consent form, the requirements for participating in the project will be reviewed with prospective participants by the research coordinator, any questions will be answered, and written informed consent will be obtained by study staff. Participants may request a copy of the consent form to take home and review with significant others, and be rescheduled for a second visit for additional discussion. They will have a chance to read the informed consent document, ask any remaining questions, and provide signed consent.

For pregnant subjects or subjects who may become pregnant, per HRP-412, each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research

on the fetus or neonate. There is no prospect of benefit to the fetus, the risk to the fetus is NOT greater than Minimal Risk and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

Providers will have the opportunity to review the summary of consent of research and may ask questions at any point in time. They may refuse to participate in the open-ended discussion and they do not have to answer any questions on the survey that they do not wish or feel comfortable answering.

Consent is obtained only by research staff (research coordinator, research assistants), and not by any clinical staff, in order to ensure that patients do not feel obligated to their clinicians to consent to the research. The consent form, and consent discussion with research staff, make it clear that research participation is voluntary and does not affect the ability to obtain treatment.

5.3 Waiver of Written Documentation of Consent

Providers engaging with the app as appropriate will be provided a summary of explanation for research to provide an overall synopsis of the study as well as their involvement. Consent will be implied by providers engaging with the app with appropriate patients and, at the completion of the study, engaging in an open-ended discussion and completing the survey about feasibility and acceptability of the app intervention. Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

5.4 Informed consent will not be obtained – request to completely waive the informed consent requirement

N/A

5.5 Consent – Other Considerations

5.5.1 Non-English-Speaking Subjects

N/A – Subjects are only eligible if they can read, write, and comprehend English.

5.5.2 Cognitively Impaired Adults

5.6.2.1 Capability of Providing Consent

If a subject is unable to provide consent as a result of intoxication (i.e.: illegal substances or alcohol) as observed by the clinician during the routine clinical care appointment, then the study will not be introduced to the potential subject during that time.

If a subject is unable to provide consent as a result of intoxication (i.e.: illegal substances or alcohol) as observed by the research coordinator or research assistant, then the consent process will stop and be rescheduled at the potential participant's discretion.

5.6.2.2 Adults Unable to Consent

N/A

5.6.2.3 Assent of Adults Unable to Consent

N/A

5.5.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

N/A

5.6.3.2 Assent of subjects who are not yet adults

N/A

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☐ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☒ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

We plan to obtain verbal authorization only from provider participants; however, PHI of providers will not be collected. The following sections do not apply to the patient participants who may receive the app intervention (based on randomization).

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

We do not plan to obtain identifiers of participant providers. Data collected from providers will be self-report surveys, which will be entered into REDcap. Completed paper surveys by providers will be stored in a secure and locked research office.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

We are not collecting PHI of participant providers.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

The verbal authorization and waiver of documentation of authorization is required, because the application intervention is being randomly administered to clinic-patients who wish to be a part

of the research study, and it is expected that the providers will engage in the application intervention with those specific research subjects.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

This RCT trial will be conducted to test the effectiveness of reSET-O as a cognitive behavioral therapy to enhance MAT treatment adherence among opioid use disorder (OUD) patients. All participants will be randomly assigned to receive reSET-O along with treatment as usual (TAU) or TAU alone.

We are collaborating with Columbia University who has worked closely with Pear Therapeutics, Inc. (owners of the reSET-O app program). Analysis of the patient survey data via REDCap as well as data collected from the reSET-O phone app, received from Pear Therapeutics through a Penn State approved file sharing system (i.e.: Accelion, File Drop, Kitedrive, etc.), will be conducted by a senior PhD-level statistician and master's level analyst located in the Clinical and Translational Science Institute (CTSI) at Penn State College of Medicine. The Columbia University biostatistician will be available for consultation and guidance throughout data analysis; Columbia University will not be directly handling study data beyond that required of routine quality assurance procedures and weekly study team meetings.

We are also collaborating with the Research Foundation for Mental Health (RFMH) as affiliated with Columbia University. RFMH will be providing quality assurance for the project including monitoring of data collection of both non-PHI and PHI, as well as monitoring the regulatory binder. All monitoring reports completed for QA will be submitted to the Penn State IRB.

7.2 Study Procedures

7.2.1 Visit 1 (Intake/Baseline)

During the subject's intake appointment, eligibility is confirmed by the provider and subjects are directed to a private research room. Research staff will introduce the research study to the participants and schedule a research appointment to discuss the project further in 7-21 days. Subjects can take a physical copy of the consent form home with them or request one be emailed to them.

During the first research appointment, research staff will confirm eligibility, complete the consent process, complete the baseline questionnaires, and randomize the subject (TAU + reSET-O or TAU alone). Participants will be asked to undergo research assessments consisting of an interview and self-report questionnaires (described below), as well as urine samples collected at all visits (baseline, week 4(+/- 2 weeks), week 8(+/- 2 weeks), week 12(+/- 2 weeks), and week 24(+2/- 4 weeks)). Urine toxicology for opioids and other drugs is collected at PPI as part of routine clinical care; however, urine collected at these specific clinic visits will also be used for

research purposes and used to confirm self-reports of abstinence. This will be outlined in the consent form and discussed with the participant.

Participants who are assigned to TAU + reSET-O will be briefed on the reSET-O app and will download the reSET-O app onto their smartphone or tablet device. Penn State research assistants will have the capability to generate and provide app access codes through the Pear Therapeutics clinician dashboard. This allows for instant access and entry into the app for the research subject, as opposed to waiting for several hours or even days for onboarding through the Patient Services Center. However, participants will still be required to complete the Pear Therapeutics reSET-O patient services center (PSC) enrollment form (completed with the research assistant), which will be transferred to the PSC via secure file transfer (e.g. Accellion or Kitedrive) or by fax. The PSC is affiliated with Pear Therapeutics, the owners of the reSET-O app. The following information is collected on the enrollment form and faxed to PSC:

- The enrollment form collects information that is used by the PSC to verify the identity of the subject including the patient's first and last name, and a date of birth, which will be a "dummy" date of birth (i.e.: 01-001-1999; dd-mmm-yyyy). The first and last name of the participant is required because PPI Hub clinicians who are also part of the research team will not be able to identify their patients who are engaged in the app through the clinician dashboard via subject IDs due to the volume of patients seen. Thus, the PPI Hub providers need to be able to see participant patient names in their clinician dashboard in order to engage with subject about their app use. The PSC form clearly indicates that this individual is enrolled in a research study, which allows staff at the PSC and Pear Therapeutics, Inc. to understand that services are not to be billed to any insurance.

- A phone number is also required for the enrollment form, which may be a phone number most commonly used by the participant, or a phone number associated with a research assistant's office phone (for participants who do not have an operating phone number). The phone number is needed because the PSC will call the subject weekly to ensure that that the participant is able to use the app without technical difficulty. The participant may opt out of these calls, which will be outlined in the consent form. reSET-O, Pear Therapeutics, Inc. (owners of reSET-O), and other entities affiliated with reSET-O do not use phone numbers for any other purpose including selling the phone number to third parties, sales calls, etc.

- An email is also required for the enrollment form, which may be an email most commonly used by the participant, or the research coordinator/research assistant may help the participant set up a free email account for purposes of this study. An email is needed because should the participant forget their username and/or password to login to the app, they will be able to reset their login credentials via email. reSET-O, Pear Therapeutics, Inc. (owners of reSET-O), and other entities affiliated with reSET-O do not use email addresses for any other purpose including selling the email to third parties, marketing or other advertisements, etc.

Participants, who do not own a smartphone, will be provided with an inexpensive tablet device that will be able to access reSET-O for the duration of the trial. These devices will be obtained and managed by research study staff. Should a participant lose or sell the tablet device, or if the device is stolen, they will be afforded a second chance with a new tablet device as provided by the study. Should the participant lose or sell the second device, or if the second device is stolen, they will not receive a third tablet device. They will still be enrolled in the study and asked to complete questionnaires at the appropriate time points; however, they may not be able to

engage with the app, reSET-O, unless they provide their own device that is compatible for use with the reSET-O app (e.g., smart phone, table). This will also be outlined in the consent form.

After obtaining consent, randomized assignment, and getting set-up with the reSET-O app (if applicable) as outlined above, all participants will complete the electronic surveys listed below.

- Eligibility checklist to assess a potential participants eligibility via inclusion and exclusion criteria.

- Demographics form will be used to collect basic demographic information on each participant (i.e.: DOB, gender, education level, etc.), and will only be collected at baseline.

- Locator form collects information that will be useful in helping research staff to locate a participant for assessment should they stop attending treatment, including address, phone number(s), and contact information of significant others who would know how to locate the participant. This is important scientifically to minimize missing data due to loss to follow up. In order to protect confidentiality of participants, if listed significant others are contacted, no information will be divulged by research staff about the participant, other than that they were participating in a survey at Penn State and the research team in attempting to contact them for follow up survey. During consent participants will be informed that it is important for research staff to be able to contact them to find out how they are doing and conduct assessments, even if they have dropped out of treatment, and the procedures for contacting significant others for locator purposes are explained.

- Timeline Follow-Back (TLFB) (Sobell and Sobell, 1992; 2000) assesses self-reported alcohol and other drug use (frequency, quantity) using calendars and memory aids to enhance recall. We will not be able to provide printed calendars; however, the participant will be encouraged to use their phone or tablet device to view a calendar app to help enhance their recall of past substance use. The TLFB has good psychometric properties, including test-retest reliability with multiple populations, and content, criterion, and construct validity across multiple related measures. Additional questions will assess intensity and number of days of urges/cravings for opioids and other substances, and HIV risk as a result of IV drug use and sharing of needles/works. Per the recommendation of the NIH, staff who are blinded to the randomization assignment of participants should complete the TLFB. Penn State research staff will complete the TLFB during baseline because it will be completed before randomization occurs. Columbia research staff will be completing the TLFB via phone/WebEx session with all subjects beginning with the 4-week follow-up visit. During the follow-up visits, Penn State research staff will complete all research tasks with the participants and help facilitate the TLFB with the Columbia team by:
    - Transferring the participants to the Columbia team by phone, text or email;
    - Providing a phone number or meeting room link so participants could reach out to the Columbia team directly; and/or
    - Providing the Columbia team with the participant's contact information (at the participant's request).
    - The research tasks with the Columbia team will occur through the participant's phone or an office phone via WebEx. Columbia University requires the use of WebEx for research outreach to participants.

- Coping Strategies Scale (CSS) (Litt et al., 2003) is a 23-item, self-report measure (originally adapted from the Processes of Change (Proschaska et al., 1998)), assessing change processes, coping skills, and problem-solving related to urges to use substances. It has good reliability across samples (α=.83 to .87). Two versions with only slight differences in directions will be administered. At intake, the directions will ask subjects to think about the last three months

when answering the questions. For all follow-up research appointments, the directions will ask the subject to think about their coping strategies used since the last research appointment. Question/prompt items remain the same between the two versions.

- PROMIS is a well validated and widely used scale that measures the quality of social and occupational functioning.

- Social Connectedness Scale (SCS) (Lee and Robbins 1995; 1998) is a 20 item, 6-point scale, self-report assessing psychological belonging or interpersonal closeness with good reliability (α=.91).

- Patient Health Questionnaire (PHQ) (Spitzer et al., 1999) was developed for use in primary health settings and screens for DSM psychiatric diagnosis of major depression and generalized anxiety at baseline.

- The Kessler 10 (K10) (Kessler et al., 2003) is a brief, 10-item self-report measure of general psychiatric distress will be collected at baseline and follow up points to address change in psychiatric symptoms over time. K10 has good reliability and is used in World Health Organization mental health surveys in 30 countries.

- HIV Risk from the Sexual Experiences and Risk Behavior Assessment Schedule (SERBAS): A summary item from the Sexual Experiences and Risk Behavior Assessment Schedule (SERBAS), used as primary outcome in large HIV risk reductions studies (Tross et al., 2010), elicits the number of episodes of occasions of vaginal or anal intercourse without a condom over the last 90 days using time-line follow back cues for recall.

- Time Line Follow-Back (see above) will query intravenous drug use, and episodes of sharing needles.

- Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2008): The C-SSRS will be administered only to subjects who have endorsed suicidal ideation (SI) per the Patient Health Questionnaire (PHQ). There is one item on the PHQ that assesses self-reported SI using a Likert scale of 0-3 (0 = not at all; 3= nearly every day). A score of 1 or higher is considered an SI endorsement, which will warrant administration of the C-SSRS. Should the C-SSRS results indicate an SI presence/plan, a Hub PPI provider (physician or nurse practitioner) will take over the evaluating situation and follow PPI's SI policy.

- Intervention Acceptability/Feedback Form (IAFF) is a 7-item self-report measure comprised of indicators of treatment acceptability on 10-point scales: interesting, useful, new information, easy to understand, satisfaction, relevance to life, and likability. This will only be administered to patients who have been assigned to TAU + reSET-O.

- TAU Tracking Form (TTF) –completed by research staff in order to capture services received in TAU per week over past 4 weeks, including modality and frequency. Research staff will verify the information with the patient for accuracy.

- reSET-O Implementation and Adherence: For participants who have been assigned to TAU +reSET-O, we will collect data from the reSET-O data system and dashboard for each patient on utilization of reSET-O features (how many and which therapy lessons are completed, incentives earned, use of the communication features).

- Weiner Intervention Appropriateness, Acceptability and Feasibility Survey: This survey will be completed by providers who are engaged with the app. This survey evaluates acceptability,

appropriateness, and feasibility of intervention implementation using a 5-point Likert scale (1=lowest score; 5=highest score).

In cases where the Timeline Follow-Back assessment cannot be completed (patient cannot access the Columbia team's WebEx room, patient must leave the research visit before completing), Penn State research staff will pull data from the Demographic Questionnaire Form that the patient completes during their intake process (attached to this modification). This questionnaire is also administered by Penn State research staff as part of routine intake. This data query is necessary because of the time sensitive nature of self-reported alcohol and drug use data (i.e. asking about a patient's alcohol and drug use in the last 30 days).

- HITS (Hurt-Insult-Threaten-Scream Screening Tool): This assessment screens for domestic violence in participants who have a romantic partner. It will be used at both the baseline and endpoint visits.

- BARC-10 (Brief Assessment of Recovery Capital): This is a 10-item measure that assesses the level of personal, social, physical and professional resources that someone has available.

- PCL-C (PTSD Checklist – Civilian Version): A self-report rating scale for symptoms of PTSD over the past 1 month.

- Overdose History: This assessment asks patients if they have ever overdosed on a substance and then goes into branching logic for details of the incident if they have, with questions like "when?", what substance, etc.

- First Response Opioid Survey Tool (FROST): This survey has questions for all research participants about the first time they used opioids.

7.2.2 Week 4 (+/- 2 weeks), Week 8 (+/- 2 weeks), Week 12 (+/- 2 weeks), & Week 24 (+2/- 4 weeks)

The same procedures and measures listed above will be repeated again at the Week 4 (+/- 2 weeks), 8(+/- 2 weeks), 12(+/- 2 weeks) & 24(+2/- 4 weeks) follow up visits – measured from completion of baseline questionnaires and randomization. Given the predicted scheduling challenges with this population, we plan to incorporate a 2-week window for completion of specific visits. For the last visit, we plan to allow for a +2/-4 window in the event that we need to allow for time to locate specific subjects who have been lost to follow-up.

A qualitative interview will be conducted and recorded with patients who have been assigned to TAU + reSET-O (n=100) at week 4 to gather their initial thoughts on the app and identify factors contributing to time spent on the app. Qualitative interviews will also be conducted at weeks 8 and 12 to elicit personal accounts of their experience using the program, acceptability of the program, and suggestions for improvement. The total time to administer these qualitative interviews is estimated at 20-30 minutes. The interview will be audio recorded. The audio recording will be stored on the Hershey Network server, accessible only by assigned study staff and the PI. The interview does not ask for PHI and therefore PHI is not expected to be in the recording; however, transcriptionists will be trained to remove PHI from any interviews.

reSET-O only works for 12 weeks at a time. Therefore, at week 12, subjects who have been randomly assigned to TAU + reSET-O will repeat the reSET-O enrollment process again, which includes the PSC form, for the continuation of their access to reSET-O. Information on the first enrollment form will be identical to the second enrollment form, with the exception of phone number and email in the event that this information has changed. There is no change in

completion of modules within the app or contingency management provided by the app from access time point 1 to access time point 2. The extended access allows the subject's account to rollover into the extended access account, enabling subjects to pick up where they left off with their contingency management, modules, and revisiting completed modules.

There will be two phone check-ins with the research coordinator/ research assistant. The phone check-ins will occur during the 16th week and again during the 20th week of the study. The phone check-in will be a simple 5-10-minute conversation to ask the subject how they are doing and determine if their contact information has changed in order to facilitate contact for the 24-week follow up.

At the completion of the study, providers (i.e.: physicians, case managers, etc.) will be complete a five-minute survey regarding the feasibility, acceptability, barriers, and facilitation of using reSET-O. They will also be asked to engage in an open-ended discussion (approximately 1-1.5 hours) to provide suggestions for improvement of the app itself or facilitation of implementation. No personal information will be collected from providers about themselves. The open-ended discussion and survey may be done remotely, depending upon the status of the COVID19 pandemic

7.3 Duration of Participation

All participants are asked to participate in 5 remote or in-person research visits over 24 weeks as listed above, as well as participate in two phone check-ins at week 16 and week 20. The baseline visit will take about 1 to 1.5 hours for subjects assigned to reSET-O +TAU, and 45 minutes to 1hour for subjects assigned to TAU only. For reSET-O + TAU subjects, follow-up appointments will last 30 to 45 minutes, with the exception of the visit that accounts for the addition of a qualitative interview (weeks 4, 8 or 12), which will last approximately 50 to 65 minutes to account for the qualitative interview. For subjects who have been assigned to TAU only, follow-up visits will take 20-30 minutes to complete.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

<u>reSET-O: Mobile App Delivering Cognitive-Behavioral Intervention to Enhance Implementation of MAT</u>

reSET-O is the commercially available version (Pear Therapeutics, Inc.) of the Therapeutic Education System (TES) originally developed by Bickel, Marsch and colleagues (2008). It was recently approved by the FDA as the first digital therapeutic adjunct for the treatment of substance use disorders. Pear Therapeutics has agreed to provide reSET-O for this proposed project without cost and to collaborate on any modifications that arise during the R21 phase. reSET-O (TES) combines two empirically supported treatment approaches, Community Reinforcement Approach (CRA) and Contingency Management (CM), translating them onto a computer-interactive learning environment, delivered by smartphone or tablet, without the direct involvement of a human therapist. CRA is based on the model that substance use disorders develop when drug reinforcers grow in salience and displace an individual's normal healthy sources of reinforcement, such as friends, family, employment, and recreation. CRA teaches patients cognitive-behavioral coping skills to resist drug use and to address factors such as craving, depression and other mood problems, and relationship issues that are associated with risk of relapse, in order to rebuild their lives and relationships without drugs. CM provides concrete monetary rewards (e-giftcards) contingent on performance of one or several key target behaviors, such as urine-confirmed abstinence from drugs or attendance at treatment appointments. CRA and CM are both highly researched therapeutic interventions for substance use disorders with broad empirical support individually (Hunt & Azrin 1973; Budney & Higgins 1998; Miller & Meyers 1998; Stitzer & Petry 2006). When delivered together, CRA and CM have

been shown to contribute uniquely to outcomes, suggesting complementary therapeutic elements that enhance overall treatment effectiveness (Roozen et al., 2004; Higgins et al., 1994; 2003).

MAT treatment (treatment as usual) when combined with counseling has a decent success rate at greater than 50% patient retention over a 6-month period. Patients retained in MAT treatment typically experience substantial improvement in their opioid use, while those who discontinue MAT typically relapse to opioid use. Therefore it is important to try to improve the rate of retention in treatment, which is why the reSET-O intervention is proposed. Patients enrolling in the study will have been prescribed their appropriate MAT as their standard of care and is not part of the research study.

7.4.2 Treatment Regimen

reSET-O is delivered as a mobile app and can be downloaded to and used by a smart phone or tablet. Buprenorphine-naloxone and buprenorphine dosing ranges from 2-24mg/day, is administered sublingually, and in combination with counseling. Methadone dosing ranges from 60-250mg/day, is administered orally, and in combination with counseling. For buprenorphine-naloxone, buprenorphine, and methadone, initial doses are started low to avoid precipitated withdrawal and titrated upwards to achieve relief of withdrawal symptoms and avoid cravings.

7.4.3 Method for Assigning Subject to Treatment Groups

Subjects will be randomly assigned to TAU alone or TAU + reset-O, but stratified by MAT into three arms: methadone, buprenorphine initiated at the Hub and buprenorphine initiated as a bridge appointment with continuation of treatment at the spoke.

Randomization will be determined through a web-based data management system. The stratification data will be entered and the data management system will conduct the randomization and communicate back with the treatment assignment within the same web-based interface.

7.4.4 Subject Compliance Monitoring

The Contingency Management system developed in TES, and adapted in reSET-O, utilizes the "prize bowl" method developed by Petry to deliver contingency management at lower cost (cost of the incentives) to make it more feasible for community-based treatment. When a target behavior is performed (completing a therapy lesson, attending a clinic appointment), the patient earns a "draw", where some draws yield motivational messages, some are low cost prizes, with the occasional higher value prize. The program keeps track of the draws earned and prizes, so that, again, burden on clinical to organize the CM intervention is minimized. Completion of therapy lessons automatically earns draws.

In order to further support buprenorphine adherence, reSET-O contains communication features, where the patient receives a daily prompt to take their buprenorphine dose, and can record taking each dose, as well as any drug use or craving. This information, along with information on which therapy lessons a patient has completed, is summarized on a dashboard for each patient available that is available on line to the prescribing physician and other clinicians (research coordinator/research assistant in the study proposed here) to help track progress and stimulate discussion between patients and their clinicians.

7.4.5 Blinding of the Test Article

Per the recommendation of NIH, the TLFB should be completed by staff blinded to the randomized assignment of the participants. Penn State research staff will complete the TLFb with participants because this occurs before randomization. All TLFB conducted after the

baseline visit will be conducted by an external research team member who is blinded to the randomization assignments. Upon completion of the TLFB, the external staff member will transmit files to the Penn State research team via Accellion/ Kite Drive for e-storage of the document (on the Hershey Medical Network server, accessible through role-based security only), and entry into REDcap. No PHI is collected or exchanged during the TLFB process.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Participating patients assigned to TAU + reSET-O will download the free reSET-O app to their own smartphones, but for those who do not own a smartphone, a smartphone will be provided for the duration of the trial.

7.4.6.2 Storage

Approximately 75 inexpensive smartphones or tablets will be maintained by study personnel.

7.4.6.3 Preparation and Dispensing

N/A

7.4.6.4 Return or Destruction of the Test Article

N/A

7.4.6.5 Prior and Concomitant Therapy

N/A

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

We will recruit and enroll 200 patients with OUD within the Penn State Hub and Spoke System (Pennsylvania Coordinated Medication Assisted Treatment (PACMAT), for this RCT.

Due to the possibility of turnover and new hires, we expect approximately 12-15 providers to engage with and provide feedback on the app. Any new hires will not engage with the app until CITI and HIPPAA training is completed and a modification reflecting a team member change has been approved by this IRB. The team member form will be reviewed on a bi-monthly basis and updated as appropriate with any changes, and the IRB will be notified as soon as possible regarding these updates.

Research subjects will not be assigned to any newly hired provider until the said provider has completed the appropriate CITI and HIPPAA training, and has officially been added to the study team and approved through the Penn State IRB.

8.2 Sample size determination

Previous studies of MAT treatment of OUD indicate substantial drop out rates--typically in the 40% to 50% range still retained in treatment at 24 weeks. Assuming 40% retention in the TAU treatment group, a sample size of 100 patients per treatment group (total N = 200) is selected to ensure sufficient power of 80% with a two-sided level of significance of 5% to be able to detect a difference of at least 19.7% between the TAU vs reSET-O + TAU treatment groups (i.e., 40% retained in TAU vs 59.7% retained in reSET-O + TAU). This difference of 19.7% is equivalent to an odds-ratio of 2.22 and would be clinically meaningful.

8.3 Statistical methods

Outcome Measures and Covariates

Primary outcome: The primary outcome will be a binary indicator of whether or not the patient is retained on MAT (methadone, buprenorphine, or buprenorphine-naloxone) treatment through 24 weeks. For those who drop out before 24 weeks, time (week) of dropout will be recorded, and they will be considered as not retained.

Secondary outcomes: 1) weeks of treatment retention (time to drop-out 0-24 weeks, survival; number of weeks retained, continuous); 2) urine-confirmed abstinence from opioids in the last 4 weeks (longitudinal (weeks 4, 8, 12, and 24), binary); 3) Days using opioids in the last 4 weeks (longitudinal, continuous); 4) Days using other drugs/alcohol in last 4 weeks (longitudinal, continuous); 5) coping strategies (CSS mean score; longitudinal, continuous); 6) social functioning (EuroQol, SCS, global scores and subscales; longitudinal, continuous); 6) overall mental health symptoms (K10; longitudinal, continuous); 7) HIV risk behavior—days in past 30 of vaginal or anal sex without a condom (longitudinal, continuous); Any needle sharing in past 4 weeks (longitudinal, binary); 7) Treatment satisfaction at week 24 (IAFF; continuous); 8) Serious adverse events (binary).

Additional variables: *Covariates, primary and secondary analyses*: *Stratification factors*: 1) any intravenous drug use (binary); 2) treatment with methadone vs buprenorphine at Hub vs buprenorphine at Spoke (categorical). *Moderators*: 1) both stratification factors will be explored as moderators; 2) demographic characteristics (gender, age, ethnicity etc.); 3) prescription opioid use only vs any heroin or fentanyl use (binary); 4) other substance use at baseline (any cannabis, any stimulant, any heavy drinking days; binary); 5) Probable major depression at baseline (binary based on PHQ score); 6) history of prior treatment for opioid use versus first treatment episode (binary). *Mediators*: 1) social functioning (EuroQol; continuous); 2) social connectedness (SCS; continuous); 3) opioid craving (continuous); 4) coping (CSS; continuous); and 5) mental health symptoms (K10; continuous).

Intent to Treat, Dropouts, and Missing Data

All analyses will be on the Intent-to-treat (ITT) sample, i.e., all randomized subjects (N=200) according to the treatment arm to which they were assigned. For the primary outcome, patients that dropped out before 24 weeks will be considered not retained. For the secondary outcome urine-confirmed abstinence, missing data (patients who cannot be located) will assumed to be opioid positive (not abstinent), a typical assumption which is reasonable based on the high rate of relapse among patients with OUD who discontinue medication treatment (Weiss et al., 2011; 2015; Hser et al., 2016; 2017). For other secondary outcomes, missing data will be treated as missing at random. Longitudinal mixed effects models do not require complete data to provide estimates of the outcome, and the estimates are considered valid under the assumption that the data are missing at random (Little & Rubin, 2002). We will additionally perform sensitivity analysis for the secondary outcomes to examine the influence on the outcomes of dropout and missing data by performing several imputation methods, for instance imputing missing weeks as all abstinent or all non-abstinent. Comparison of the inferences from assuming various models for the missingness provides a measure of the validity of the efficacy estimate from the initial model.

Significance Testing and Preliminary Analyses

All tests for main effects will be performed at two-sided significance level of 5%. Before performing specific analyses, we will examine the distribution of outcome measures and covariates and investigate for outliers. The distributions of continuous variables will be checked for normality, and transformed, if necessary. Distribution of demographic variables will be examined and described in terms of means, standard deviations, proportions and 95% confidence intervals. Covariates will be examined for association with treatment outcome. Covariates associated with treatment outcome will be adjusted for in models used to test study hypotheses.

Primary outcome

Statistical Model: *Hypothesis: Adding reSET-O to TAU (reSET-O + TAU arm) will promote greater 24 week retention in treatment on buprenorphine compared to the TAU arm.* The positive effect of randomization to the reSET-O+TAU group compared to TAU group will be estimated using logistic regression with the binary outcome of retention in treatment for 24 weeks (yes/no) modeled as a function of treatment condition (reSET-O + TAU vs TAU) and stratification factors (methadone treatment; buprenorphine treatment at Hub; buprenorphine treatment initiation at hub and continuation at spoke) and intravenous drug use in last 30 days (yes/no). The odds ratio of the treatment term and its confidence limits will estimate the treatment effect. The raw retention rates in each treatment group and rate differences will be computed for descriptive purposes.

Secondary outcomes

Statistical Models: For each of the secondary outcomes (see above) the effect of randomization to the reSET-O+TAU arm compared to the TAU arm will be estimated with a model of the same general form as for the primary outcome (three independent variables: treatment assignments (reSET-O+TAU vs TAU) and the two stratification factors) using logistic regression model (for binary outcomes), generalized linear model (for continuous outcomes), or longitudinal generalized mixed effects model (for longitudinal outcomes) with appropriate link functions (e.g. logit for binary outcomes). Longitudinal outcomes analyzed using a mixed effects models will utilize a generalized estimating equation with an autoregressive correlation structure to account for within subject correlation over time, as well a random intercept accounting for between subject variability. Retention data will be displayed with Kaplan-Meier curves that show the observed probability of retention in the program until time t, over time across the 24-week trial. The time to not-retained (dropout) data for reSET-O +TAU and TAU groups will be analyzed using proportional hazards models with covariates. If proportional hazard assumption is not satisfied, the data will be analyzed using a non-parametric log-rank test. In addition to stratification factors, covariates that are found to be related to the outcomes will be also added to the models to improve the power for detecting significant differences.

Moderation and Mediation

Moderation Statistical Models: The effect of randomization to the reSET-O+TAU arm will be estimated for subpopulations based on the demographic and baseline characteristics selected as moderators (see above). We will estimate the moderation effect on primary outcome using a similar model to Aim 1 primary outcome with the inclusion of moderator by treatment interaction: $\boldsymbol{Y_i = \beta_0 + \beta_1 Trx_i + \beta_2 M_i + \beta_3 Trx_i M_i + \beta_4 C_i + s_i}$ where M_i is the moderator status for i^{th} subject and $\boldsymbol{Trx_i}$ is subject's treatment assignment. Regardless of the significance of the interaction term, we will use the model to estimate the 95% confidence interval of the treatment effect for each level or category of the moderator variable. The moderator analyses are exploratory and hypothesis generating, but significant moderator effects can be useful in planning future efforts at implementation of reSET-O by identifying subgoups that may particularly benefit. Identifying subgroups where there is less benefit may suggest future modifications to reSET-O or its implementation strategy to achieve better effect in those subgoups.

Mediation Statistical Models: The effect of randomization to the reSET-O +TAU arm will be estimated when accounting for potential mediators (see above). In particular, we are interested in testing whether an impact of treatment on the primary outcome of 24 week buprenorphine retention is mediated by craving and by coping skills (CSS), which are targets of the therapy lessons or modules of reSET-O, as well as social functioning (PROMIS) and social connectedness. We will simultaneously estimate both the total effect of treatment assignment on primary outcome and the indirect of treatment assignment on primary outcome mediated through the intended target mediators using structural equation modeling (SEM) in software MPlus (Taylor, MacKinnon and Tein 2008). The indirect effect is estimated by the product of the effect of treatment assignment on the mediator and the effect of the mediator on the primary outcome while adjusting for treatment assignment. SEM will provide an estimate of the indirect effect of each mediator as well as its bootstrapped 95% confidence interval. These mediational analyses explore whether the effect of reSET-O on the primary outcome is being channeled through reSET-O

having an impact on its intended targets (abstinence/relapse prevention, and psychosocial functioning) (i.e. main effects of treatment assignment on mediator). This can, again, be of heuristic value in suggesting aspects of either reSET-O itself or its implementation that might need strengthening in future research or implementation efforts.

Implementation Outcomes

Measures of reSET-O utilization and adherence (number and types of therapy lessons completed, incentives earned, utilization of communication features) will be summarized with descriptive statistics, and associations with baseline covariates explored to understand what factors may drive reSET-O utilization, including patient characteristics and clinical setting (Hub vs Spoke).

Qualitative Interviews conducted with reSET-O patients will elicit personal their experiences with reSET-O and its acceptability, feasibility, barriers and facilitators, and suggestions for improvement. A Qualitative Interview was previously developed in consultation with the Advisory Board, for the R21 pilot trial (Penn State IRB 00009931). Qualitative data analyses from the result of the qualitative interview, as well as using experiences from the R21 pilot trial and adaptation process, may indicate changes to improve the current qualitative interview that is expected to be used and incorporate standard implementation outcomes (Glasgow et al., 1999). Using Atlas.ti© software and a coding framework developed from the qualitative interview, research staff (Campbell, Aydingolo) will systematically code transcripts of the interviews, resolving discrepancies in consensus discussion. The descriptive implementation data and interviews will be presented to the Advisory Board and used to help understand the feasibility of future implementation efforts across the State and beyond.

9.0 Data and Safety Monitoring Plan

9.1 Periodic evaluation of data

Data is directly entered into REDcap by the research assistants. The research coordinator will periodically check the data as it is entered to ensure REDcap is working properly and recording the data as appropriate. Regular quality assurance monitoring will be conducted by Ms. Aydingolo (Columbia) who will remotely review regulatory documentation, data collection and data management procedures, and review other study documentation (e.g., progress notes, error corrections, contingency management logs). These reviews will also include: 100% review of informed consents, eligibility criteria, AE and SAE documentation, and protocol violations.

9.2 Data that are reviewed

Data reviews include regulatory documentation, data entered directly into REDcap, progress notes, error corrections, contingency management logs, informed consent and eligibility criteria, AE and SAE documentation, and protocol violations.

9.3 Method of collection of safety information

Study progress and safety will be reviewed weekly via conference call with the Study PIs and research team. Progress reports, including patient recruitment, retention/attrition, and AEs, will be provided to PIs following each of the QA monitoring visits. An Annual Report will be compiled and will include a list and summary of AEs. The Annual Report will be submitted to the data safety monitoring board (DSMB), IRB and NCCIH per their requirements. The IRB and other applicable recipients will review progress of this study on an annual basis.

9.4 Frequency of data collection

Data collection is ongoing as it includes cumulative data (data received from the reSET-O app) and discrete data (data collected by surveys as completed at the research visits – baseline and week 4, 8, 12, and 24 visits).

9.5 Individuals reviewing the data

Oversight of data management, including data collection, storage, and export, security, tracking, data analysis software and hardware, and quality assurance will be the responsibility of Drs. Kawasaki and Nunes. A senior (bio)statistician and master's level analyst from the CTSI at Penn State College of Medicine will conduct analysis of REDCap survey data as well as app data from Pear Therapeutics. Dr. Pavlicova, senior Biostatistician at CUMC, will be available for consultation as needed throughout the data analysis process but will not play an active role in the analysis itself. Ms. Aydingolo, under supervision of Drs. Kawasaki and Nunes, will be responsible for monitoring of data export, storage, and management. Weekly remote meetings will take place between Drs. Kawasaki and Nunes, Ms. Aydingolo, and study site research staff.

9.6 Frequency of review of cumulative data

Cumulative data includes data collected by the app, reSET-O. Data checks will occur regularly including anytime a subject who has been assigned to reSET-O+TAU meets with a research coordinator for a research appointment or meets with their clinician involved in their substance abuse treatment and is affiliated with the PPI Hub and/or RASE or JFT These clinicians are defined as reSET-O research study coordinators, PPI Hub counselors, PPI Hub physicians, PPI Hub nurse practitioners, JFT "Certified Recovery Specialist's" or RASE care coordinator. These clinicians will login to the clinician dashboard side of the app and view how many modules the client has completed and the amount of rewards the client has earned, as well as logging urine drug screens as favorable or unfavorable. If a subject reports problems with the app or a clinician notes problems with the app and how data may be recorded, Pear Therapeutics, Inc. will be notified immediately to mitigate the issue(s).

9.7 Statistical tests

Drs. Kawasaki and Nunes will provide oversight to the statistical analysis process, ensuring timely provision of cleaned and locked data to the statistics team; data will be shared with the CTSI statistician and analyst following data lock, and Dr. Pavlicova (Columbia) will provide as needed consultation on data and statistical issues throughout the trial. Detailed statistical analysis plan is described under Section 8.3, above

9.8 Suspension of research

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

10.0 Risks

In general, risks associated with research comprised of behavioral interventions are low. reSET-O is a behavioral intervention that provides education about skills for avoiding drug use and otherwise improving health, modest incentives for adherence to treatment, and enhanced communication with providers, features which entail little anticipated risk. Potential risks for the research participation include psychological discomfort, answering sensitive questions related to substance use, mental health, and sexual behaviors, loss of confidentiality, and disclosure of information that meets reporting requirements. The interventions (reSET-O + TAU; TAU alone) may be ineffective, and patients' opioid use or associated problems may get worse.

There is a risk of loss of confidentiality as absolute confidentiality cannot be guaranteed. However, research staff will take precautions and maintain data created by participants to the degree permitted by the technology used in order to attempt to prevent loss of confidentiality.

There is a risk of randomization as only half of the participant population will receive reSET-O + TAU (n=100). Therefore, subjects who are assigned to TAU alone will not be exposed to the content affiliated with the reSET-O

app, including psychoeducation about skills for avoiding drug use and otherwise improving health. These subjects will also not receive the monetary incentives for adherence to treatment as affiliated with the app, or the monetary incentive to complete the qualitative interview as this interview is specific to the use of the reSET-O app.

All of the assessment surveys or questionnaires outline above may lead to some psychological discomfort as participants discuss sensitive areas related to high risk drug or sexual behaviors. They may feel uncomfortable answering such questions and/or become distressed when faced with reviewing their involvement in high risk behaviors.

Some of the questionnaires and interview questions will ask about participant feelings, such as depression, sadness, and anxiety. If responses indicate suicidal thoughts or risks of the subject hurting themselves or others, then we may need to break confidentiality and contact a licensed mental health professional or law enforcement officer. All subjects who express any suicidal thoughts will be referred for follow-up mental health counseling.

For subjects assigned to TAU + reSET-O, reSET-O should not induce any more discomfort than other treatments offered as part of outpatient substance abuse treatment. If participants become overly distressed, they will be directed to clinical staff working at their treatment program. Research staff (Research Coordinator and Research Assistants) will be trained in a safety protocol, so that if patients reveal acute distress or serious symptoms (e.g. depression or suicidal ideation) during a research assessment, the research staff will alert clinical staff at PACMAT, who will take over evaluating the situation and determine the severity of distress and if any additional evaluation or treatment is needed.

Subjects assigned to TAU + reSET-O will interact with reSET-O on the participant's mobile device (smartphone or tablet). A patient may interact with all the functionalities of reSET-O whether or not in the presence of a wireless signal or wifi. The program will update whenever coming in contact with wifi. Although information and answers within reSET-O cannot be accessed, the reSET-O website could become known and someone could look up the general website of the developer. They would be able to see that reSET-O (in general) and Pear Therapeutics, Inc. (the company that developed the reSET-O) are generally linked to substance abuse prevention and treatment.

Providers who are also considered subjects as a result of providing data about the app may be exposed to minimal risk. For instance, providers may find it cumbersome and time consuming to add some study related tasks to their overall workload; however, the goal of this study is not to add a significant amount of work to the providers; rather, the goal is to have the providers incorporate the use of the app during their clinical appointments with appropriate participants. We expect this workload to add approximately 6-12 minutes of additional time related to work tasks. Providers are free to engage in the app for longer than this if they plan to explore the app more and its resources. Providers may also find the open-ended discussion time consuming; however, they will only be asked to do this once.

The consent process will indicate the potential risks of participating in the study and participants will be advised that they do not have to answer questions with which they do not feel comfortable. The assessment will allow participants to skip any question they do not want to answer. The consent form will also indicate that participants are free to discontinue the study at any time for any reason with no explanation.

The summary of explanation of research for providers will outline any risks. It will be explained to providers that they are not required to participate in the open-ended discussion. They are not required to answer any questions about the app on the survey that they do not feel comfortable answering.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

There may be no benefit to participants in the research. Prior evidence suggests reSET-O may improve adherence with appointments, adherence to medication, and skills to avoid drug use and relapse. However, the purpose of the research is to determine whether this benefit will be observed when reSET-O is implemented within a Hub and Spoke system.

There is no benefit to the provider subjects.

11.2 Potential Benefits to Others

This study addresses one of the key barriers to implementation of MAT within efforts to expand MAT into underserved communities and primary care settings, namely the need to deliver evidence-based psychosocial treatment to help prevent relapse and foster a healthy lifestyle when behavioral health specialists are rarely co-located. Since reSET-O is a commercially mobile app, downloadable from the web, if found effective in supporting MAT in the Hub and Spoke setting under this research, it has the potential to be rapidly implemented across the U.S. health system in support of the STR initiative.

12.0 Sharing Results with Subjects

N/A

13.0 Subject Payment and/or Travel Reimbursements

All patients will be compensated for their time spent completing research evaluations, with $40 for the intake/baseline visit and $25 for each of the week 4, 8, 12, and 24 research visits (regardless if all tasks are completed onsite or if some tasks are completed remotely). An extra $25 will be provided at the week 8 or 12 visit, when a participant completes the qualitative interview. Since the qualitative interview is specific to the use of the reSET-O app, only subjects who have been assigned to TAU + reSET-O will participate in the qualitative interview. Thus, total compensation will be $165 in the form of gift cards for individuals assigned to TAU + reSET-O, and the total compensation for individuals assigned to TAU alone will be $140 in the form of gift cards.

Gift cards earned based on completed research appointments will be printed and handed to the participant or emailed to the participant – based on participant preference. If emailed, research assistants will follow-up with the participant to ensure that the gift card was received; however, it will be outlined in the consent form that "lost" gift cards will not be replaced. This study does not plan to use Greenphire because the ability to withdraw actual cash from the Greenphire card would allow a vulnerable patient with addiction to potentially withdraw money to purchase drugs or alcohol. Gift cards provided in this study are never associated with vendors that sell alcohol, drugs, or weapons (e.g., Target).

Additionally, patients assigned to TAU + reSET-O may receive contingency management rewards as part of the reSET-O application program. Participants also have the possibility of earning monetary prizes ranging from $5 to $100, in the form of a vendor gift card (e.g. Amazon or Starbucks), on a varying reinforcement schedule. Participants may earn prizes through a wheel-spin gaming system as coded within the app. Wheel-spins are earned from having favorable urine drug screens, meaning no illegal substance is present in the participant's urine, and learning module (within the app) completion. Urine drug screens are evaluated based on urine screens collected at visits 4, 8, 12, and 24, in which the assessing clinician or research coordinator will use the Clinician Dashboard on the reSET-O app to activate the lottery-based reward. The reSET-O app will manage the administration and activation of lottery-based rewards for participant completed modules.

Half of the lottery-based rewards will be e-language positive reinforcement (i.e.: "Good Job!"). 41.8% of the rewards will be $5 electronic gift cards; 8.0% of the rewards will be $20 electronic gift cards; and 0.2% of the rewards will be $100 electronic gift cards (see uploaded power point document as an example of e-gift card administration from the reSET-O app). All electronic gift cards are managed and administered by the reSET-O application and ultimate owners (Pear Therapeutics, Inc.). Participants may earn a maximum of approximately

$599 if they earn all possible draws; however, based on prior experience with such schedules, we predict that they will likely earn about 45%-65% of possible earnings (approx. $270-$390).

Provider subjects will not be compensated.

14.0 Economic Burden to Subjects

14.1 Costs

N/A

14.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Resources Available

15.1 Facilities and locations

The study sites will be the SAMHSA STR funded Pennsylvania Psychiatric Institute (PPI)-based Hub and Spoke system, called Pennsylvania Coordinated Medication Assisted Treatment (PACMAT), for which Dr. Kawasaki is the Principal Investigator. The PACMAT PPI Hub is a new specialized Addiction Treatment Program at Pennsylvania Psychiatric Institute (PPI) in Harrisburg, PA, and Spokes are medical practices in the surrounding, largely rural counties of central Pennsylvania, including Dauphin, Cumberland/Perry, Franklin/Fulton, Lancaster, and Lebanon counties.

All research procedures will occur in a hybrid of remote and in person, depending on patient preference and the current COVID situation in Dauphin County, PA.

15.2 Feasibility of recruiting the required number of subjects

Since the opening of the PACMAT PPI Hub in and collaboration with spoke providers through RASE in November 2017, over 700 OUD patients have been treated at the PPI Hub, whereas Spoke providers have treated over 900 OUD patients collectively. The majority of this combined patient population use MAT. Thus, the patient flow appears adequate especially given the broad eligibility criteria. We are excited about our new collaboration with Just for Today for this research project as they have locations in several counties in southern Central Pennsylania and have a broad reach of patients on MOUD.

15.3 PI Time devoted to conducting the research

20% research time

15.4 Availability of medical or psychological resources

Medical and psychological resources are available at PPI should a subject endorse suicidality on the PHQ-9 and subsequent C-SSRS. If a subject endorses suicidality, trained and certified research staff will administer the C-SSRS. If the C-SSRS administration determines that suicidal ideation and plan are present, then the research staff will contact a doctor or nurse practitioner to take over the evaluating situation. At the opioid treatment program at PPI, there are currently three medical doctors and one nurse practitioner.

15.5 Process for informing Study Team

N/A

16.0 Other Approvals

16.1 Other Approvals from External Entities

This study is being considered for funding through NIH and, as such, has undergone scientific review as part of the application approval process.

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of "HRP-901 - Human Body Fluids for Research Form" in CATS IRB.

☐ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of "HRP-903 - Radiation Review Form" in CATS IRB.

☐ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

17.0 Multi-Site Study

17.1 Other sites

N/A

17.2 Communication Plans

N/A

17.3 Data Submission and Security Plan

N/A

17.4 Subject Enrollment
N/A

17.5 Reporting of Adverse Events and New Information
N/A

17.6 Audit and Monitoring Plans
N/A

18.0 Adverse Event Reporting

18.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that 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 or prolongation of existing hospitalization, a persistent or significant incapacity or 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, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject 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.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:

Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

18.2 Recording of Adverse Events

N/A

18.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.4.1 Written IND/IDE Safety Reports

N/A

18.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

N/A

18.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

18.6 Unblinding Procedures

N/A

18.7 Stopping Rules

N/A

19.0 Study Monitoring, Auditing and Inspecting

19.1 Study Monitoring Plan

19.1.1 Quality Assurance and Quality Control

Monitoring will be done by the PI. RFMH team staff member Nicole Aydingolo will periodically monitor Penn State's regulatory binder and data collection for quality assurance purposes.

19.1.2 Safety Monitoring

N/A

20.0 Future Undetermined Research: Data and Specimen Banking

20.1 Data and/or specimens being stored

N/A

20.2 Location of storage

N/A

20.3 Duration of storage

N/A

20.4 Access to data and/or specimens

N/A

20.5 Procedures to release data or specimens

N/A

20.6 Process for returning results

N/A

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22.0 Confidentiality, Privacy and Data Management

IMPORTANT: The following section is required for all locations EXCEPT Penn State Health and the College of Medicine. Penn State Health and College of Medicine should skip this section and complete "HRP-598 Research Data Plan Review Form." In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all other sub-sections of section 22.

See the Research Data Plan Review Form