Study Protocol and Statistical Analysis Plan

Study Title: Reward-Based Recovery Outcomes Management for Opioid Use Disorder

NCT #: NCT04669249

Current Date: 09/30/2022

Last Update/Approval Date: 02/09/2022

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PROTOCOL:

Study Purpose

This project will evaluate a reward-based recovery management mobile app (PROCare Recovery), which seeks to address two ubiquitous problems facing Office-Based Opioid Treatment (OBOT)/Opioid Treatment Programs (OTP): (1) poor medication adherence/ treatment retention, and (2) lack of standardized and valid outcomes monitoring systems to inform care.

Given the chronic, relapsing course of opioid use disorder (OUD), effective treatment requires long-term management. Treatment with buprenorphine is a viable option, associated with a variety of positive outcomes, including most notably, reductions in overdose mortality [3-12, 36]. Poor medication adherence is associated with program attrition, which in turn is linked to several negative outcomes [7, 12, 17-19]. Another widespread problem in OBOT/OTP settings is the relative absence of standardized and objective instruments. Although monitoring of treatment response is standard practice for many chronic medical conditions, addictions treatment providers have been slow to adopt these practices. Outcomes data collected from a standardized, valid, and reliable remote patient monitoring system holds great potential to drive clinical decision-making, and ultimately help payers, patients, and families identify programs from which patients have been empirically found to achieve remission. Despite the tremendous value in tracking patients post-detoxification and documenting outcomes, monitoring efforts are often hindered by relying on traditional methods and using existing staff to collect outcomes.

The proposed PROCare Recovery patient-facing mobile app will leverage the power of two established evidence-based approaches (i.e., contingency management and self-monitoring) to incentivize recovery and increase adherence to buprenorphine, engagement in care plans, as well as participation in routine outcomes monitoring. The PROCare Recovery mobile app offers providers real-time, clinically meaningful patient-reported outcomes data in accordance with best practices (measurement-based care) and national standards. Patients can earn both non-monetary and monetary-rewards (via funds deposited to a smart debit card blocking cash withdrawals and purchases at certain vendors) for medication adherence, engagement in care, and completing outcomes monitoring surveys. Remote adherence tracking and electronic outcomes monitoring extends care management and coordination outside the treatment facility or provider's office and into the patient's home. Based on trends in patient-reported outcomes collected remotely, providers can modify the care plan accordingly in real-time.

Study Aim

Specific Aim: *Study preliminary effectiveness of PROCare Recovery on medication adherence, engagement in care, participation in remote patient monitoring, and clinical health outcomes*. A 4-week, randomized proof-of-concept pilot study will be conducted. Primary outcomes (and endpoints) include rates of: buprenorphine adherence (>90% daily doses; [14]), care plan adherence (>50% of weekly care plan activities; [53]), and participation in daily outcomes monitoring surveys (>90%; [44]) using a combination of patient/provider self-report and verification via app/dashboard, GPS location tracking data (to confirm attendance at outpatient appointments), and clinic urinalysis drug screen (UDS) results.

Study Procedures & Statistical Analysis Plan

Recruitment: Patients will be recruited for the 4-week proof-of-concept trial from the South Florida Behavioral Health Network in Miami, FL. A targeted educational and recruitment in-service meeting will be conducted with the participating South Florida Behavioral Health Network opioid treatment program site, as facilitated by the President/CEO. The goal of the in-service meeting will be to make providers and clinical administrators aware of this project, and to assist in identifying eligible participants. Providers and administrators at the site will be informed about the purpose, procedures, risks, and benefits of the protocol, as well as the inclusion and exclusion criteria, so that they can best discuss the research project with individual staff and patients that might be eligible and interested, and make appropriate referrals to the research team for study inclusion.

Participants will be recruited by designated site staff under the direction of the PI. Treatment center intake staff will identify potential participants based on study inclusion/exclusion criteria and refer to research staff to confirm eligibility and enroll in the trial. Treatment staff will be made aware that participants must be >18 years of age, own a smartphone, have a primary DSM-5 opioid use disorder diagnosis, be receiving buprenorphine, and cannot have any severe mental illness (e.g., schizophrenia) or other condition that would preclude them from participating. Research staff will conduct a second layer of verification (following referral from treatment staff) to ensure all participants are eligible and able to fully participate. To aid in recruitment and retention, all participants will be compensated for their time (see *Procedures* sections below for more information regarding compensation amount). Once participants are actively enrolled in the 4-week pilot study, research staff will maintain at least weekly personal contact with participants. The research team has relevant experience working with addictions treatment populations, and efficiently performing recruitment, screening, and follow-up to maintain participant flow and high follow-up rates. Recruitment and retention tracking will be reviewed on weekly study team conference calls so that potential recruitment shortfalls can be identified proactively and recruitment efforts broadened.

Procedures: A 4-week, randomized proof-of-concept pilot study will assess the feasibility, acceptability, and effectiveness of the PROCare Recovery app. Participating providers will be trained on the PROCare app prior to enrolling patients. Eligible patients will complete an electronic informed consent form prior to enrollment in the trial. Participants will complete baseline measures of study outcomes. Patients will be oriented to the app at the outset of treatment during the induction phase and continued throughout the 4-week trial. Remote patient outcomes data will be collected during treatment and at the end of the study via the PROCare app, which will include the same measures completed at baseline. Following 4-week participation, patients will be contacted to provide qualitative/quantitative feedback on PROCare usability.

Primary outcomes (and established endpoints) include rates of: buprenorphine adherence (>90% daily doses [14]), care plan adherence (>50% of weekly care plan activities [54]), and participation in daily outcomes monitoring surveys (>90% [45]) using a combination of patient/provider self-report and verification via app/dashboard, clinic UDS results, and GPS location tracking data (to confirm attendance at outpatient appointments). Pre/post change in the secondary outcomes will be assessed using validated measures: opioid/other substance use (days of use), craving (Opioid Craving Scale [63]), motivation (Readiness Ruler [64, 65]), self-efficacy (Brief Situational Confidence Questionnaire [70]), quality of life (WHO EUROHIS Quality of Life Scale [66]), DSM-5 OUD diagnostic criteria [71], depression (Patient Health Questionnaire-9 [PHQ-9])/anxiety (General Anxiety Disorder-7 [GAD-7]). The System Usability

Scale [72] will be used to objectively quantify the usability of the PROCare prototype using a naive sample (Aim 2 sample is distinct from Aim 1 sample). Participants assigned to the PROCare group will also be asked to complete ultra-brief daily check-in measures. Additional information collected from PROCare participants will include activity data within the app (e.g., clicks, timing). Pre/Post data will be entered into a web form on tablet, laptop, or mobile device, and immediately sent (and stored), item-by-item, to the cloud platform that is hosted in a HIPAA secure physical and software environment. The entered data is visible to the participant in the screen of the device at that time, but is not stored locally.

Participants in both conditions (PROCare and treatment as usual/control) will receive $50 for their study participation. As stated in the consent form, participants will only receive the $50 gift card after they complete the 4-week follow-up. In order to receive the $50, the participant must complete both the baseline and follow-up measures. Patients allocated to the PROCare group will have the opportunity to earn an additional $150 in monetary incentives over the course of the 4-week trial based on their level of participation in various activities using the app (competing brief daily check-in surveys, reading psychoeducational materials in the content library, answering questions about adherence to their buprenorphine medication, attending treatment appointments, etc.). Participants in the PROCare group will receive monetary incentives using a smart debit card (*True Link*), which has a feature that can block purchases from certain vendors (liquor stores, etc.) and also block cash withdrawals. True Link smart debit cards have been used to good effect in numerous addiction treatment settings and similar reward-based research studies, and represent the most feasible option relative to cash payments. Due to randomization, participants will have an equal chance of being allocated to the PROCare group and having the opportunity to earn additional incentives. The amount of additional incentives for completing various activities within the app ($150) is consistent with other similar reward-based substance use disorder apps.

Statistical Analysis Plan: Consistent with best practice guidelines for pilot trial sample size calculations with a medium effect size [73, 74] the proposed pilot study will attempt to include a minimum of 15 participants per arm. Accounting for an expected 30% attrition rate, we will attempt to recruit 40 patients. Independent samples t-tests and Pearson's chi-squared tests will determine mean differences on continuous and dichotomous variables, respectively.

Specify study eligibility criteria.

Patients/providers for pilot testing will be recruited through the South Florida Behavioral Health Network, Inc. in Miami, FL. Patients must be ≥ 18 years of age, own a smartphone, have a primary DSM-5 (APA, 2013) opioid use disorder (OUD) diagnosis, be receiving buprenorphine as part of their treatment, and no current suicidal ideation or severe mental illness (e.g., schizophrenia).

Background/significance and preliminary studies related to this project.

Background/Significance: Given the chronic and relapsing course of severe opioid use disorder (OUD), effective treatment requires long-term management. Medication treatment is a viable treatment option, associated with a variety of positive outcomes [3-12]. Poor adherence and premature discharge (early dropout) are widespread issues in Office-Based Opioid Treatment (OBOT)/Opioid Treatment Programs (OTP) settings [13-15]. Only 31% of patients receiving OUD medication are adherent for > 1 year and less than half are adherent at least 90 days [14].

Poor adherence is associated with attrition, which in turn is associated with unfavorable long-term outcomes [16]. Problems of poor adherence and attrition are salient issues in OBOT/OTP settings given they are associated with higher rates of relapse, mortality, and treatment re-admissions [7, 12]. OUD patients who are adherent to their medication regimen, however, have been found to demonstrate favorable outcomes [17-19].

According to the U.S. Surgeon General [20], effective, evidence-based medications and interventions for the treatment of OUD exist, but they remain under-utilized. In addition to 3 FDA-approved medications for OUD (buprenorphine, methadone, and naltrexone), there are psychosocial interventions—such as contingency management—with demonstrated effectiveness. Contingency management, which involves the provision of patient rewards/incentives for exhibiting desired behaviors (e.g., drug-free urinalysis drug screens [UDS]), has been linked to longer periods of abstinence, longer treatment engagement, and greater improvements in social functioning among OUD populations [21-25]. Despite positive findings, there are a number of limitations. Maintenance of long-term benefits has proven difficult due largely to the eventual withdrawal of reinforcement [26]. Many contingency management procedures reward drug-free urinalysis screens exclusively, and there is only a low chance that the desired behavior will actually be rewarded in the commonly used probabilistic “prize-based” procedure (i.e., patients earn draws from a prize bowl every time the target behavior is exhibited and the prize bowl contains slips of paper that either have no monetary value or indicate a low-value prize).

Another well-studied and effective intervention is self-monitoring, which in and of itself has been found to reduce substance use and related problems [27, 28]. Self-monitoring (also known as ecological momentary assessment [EMA] when field assessments utilize various devices) has been used as both a means to study behavior as well as a standalone intervention [29, 30]. Contingency management and self-monitoring have been around for decades, but they remain underutilized in the current digital health era. Many elements of these approaches are rudimentary, outdated, and onerous (requirement for in-person appointments, use of a “fish bowl,” paper-and-pencil, separate single-function device or electronic diary), which warrants the need for development of technology-enabled solutions that can leverage the power of these evidence-based approaches in a way that is viewed by patients/providers as acceptable and feasible relative to traditional methods. With automation, prompts, and a meaningful user-friendly interface, PROCare seeks to address traditional barriers that have precluded uptake and widespread adoption of these two effective approaches to increase medication adherence [19]. Although treatment lasting of 12 months is essential for long-term OUD recovery [35], most patients do not engage in treatment for the needed duration [14]. This creates a strong case for technology-enabled solutions to enhance adherence/engagement in treatment.

A key indicator of quality treatment is having valid and reliable measurement-based and outcomes monitoring systems in place to track patients’ response to treatment. When providers use such information to drive clinical decision making and inform patients’ treatment, this is known as measurement-based care. In the current OUD treatment landscape, providers are increasingly tasked with the expectation to not only measure patient performance, but to demonstrate the success of their clinical services. Data collected from a well-designed (i.e., standardized, valid, reliable, and free of bias) measurement-based outcomes monitoring system will help payers, patients, and patients’ families identify effective and outcomes-informed programs. Unfortunately, in the cost-conscious times many programs operate, it is unrealistic to expect providers to collect routine outcomes data from their caseload in addition to their day-to-day responsibilities. Despite the tremendous value in tracking and documenting outcomes, monitoring efforts are often hindered by relying on outdated methods as well as limited staff time

to collect outcomes data given their primary responsibility is to provide direct patient care. Training and then relying on clinical/support staff to handle outcomes monitoring is expensive and time-consuming, and requires ongoing supervision and quality management. Fortunately, many outcomes measures are self-report, which lend themselves well to being delivered remotely by computer, smartphone, or tablet using interactive technologies found to be valid approaches relative to traditional methods [30, 43]. Offering reinforcements or incentives for patients to complete routine assessments is a viable option associated with high response rates among addictions treatment populations [44, 45].

OBOT/OTP settings often fail to use standardized/objective instruments. Without formal, psychometrically sound measures, providers are unable to document outcomes and quantitatively demonstrate any kind of meaningful impact. The adoption of a measurement-based care system is required for all treatment providers, irrespective of level of care. The top two national accrediting bodies, *The Joint Commission* [46] and *CARF International*, now seek evidence of compliance to this outcome measures standard and describe requirements for a reliable performance measurement system. All of the items included in the PROCare app are valid and backed by empirical research, thereby ensuring providers are in compliance with national standards. With PROCare, many tasks of measurement-based care are automated, and patients are incentivized to provide clinically-meaningful outcomes data using the app, which can be reviewed by the provider in real-time using the clinical dashboard to inform care.

Preliminary Studies: Dr. Proctor (PI) has been involved in relevant addictions outcomes work through his role as an expert advisor and researcher to several agencies ranging from individual OTPs to national health care organizations. Dr. Proctor has led a number of studies focused on solutions to increase adherence to care plans and their impact on outcomes [54-56], and has published numerous articles involving opioid medication treatment populations [15, 57-60]. He frequently consults with treatment agencies (buprenorphine clinics) on measurement-based care and improving their systems through recovery monitoring. Preliminary results from Dr. Proctor's research show that protracted care plan management—delivered via telephone—is associated with high rates of abstinence, adherence, and quality of life up to 1 year after treatment [56]. These favorable but preliminary indications of the effectiveness of telephone-based care management require replication in a well-powered study. Investigation of alternative, more acceptable digital health solutions (mobile app) is warranted; the proposed project will fill these gaps.

Dr. Tien (PI) has over three decades of experience with the application of public health and biomedical science to guide development of information technologies, and since 2004 has led the development and commercialization of BH-Works, a uniquely health science architected cloud platform and web tools for behavioral health and social determinants integration. BH-Works will serve as the innovation infrastructure for the proposed PROCare platform, which supports efficient and reliable implementation of new software features, greatly reduces technology uncertainties/risks, and assures commercial scalability. Existing incorporation of the HL7 FHIR (Fast Healthcare Interoperability Resources) standard in BH-Works enables efficient integration with other systems such as EHRs, and will facilitate bringing research and practice closer together at data, information, and scientific knowledge levels.

PERFORMANCE SITES:

South Florida Behavioral Health Network, Inc. (d.b.a. Thriving Mind South Florida), Miami, FL

INFORMED CONSENT:

Consent Procedure: Participants will be identified by the program and referred to the research team to obtain consent, randomize, and enroll in the pilot trial. Eligible participants will receive an email from the research study with a link to the electronic consent form. The consent form will provide information about what participation in the study will entail, the risks and benefits of the study, and their rights and responsibilities as a research participant. By electronically signing the form, participants will indicate that the research study has been explained to them, their questions have been answered, they have had the time to consider fully whether to participate, and that they agree to participate in the study.

RISKS & BENEFITS:

Data collected will only be used for research purposes. Only members of the research team will have access to the data collected as part of this proposed study. No individual's data will be provided to any individual outside of the research team. Participants may find that some survey questions are uncomfortable to answer. Participants will be made aware of their right to refuse to answer any question, that their participation in the research study is completely voluntary, that they may choose not to participate in the study, and that they may withdraw their participation in the research study.

Although there is low risk associated with this research study, Protected Health Information (PHI) may be accidentally disclosed outside of the study. To take part in the research study, participants must give the research team permission to collect PHI as disclosed in the informed consent form. The research team will use their best efforts to keep information secure and will only use or share health information of participants as disclosed in the informed consent form or as permitted or required by law. No names or individually identifying data will be associated with any published reports. Furthermore, the research team will ensure that steps used to maintain data confidentiality are current and in compliance with human subjects protection regulations.

All study team members and site staff will be trained in the Health Insurance Portability and Accountability Act (HIPAA), study privacy policies, and research ethics. Only HIPAA and CITI trained research staff will be involved in the proposed study and have access to the data collected. The study team will make best efforts to keep the information secure. Furthermore, the research team involved in the study will work closely with the IRB to ensure that steps used to maintain data confidentiality are current and in compliance with human subjects research protections regulations.

All risks will be clearly explained in the approved study consent form. All participants will be informed of potential risks prior to enrollment. During data collection, it is possible there might be some distress associated with questionnaires. All measurements in this study have been tested and validated for use in addictions treatment populations. Participation is voluntary, and the participant may choose not to participate in the research study or to withdraw at any time. Every effort to minimize risks will be made.

Participants may not benefit from being in the study; however, the information collected from these participants will provide valuable information for individuals receiving treatment for opioid use disorder to test the preliminary acceptability, feasibility, and effectiveness. This study is no more than minimal risk and has the potential to greatly benefit public health and Opioid

Treatment Program (OTP)/Office-Based Opioid Treatment (OBOT) settings. The benefits of this study and the impact for future treatment of individuals with opioid use disorder greatly outweigh the risks.

Procedures for monitoring ongoing progress of the research and reporting adverse events.

Data safety and monitoring will be the responsibility of the project PIs (Dr. Steven Proctor/Dr. Allen Tien). Prior to the study, all current and ongoing health issues and medications will be asked and logged, to document that they predate the study. Over the course of the study, participants will be asked to report any health events, changes in medication, and hospitalizations, and a determination will be made as to whether these may be related to their participation in the study protocol. Follow-up data will be collected on potential adverse events, and the study team will track dates of each event, intervention needed (if applicable), severity, and likelihood that the event is related to the study.

The research team defines an Adverse Event (AE) as any untoward medical occurrence in a participant that is temporally associated with participation in the study, whether or not it is attributed to the study. Unanticipated Adverse Events (UAE) are those occurrences not noted in the study consent form. A Severe Adverse Event (SAE) will be defined as an AE that is life-threatening, requires inpatient hospitalization, and/or results in death or severe disability. All events will be graded as to their attribution (related or unrelated) and their severity. Medical occurrences that are reported to the PI or study staff will be documented, and it will be determined whether the event was pre-existing before the study and whether it meets criteria for an AE or SAE. All AEs will be reviewed by the PIs within 72 hours; the PIs will review SAEs within 24 hours. AE and SAE reports will be generated for each event. Reports will include all relevant information (e.g., description of the event, when and how it was reported, as well as any official chart records or documentation to corroborate the event; determination of attribution). AE and SAE reports will be sent to the mdlogix IRB, and the NIH Program Official.

We will use established reporting timeframes. UAEs (those not noted in the study consent form) will be reported to the IRB within 10 working days of when we become aware of the event, or sooner as required by the IRB. Any deaths related or possibly related to participation in the research will be reported immediately within 24 hours of when we become aware of the event. Anticipated AEs will be reported to the IRB at the time of continuing review. Any study-related serious AE will be reported to the NIH within 2 weeks; all others will be included in the annual report to NIH.

PRIVACY & CONFIDENTIALITY:

Methods and procedures that will be used to safeguard the confidentiality of participants and their data.

Only the minimum necessary private information is collected for the purposes of the study. The app will be on cell phones and will be connected to BH-Works. No PHI other than cell phone registration data will be stored in the app on the phone. All clinical data will be stored in BH-Works private cloud that is fully HIPAA compliant. Any procedures conducted as part of the study will be conducted in private settings to the extent possible. Recruitment/consent will occur

in a private setting. Participants will be able to ask questions in a private setting. To further protect participant privacy, this research will be covered by a Certificate of Confidentiality issued by the funding agency to the research team. A Certificate of Confidentiality allows the researchers to refuse to disclose information that may identify participants in any legal or court proceeding or to anyone who is not connected with the research except if there is a law that requires disclosure (reporting child abuse and neglect, harm to self or others), or the participant gives permission to disclose their information.

To achieve maximum confidentiality, all data collected as part of the study will be coded with a unique study identification number. A master list linking the identification number and participant name will be kept separately. The participant's identity will not be revealed to anyone outside of the research team without his or her written permission. Only HIPAA and CITI trained research study staff will have access to the data collected. Only designated members of the research team will have access to the data files. All electronic files (database, spreadsheet, etc.) containing identifiable participant information will be password-protected. Databases that contain private health and identifiable information will be behind firewalls. Project computers will all be password-protected and stored in locked offices in a secured environment.

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