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Technology Improving Success of Medication-Assisted Treatment in Primary Care: Phase II

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LIST OF ABBREVIATIONS AND ACRONYMS

DATA-2000	Drug Addiction Treatment Act of 2000
EHR	Electronic Health Record
GCP	Good Clinical Practices
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
MAT	Medication Assisted Treatment
NIDA	National Institutes of Drug Abuse (United States)
NIH	National Institutes of Health (United States)
OARS	Opioid Addiction Recovery Support
OUD	Opioid Use Disorder
PI	Principal Investigator
PWID	Persons Who Inject Drugs
ROI	Return on Investment
TAU	Treatment as Usual
UCLA	University of California, Los Angeles

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1 INTRODUCTION

1.1 Background

Drug overdose is the leading cause of accidental death in the United States (U.S.), with over 72,000 fatalities in 2017,[1] of which 47,600 (66%) are attributable to opioid overdose.[2] This opioid epidemic has become North America's most widespread behavioral public health problem, with a higher number of deaths due to drug overdose in 2016 compared to deaths due to HIV at the peak of the AIDS epidemic in the U.S.[3] Individuals with opioid use disorders (OUD) in the U.S. comprise three contemporary epidemics: (1) younger persons in rural areas, (2) younger persons in suburban areas, and (3) older, experienced users in urban areas.[4,5] Moreover, the growing epidemic now significantly involves Black and Latino individuals in urban areas such as New York City, where opioid overdose rates among Black individuals surpassed those of White individuals for the first time last year. Progression from prescription opioid use to injection heroin use is common for the first two groups; all three groups are affected by the increased availability of fentanyl. Fentanyl and its analogues represent the "third wave" of the domestic opioid epidemic and are major contributors to the massive increase in drug overdose deaths.[6] Injection drug use is the primary driver for doubling the incidence of Hepatitis C virus (HCV) infection in the U.S., with several recent HCV outbreaks among people who inject drugs (PWID).[7-11] Moreover, unsafe injection practices that drive HCV incidence often foreshadow increases in HIV incidence and most PWID living with HIV are co-infected with HCV.[12]

Despite the staggering overdose deaths and the increasing rates of OUD across the country, the number of providers who have waivers to prescribe or dispense buprenorphine under the Drug Addiction Treatment Act of 2000 (DATA-2000 waivers) cannot close the gap for the number of patients who need treatment.[13,14] Moreover, among those who enter medication-assisted treatment (MAT) for OUD, the majority discontinue early in the course of treatment.[15,16] Current gaps in the referral process contribute to delays to care, with the obvious solution being the improvement of systems to address these issues and to expand the use of MAT for the many patients out of care.[17] Office-based buprenorphine treatment is a safe and effective form of MAT that can be delivered in most primary care settings,[18] and retention in treatment is associated with decreased morbidity and mortality among people with OUD.[19,20] Another factor that interferes with primary care providers treating patients in their practices using buprenorphine involves national clinical guidelines that recommend treatment be accompanied by psychosocial interventions,[21,22] but such interventions are not available within many practice settings,[23,24] and evidence for effective psychosocial interventions for buprenorphine treatment is limited.[25]

There exists an outstanding opportunity for the power of the electronic health record (EHR) to be harnessed and leveraged to assist primary care providers (PCPs) in being able to have immediate reports on the response (or lack of) to MAT among their patients (e.g. monitoring attendance to clinic visits; reviewing urine drug screen results) and to track attendance by their patients with their counselors and affiliated psychosocial providers. Examples of successful application of software solutions within the electronic health record for management of chronic diseases other than addiction include products for screening and treating HCV,[26] lung cancer,[27] and diabetes.[28] These studies and projects provide a sound premise for the current proposal to develop and evaluate an electronic health record tool to improve outcomes when treating OUD in the setting of primary care clinics.

The **O**pioid **A**ddiction **R**ecovery **S**upport (OARS) software, a solution provided by Q2i (a company based in Boston, MA), is designed to improve clinical management of patients receiving MAT for OUD using a dashboard that shows real-time measurement of patient achievements in their recovery progress. The software also provides opportunities for patients to interact with their clinical providers. As such, patients may be better connected to and supported by the healthcare team throughout their recovery. This extended connection and support may foster clarity and adherence to treatment plans,

better retention in treatment, and a corresponding reduction in negative treatment outcomes such as relapse and overdose.

OARS is designed to be used as a standalone solution or integrated into an existing EHR. At the center of OARS is a software program, MATRA, that uses artificial intelligence to analyze information from the EHR and from patients to provide an early and accurate relapse risk assessment for patients receiving MAT for OUD. The MATRA system determines risk factors and generates risk estimates by mining and correlating past data and results (i.e., what past patients did and whether they relapsed), allowing for earlier risk detection and consideration of a variety of subtle factors. The system continues learning from real-time data, including how well results fit the known models. The resulting MATRA score is used by clinicians as a factor for considering early interventions and case management decisions to prevent lapse or relapse. The advantage of MATRA and its use of artificial intelligence is that it continuously mines data used to refine risk scores that are used to inform treatment decisions. Data used by MATRA in the continuous learning algorithms include the patient's attendance and levels of engagement in treatment, an electronic "journal" that patients use several times per week to self-report mood (levels), ongoing responses to their treatment, the frequency and extent of use of educational and motivational materials available to patients in OARS, and results of urine drug tests. An algorithm compiles these various types and formats of data, with training to predict future outcomes using real-time data. The algorithm continues to learn and refine predictions using training and validation datasets, which is consistently improving accuracy for predicting treatment outcomes, particularly drug relapse.

1.2 Study Rationale

As of 2015, there were 3,404 buprenorphine clinics servicing around 77,000 patients; whereas, in 2017, over 2.4 million people in the United States experienced OUD.[29] The greater number of deaths among OUD patients in general medicine settings compared to those in specialty care settings indicates that lack of access and treatment availability is a significant barrier that needs to be addressed.[30] Increasing MAT program availability in primary care is crucial to resolving this issue, though many providers elect not to treat OUD using buprenorphine due to stigma related to treating patients with addiction and lack of confidence in treating patients who can be challenging.[31-33] Equipping and empowering providers with technology that provides decision support and enables better connection, insight, and overall management of their patients with OUD could increase confidence in establishing or expanding a MAT program, and thereby increase the availability of MAT in the primary care setting.[34]

In phase I of this study we sought to modify the OARS platform for use in primary care settings by conducting interviews with primary care providers and their patients with OUD. These qualitative data together with additional quantitative data collected as participants used the OARS platform were used to estimate the feasibility and acceptability of using OARS for the treatment of OUD in the primary care setting. The go / no-go criteria of phase I were appropriately satisfied leading to the initiation of this phase II study protocol.

2 OBJECTIVES

2.1 Primary Objective

The primary aim of this study is to test the effectiveness of the OARS platform in improving clinic-level outcomes associated with the treatment of opioid use disorder, including the number of patients treated with MAT, opioid abstinence (opioid-negative urine toxicology results), and program retention (appointment attendance), compared to treatment as usual (TAU) for patients from six primary care clinics.

2.2 Secondary Objective

The secondary aim of this study is to assess the effect of provider and patient engagement with the OARS platform (number of days of OARS engagement, number of interactive features used) on patient opioid abstinence (opioid-negative urine toxicology).

2.3 Exploratory Objective

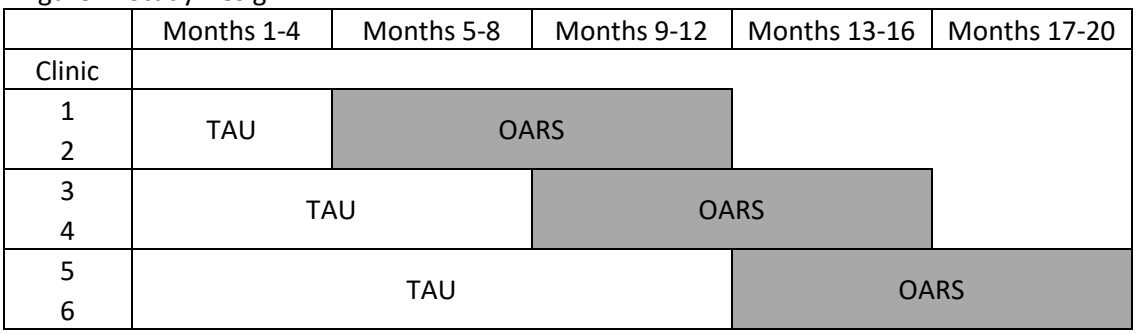
Exploratory data will also facilitate the estimation of return on investment (ROI) for OARS under a variety of scenarios. The perspective for the ROI is that of a provider using OARS and the emphasis is on changes in revenue associated with OARS compared to TAU. The alternative scenarios will reflect alternative treatment financing regimes as well as sensitivity analyses around key parameters.

3 STUDY DESIGN

3.1 Description of Study Design

This study tests whether MAT in the primary care setting delivered via the OARS platform can result in improved clinic-level outcomes compared to TAU using a stepped-wedge effectiveness trial design (see Figure 1). This design facilitates data collection on patient outcomes prior to implementation of OARS, data that is individual to each clinic and that will serve as baseline values. In turn, baseline data collected under TAU will be compared to corresponding data collected through OARS for the purpose of assessing whether OARS use results in improved outcomes. This study design necessitates data collection only through EHR data review and abstraction; no information is required directly from patients for the purpose of this study.

Figure 1. Study Design



3.2 Summary of Study Endpoints

The following primary outcomes will be assessed under TAU and OARS conditions:

1) Number of patients PCPs can treat using MAT in primary care settings;
2) Retention in treatment (number of patient visits kept with PCPs, length of stay in treatment);
3) Proportion of opioid-free urine tests.

The secondary outcome of opioid abstinence, defined as opioid-negative urine toxicology, will be assessed on a patient level as patients are treated for OUD under the OARS condition.

Exploratory outcomes will include additional elements from several administrative sources, namely meta-data from OARS software and additional detail on records of service delivery from the providers'

electronic health records, claims database, and OARS. OARS meta-data will primarily be time stamps around key service delivery or key OARS activities to account for differences in time spent during traditional clinical service delivery and possible additional wrap-around activities. Service delivery measures will include the number of units of different services provided to each patient over time.

3.3 Time to Complete Enrollment

This study is projected to take 20 months to complete. Study start-up activities will involve informational procedures at the clinics over a period of two to four months prior to study commencement.

3.4 Expected Duration of Participation

Primary care clinics can expect to be in the study for a period of 12 to 20 months depending on the date of OARS implementation that is determined for each clinic.

4 STUDY POPULATION

4.1 Selection of the Study Population

The study population will consist of six primary care clinics who prescribe MAT (Suboxone or buprenorphine) to patients with OUD. Across all six clinics, there is a minimum of 200 patients needed to provide statistical power to assess primary and secondary objectives.

4.2 Inclusion Criteria

The research conducted in this study involves a review of patient medical records. In each clinic, the research team will work with clinic administrators to identify PCPs and patients treated by the PCPs using MAT who will contribute data to baseline and who will use the OARS platform when it is integrated into the EHRs at the determined date.

Clinics will need to meet the following criteria to participate in the study:

- Provide treatment to patients in the setting of primary care (e.g. family medicine, internal medicine)
- Have at least one provider with a DATA-2000 waiver who provides primary care and MAT to patients
- Have at least 35 patients receiving MAT for OUD
- Have an established EHR

4.3 Exclusion Criteria

Clinics will be excluded from participation in the study based on the following criteria:

- Provide only specialty care (e.g. addiction medicine, behavioral health)
- Have fewer than 35 patients receiving MAT for OUD
- Do not have an established EHR or cannot provide appropriate access to allow integration of OARS within the clinic's EHR

5 STUDY PROCEDURES

The OARS platform is owned and maintained by Q2i. For the purpose of conducting this study, Q2i is partnering with researchers from the UCLA Departments of Family Medicine and Psychiatry and Biobehavioral Sciences to execute the research at each of the six participating clinics.

The research team, composed of study staff at both Q2i and UCLA, will determine the order of implementation of the OARS platform by clinic. Study staff will then notify each clinic of the start date of the OARS platform implementation for their clinic. Following start date assignment, the baseline phase of the study will commence in which patients will receive standard treatment for OUD provided by each clinic (TAU).

Data collected will include both patient-level indicators from each clinic's EHR (see data collection tool) and provider-level indicators obtained from interviews with PCPs. .Baseline data will provide an assessment of TAU for up to a period of four (clinics one and two), eight (clinics three and four), and 12 (clinics five and six) months prior to implementation of the OARS platform. Study staff will provide each clinic with relevant data collection specifications and each clinic's IT staff will be responsible for submitting requested data elements from the clinic's EHR to Q2i through secure file transfer. Up to two PCPs from each clinic will be interviewed (see semi-structured interview guides) during TAU, at one month after OARS implementation, and at the end of the OARS period. Eligible PCPs will receive a recruitment letter that outlines the study activities with a request for interested providers to contact study staff at UCLA.

Concurrently with baseline data collection, study staff will also work with clinics to initiate the OARS platform according to the determined start date. Clinics will begin using the OARS platform with all MAT patients seen at that time. Therefore, patients receiving TAU when the OARS platform is implemented will shift care to using OARS. Patient care and treatment of OUD will then commence under the OARS condition for a period of eight months for each clinic. To compare outcomes under the OARS condition to those that occurred under TAU, comparable data will be directly collected through the OARS platform. Additionally, patient-level data collected during the OARS condition will be used to assess to what extent different levels of provider and patient engagement with OARS relate to opioid abstinence among patients. Data elements of interest (patient demographics, medications, and billing information) that are not transmitted through OARS will be obtained from each clinic's EHR and delivered directly to Q2i through secure file transfer.

All patient-level data will be collected via the EHR and transmitted to Q2i study staff via a secure file transfer system. Patients' medical record identifier will be included in each of the data transmissions to link data across TAU and OARS conditions. No one outside of the Q2i engineer will have access to patient identifiers across both conditions. Patients will not be required to submit any data for the purpose of this research. Providers will be interviewed by UCLA study staff. Interviews will be transcribed and the transcripts will be de-identified prior to sharing with Q2i staff.

6 DATA MANAGEMENT

6.1 Source Documentation Requirements

Source documents and access to source data and documentation will be maintained according to Good Clinical Practice (GCP) guidelines. The investigators will maintain and securely store complete, accurate, and current study records throughout the study. In accordance with U.S. regulations, the investigators will retain all study records on-site for at least two years after study closure. Applicable records include survey instruments and recordings, data collected in the OARS platform, and notations of all contacts with participants.

6.2 Quality Control and Quality Assurance

Study investigators will maintain ongoing quality control procedures which include standard source documentation practices and accurate informed consent procedures, among others. They will also be responsible for providing proper training to study staff and documentation of this training.

6.3 Data Analysis

Data will be collected pre and post integration of the OARS platform within the EHRs of six clinics. The primary analyses will focus on examining outcomes from the index visit versus 6 months post implementation of OARS. The analyses will assess the effect of OARS on study outcomes. The primary predictor of interest will be the OARS intervention compared to TAU. Descriptive and repeated measure analyses will be conducted to test the hypotheses that OARS condition will result in increased number of patients treated with MAT, increased retention, and increased opioid abstinence compared to TAU. We will consider several clinic-level factors potentially associated with the study outcome, including clinic size, duration of the clinics' MAT program, and ancillary clinic services.

The secondary analysis will use data from patients treated after OARS implementation. A logistic regression model will be employed to estimate effect of provider and patient engagement with the OARS platform (number of days of OARS engagement, number of interactive features used) on patient opioid abstinence (opioid-negative urine toxicology). We will adjust for patient-level covariates including demographic variables (age, gender, race/ethnicity, level of education), other substance use, severity of opioid use, and medical comorbidities.

Exploratory analyses will facilitate estimation of ROI for OARS. We will use estimates from the primary analysis of the relative counts of services provided to patients before and after OARS as a key parameter. Additional service utilization will be added in order to estimate a distribution of service utilization beyond the six month study period and for a hypothetical, broader group of patients. We will vary the parameters for the distribution of service utilization in order to show sensitivity of subsequent ROI estimates to key assumptions. The service utilization estimates will be applied to financing scenarios in order to calculate alternative ROI estimates. These will include a traditional fee-for-service model, essentially multiplying utilization by their associated reimbursement amounts (e.g., outpatient counseling visit, medication management visit) under different payer scenarios, including Medicaid. We will also estimate ROI under value-based payment (VBP) models with quality incentives, e.g., CMS' Merit-based Incentive Payment System (MIPS). Under these types of models, eligible providers can receive bonus revenue for achieving quality and other goals. Such criteria can include the use of telehealth, provision of enhanced services, and treatment retention. Because many of these models are still being developed and modified, we will also use sensitivity analyses to characterize uncertainty in the future payer landscape. In addition to the revenue component of ROI, we will also account for changes in costs to payers including additional labor effort in service delivery with OARS and direct software costs.

All analysis will be conducted using SAS version 9.4 (Cary, NC).

7 HUMAN SUBJECTS PROTECTIONS

7.1 Institutional Review Boards

The study team will make efforts to minimize risks for participating clinics, providers, and patients. Study staff are responsible for assuring that this protocol is followed and the appropriate materials are provided to clinics at the time of enrollment. Any modifications to the protocol other study-related documents will be approved by the IRB prior to implementation.

7.2 Risk/Benefit Assessment

7.2.1 Risks

Because these research activities are limited to collection of data through the EHR and use of the OARS platform, this study poses minimal physical risks to participants. However, due to the highly stigmatized

nature of opioid use disorder and its treatment, the biggest factor leading to risk in any or all of these domains is loss of confidentiality (see below for a detailed description of safeguards to protect against loss of confidentiality).

7.2.2 Benefits

There may be no direct benefit to clinics, providers, or patients to participating in these research activities. There may be an indirect benefit to participants in the use of these data to inform quality improvement efforts surrounding the treatment of OUD in the primary care setting.

7.3 Informed Consent Process

The research team is requesting a waiver of consent for patient participants since this research involves no more than minimal risk and involves no procedures for which written consent is normally required outside of the research context. The risk of contacting patient participants and documenting their informed consent provides a possible risk of breach of confidentiality since there is no other need to contact patient participants. Therefore, this risk is determined to be greater than the risk of the study procedures. Additionally, informed consent would not be possible within this study design since the primary outcomes are meant to be evaluated with each clinic's entire patient population. Requiring informed consent may actually result in biased results since individuals who choose to consent (or not consent) may have a different probability of experiencing the outcomes of interest.

In addition, UCLA study staff will obtain verbal consent from provider participants who choose to participate in the sem-structured interview. The verbal consent process, and the interview that follows, will be conducted over a secure Zoom line to ensure participant confidentiality.

7.4 Participant Confidentiality

All study databases will be secured and encrypted with password-protected access systems. Any Q2i staff who have access to patient information will be members of the research study team, and as such, have completed relevant human subject research and HIPAA trainings.

In addition, a Certificate of Confidentiality will be acquired from the U.S. Department of Health and Human Services that will be applicable to this study. This certificate protects study staff from being compelled to disclose study-related information by any U.S. Federal, State, or local civil, criminal, administrative, legislative, or other proceedings. It thus serves to protect the identity and privacy of study participants.

7.5 Special Populations

Pregnant Women

Opioid use disorder affects pregnant women and many women may choose to receive treatment while pregnant. The collection of medical record data is of minimal risk to all patients receiving treatment for OUD including pregnant women. The understanding of the impact of providing medical care for the treatment of OUD in pregnant women presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women or fetuses.

Children

We will exclude data related to minors treated for OUD from inclusion in the study database (both baseline and OARS).

Non-English speaking individuals

We will exclude non-English speaking providers and patients since participation is contingent on using the OARS platform (which is currently only available in English) once it is implemented. Therefore, non-English speaking providers and patients are not eligible to participate in the study.

Cognitively impaired individuals

Opioid use disorder is common in patients with psychiatric, organic, developmental, or other disorders that affect cognitive or emotional functions that may cause diminished capacity. The collection of medical record data is of minimal risk to all participants including those individuals who are cognitively impaired. The understanding of the impact of providing medical care for the treatment of OUD among those who are cognitively compared presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare in this patient population.

7.6 Compensation

Patients will not be compensated since no direct patient contact will be required and patients do not need to perform any study specific research activities.

For participating in the provider interviews, PCP participants can receive a total of $150 compensation for completion of all research activities broken into the following segments:

- $50 for completion of the first interview prior to OARS implementation
- $50 for completion of second interview one month after OARS implementation
- $50 for completion of third interview 6-8 months after OARS implementation

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