mHealth to Help Pregnant and Postpartum Women in Recovery for Opioid Use Disorder or Stimulant Use Disorder

Principal Investigators: Patricia Cavazos-Rehg, Ph.D.

Hannah S. Szlyk, Ph.D., LCSW

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Table of Contents

Contents

Introduction

A1 Study Abstract

The opioid and stimulant epidemic has resulted in widespread detrimental consequences among vulnerable populations, especially among pregnant and postpartum women and people (PPWP) with opioid use disorder (OUD) and stimulant use disorders. Although perinatal use of medication for OUD (MOUD) (previously called medication assisted treatment, MAT) within a comprehensive treatment plan is the current standard of carefor those with OUD or SUD, PPWP struggling with addiction may underestimate or misjudge its benefits. Inthis project, we will utilize a theory-based digital therapeutic tool, uMAT-R mobile application ("app"), to educate and motivate PPW) with OUD or SUD. We will assess uMAT-R's usability among PPWP recruited from the addiction treatment facilities. We will also educate PPWP about local recovery community centers (RCCs) and link participants to these centers, in attempt to cultivate recovery capital. Recovery capital includes personal and environmental resources, such physical and mental health, social networks and support, and motivation for recovery. RCCs are primed to help individuals acquire recovery capital and often feature voluntary, peer-led recovery focused initiatives.

With Aim #1, we will garner qualitative input from PPWP with OUD or SUD (target users) on the intervention components of uMAT-R for feedback on adaptation and implementation. Participants' input on methods to increase participation and retention for follow-up assessments will also be obtained. We will conduct interviews with PPW with OUD or SUD (total n= 64) recruited from addiction treatment facility, with 24 local providers who serve PPWP with OUD or SUD and/or work at local recovery community centers (RCCs). We will also collect survey and follow up interviews among PPWP participants at 1-month to further assess the usability and acceptability of this tool among PPWP to inform future evaluations of preliminary efficacy among this group. This novel technology-based intervention could be an invaluable tool to assist providers in the treatment of OUD or SUD among PPW.

A2 Primary Hypothesis

AIM #1: We will garner qualitative input from PPWP with OUD or SUD (target users) and local providers on the intervention components of uMAT-R for feedback on the adaptation and implementation. Participants' input on methods to increase participation and retention for follow-up assessments will also be obtained. We will conduct interviews with PPWP with OUD or SUD (total n= 64) recruited from addiction treatment facility, and with 24 local providers who serve PPWP with OUD or SUD. We will also follow up with participants to gather additional feedback on their experiences with uMAT-R and recovery after at 1 month (survey, interview).

- **Hypothesis:** We hypothesize that our participants will report good efficiency, technical effectiveness, and satisfaction with uMAT-R, and will provide useful feedback for app improvements.

A3 Purpose of the Study Protocol

The purpose of this protocol is to outline the methods utilized in this study. As we are researching a particularly vulnerable population (PPWP) with opioid use disorder or stimulant use disorder, this protocol also details the protections we have taken to ensure the safety of our participants.

B Background

B1 Prior Literature and Studies

Prevalence and Treatment of Opioid and Stimulant Misuse. Recent trends indicate increased use of opioids and stimulants among adults, contributing to several adverse public health outcomes. Opioids are a main contributor of overdose deaths across the US.The prevalence of OUD and stimulant misuse during pregnancy is likewise increasing.[1]

Stimulants such as methamphetamine pass through the placenta and blood brain barrier and can have significant effects on the fetus and the newborn. Opioid agonists will also cross the placental barrier in concentrations consistent with maternal dose,[3-5] and may adversely affect the fetus. Additionally, the postpartum period represents a time of increased vulnerabilities, and women and people with opioid use disorder relapse far more often in the postpartum period compared to with during pregnancy.[7]

The Benefits of MOUD. Perinatal use of MOUD within comprehensive treatment is the current standard of care alternatives (i.e., withdrawal or detoxification) run the risk of relapse and treatment dropout.[1] Unfortunately, PPWP struggling with OUD may underestimate or misjudge the benefits of MOUD and/or may lack support outside of the clinic to sustain motivation for recovery; these barriers could compromise treatment compliance.[8-10] For instance, common misperceptions about MOUD are that MOUD is substituting one addiction for another; MOUD is ineffective because it does not immediately cure dependence;[8,11,12] and for PPWP with OUD, it is not well known how MOUD will affect both them and their unbornchild.[1,13,14] To supplement providers' efforts at educating patients, we will develop a digital therapeutics tool, uMAT-R, to target one's (lack of) knowledge and/or negative beliefs that may deter MOUD use. To supplement traditional in-person psychiatric care, we will also include features within uMAT-R to encourage adherence to MAT, support women and people in their everyday lives, and help keep them motivated on their path to recovery.

The Role of RCCs. Guided by stress and coping theory, it can be assumed that greater access to recovery capital may enable persons with OUD or SUD to be better prepared to manage life's stressors and achieve recovery. RCCs are primed to help individuals acquire recovery capital. RCCs are not aligned with a specific recovery framework, allowing for RCCs to be a part of various pathways to recovery. In the greater St. Louis area (including Missouri and nearby Illinois), more RCCs are emerging. Overall, these RCCs provide recovery support and resources in person and virtually, which allows for flexibility during the COVID-19 pandemic and for individuals who may have barriers to transportation. While there is a regional need for OUD and SUD care for PPWP, there is little knowledge on how this population transitions to the next stage in their recovery post-discharge from a structured, clinical program. In the current proposal, in addition to a focus on continued MOUD uptake/ adherence via improved MOUD attitudes and beliefs, app-based content and within app e-coaching will promote engagement in local RCC's by increasing participants' knowledge about recovery and improving their recovery capital and motivation to stay sober.

Preliminary Study: Testing a prototype of *uMAT-R.* The use of a prototype of uMAT-R that we developed in partnership with iTether (IRB ID 201706044) was piloted with 29 participants with OUD.For this pilot, we recruited individuals who were socially networking about opioid abuse on social media. The features of uMAT-R were guided by SAMHSA online resources about MOUD.[15]Our uMAT-R prototype described the cost of MOUD, presented the latest research about MOUD efficacy, and described potential side effects of MAT. Video testimonials from individuals who have had success with MOUD were also provided. Following their use of this digital therapeutic tool, feedback from participants was overwhelmingly positive. In addition,

the app increased positive attitudes about MOUD (pre-app mean score 3.31, sd 0.46; post-app mean score 3.46, sd 0.52; t(25)=2.12, p=0.044) and interest in starting treatment (pre-app 32%, post-app 48%; McNemar's test p=0.046). This study demonstrates our ability to partner with iTether to develop an efficacious digital therapeutic tool that improves MOUD attitudes among individuals struggling with OUD. We will adapt the educational content of this prototype to address the concerns of PPWP who misuse opioids as well as add daily tips and tailored guidance from an online coach.

B2 Rationale for this Study

Digital therapeutics can help to combat the opioid and stimulant epidemic. Many individuals,including those who are struggling with substance use disorder, have interest in using apps to support their recovery;[16] likewise, our preliminary research has shown that individuals with OUD and stimulant use disorder have also demonstrated a willingness to try digital therapeutics and that they can efficaciously improve MAT attitudes. Furthermore, digital therapeutic tools have the potential to deliver therapeutic content in an accessible and engaging modality that exists at one's disposal, encourages adherence to treatment, and delivers personalized supportoutside of clinical care. However, there are no known published studies that evaluate the efficacy of an app focused on supporting PPWP with OUD towards MOUD treatment adherence. Toaddress this critical gap, we will develop and pilot test the components of uMAT-R*,* a digital therapy, to provide a sustainable, low-cost intervention to educate, motivate, and support OUD and SUD recovery among PPWP with OUD and/or OUD.

C Study Objectives

C1 Primary Aim

To assess the feasibility of linking PPWP with the uMAT-R app as a supplement to addiction treatment and explore usability characteristics of and engagement with uMAT-R.

Activities for Aim #1: We will garner qualitative input from PPWP with OUD or SUD (target users) on the intervention components of uMAT-R for feedback on the adaptation and implementation. Participants' input on methods to increase participation and retention for follow-up assessments will also be obtained. We will conduct interviews with PPWP with OUD or SUD (total n= 64) recruited from addiction treatment facility and/or through referrals received from other participants and members of the community. Twenty-four local providers who treat OUD will also be recruited to provide their feedback Guided by the International Organization for Standardization,[17] we will assess 3 domains of usability characteristics: efficiency, technical effectiveness, and satisfaction with uMAT-R, as well as the level of engagement with the app. Using a mixed methods approach, we will explore how uMAT-R fared in regard to its ease of understanding, helpfulness, intuitive flow, presentation, and pacing.

We will also collect survey and follow up interviews among PPWP participants at 1-month to further assess the usability and acceptability of this tool among PPWP to inform future evaluations of preliminary efficacy among this group.

C2 Rationale for the Selection *of Outcome Measures*

This study will use a combination of quantitative and qualitative measures to examine the usability characteristics of and engagement with uMAT-R (Aim #1).

D Study Design

D1 Overview or Design Summary

In this study, we will recruit 64 adult (≥18 years) PPWP for their opioid use disorder at various addiction treatment facilities. An additional 24 local providers who treat OUD will be recruited to provide their feedback. All participants will receive access to uMAT-R. PPWP participants will complete quantitative online survey assessments at baseline and at 1 month follow up. After having access to the app for 1 week, all participants will be asked to take part in an interview to provide in-depth feedback about their experience with uMAT-R (conducted in-person or via Zoom or phone). After 1 month, PPWP participants will also be asked to take part in a follow up interview to provide additional information on their lieved experience with SUDs and other recovery-related constructs. All interviews will be transcribed verbatim for qualitative analyses.

D2 Subject Selection and Withdrawal

2.a PPWP Inclusion Criteria

1) Receiving treatment at a consenting treatment facility and/or referred from other participants or community partners
2) Misused opioids or stimulants at some point in their life
3) Pregnant (second or third trimester) or postpartum within the past three years
4) Adult (≥18 years of age)
5) U.S. resident
6) Own a smartphone with an iOS or Android operating system

Provider Inclusion Criteria

1) Works with pregnant and postpartum people with opioid use disorder and/or at a recovery community center (e.g. a staff person, counselor, social worker, psychiatrist, nurse).
2) Adult (≥18 years of age)
3) U.S. resident
4) Fluent in English
5) Own a smartphone with an iOS or Android operating system

2.a Exclusion Criteria

1) Currently incarcerated

2.b Ethical Considerations

Participation in this study is voluntary. All participants will be required to provide verbal consent prior to participation. A member of the study team will go over the consent document and answer any questions.

2.c Subject Recruitment Plans and Consent Process

Eligible participants (N=64) will be recruited from various addiction treatment facilities or community referrals. PPWP coming to the facility receive addiction treatment (medication + counseling), and are closely supervised (e.g., weekly visits, urine drug screens, counseling session attendance) by the medical team. The research team will meet with various groups that could be eligible for the study. We are also requesting a waiver of documented consent for participants in this study, as this study poses minimal risk, and we have systems in place to protect the confidentiality of our participants. The research team will review the informed consent document with participants viaphone, and participants may provide verbal consent to take part in the study. The research teamwill continue to follow up with participants via phone, email, and within the app to complete necessary follow-up activities. Prospective participants who have been

referred by another participant or another community partner can reach out to our team via phone to complete the screener over the phone and can enrolled if they are eligible. In some cases, the study team may ran into the same participants at the treatment facilities. If the participants expresses interest in the study again, the participant will be asked to fill out a screener. A research team member will then check to see if the participant has accessed the uMAT-R app during their previous participation. If the participant has accessed the uMAT-R app in their previous study participation, they are not eligible to be reconsented to the study. Participants who are enrolled into the study but have yet to complete their baseline survey and log into the app will be able to be reconsented to the study as they approach their 1-week study period.

Specifically, for the CARE Clinic at Washington University School of Medicine, the research team will view their Monday afternoon clinic schedule in EPIC to see when individuals are scheduled that could be eligible for the study.

2.d Randomization Method and Blinding

There will be no randomization or blinding. We will recruit 64 PPW and 24 local OUD providers, all of whom will test the uMAT-R app to provide feedback to inform future iterations of the digital tool.

2.e Risks and Benefits

Potential Risks
The potential risks to respondents from participating in this study are unlikely and low risk. The uMAT-R mobile app, online questionnaires, and interviews will be confidential.

PPWP participating in this study will be patients of various addiction treatment facilities. If there is any concern that a participant is at risk for injury or relapse during conversations with the in-app coach, then the participant's treatment team will be notified.

Participation in all aspects of the study will be on a volunteer basis; participants will have the right to refuse answering and/or taking part in particular aspects of the study, and they will be told of their right to refuse and/or withdraw from this study at any time. Participants will also be instructed of the risks and benefits of their participation in the research and of all the procedures to be followed in case of adverse events. These details will be explained to participants during the informed consent process.

Potential Benefits
uMAT-R will educate adults to improve deficits in recovery knowledge and ultimately increase the likelihood of adhering to recovery. Furthermore, because adults with substance use disorder (specifically OUD or SUD) may lack support outside the clinic office, uMAT-R will be designed to support one's motivation towards recovery. We expect that after engaging with uMAT-R, PPWP participants will better understand the facts about recovery benefits and have increased acceptance of recovery. We also expect the PPWP participants to have increased favorable recovery attitudes, and recovery capital. Additionally, there areimportant potential benefits to the medical community seeking to improve substance use treatment outcomes. Our findings would help to demonstrate whether uMAT-R has the potential to be a beneficial tool for adults who misuse substances and could help to bridge the gap between what occurs during a clinical visit and what one does and needs in everyday life in order to successfully recover. Client will be able to continue accessing the app post study timeframe as a service from our team.

2.f Early Withdrawal of Subjects

Participants will be able to stop participating in the study at any time. If a participant chooses to withdraw from the study and intervention, they will no longer have access to uMAT-R and will only be compensated for completed assessments.

2.g When and How to Withdraw Subjects

In the case of an adverse event (detailed below), the research team could determine that it is no longer safe for a participant to continue in the study. The research team will inform both the participants treatment team and the participant that they are being removed from the study. The participants treatment team will then assume responsibility for appropriate follow-up and care.

2.h Data Collection and Follow-up for Withdrawn Subjects

In the event that a participant withdraws from the study, there will be no further data collection or follow-up.

D3 uMAT-R Intervention

3.a Description

The uMAT-R intervention will consist of several features designed to educate PPWP with OUD about MOUD in order to counter their misconceptions and/or improve deficits in MOUD knowledge. Lastly, the app will include general tools to promote a healthy pregnancy, postpartum recovery, and overall recovery skills.

Educational content: uMAT-R delivers educational content in plain, understandable language, which promote the use of and adherence to MOUD, engagement with RCCs, sustained OUD and SUD recovery, general pregnancy and postpartum knowledge, sexual health, and other topics regarding healthy lifestyles and emotional wellbeing. Educational materials will be derived from sources such as Journey Recovery Project (https://journeyrecoveryproject.com/#/home), the American College of Obstetricians and Gynecologists (ACOG), HealthWise, and other government websites. Materials from these sources will be compiled and reorganized into topics that are easy-to-navigate.

Brief recovery tips: uMAT-R contains a "library" of brief recovery tips that are informed by cognitive behavioral therapy (CBT).[18,19] These tips will focus on their cognitive restructuring and behavioral changes, including (a) psychoeducation about dependence, craving, and relapse; (b) how to identify risk factors and triggers for relapse; (c) techniques for avoiding situations with a high risk of relapse and how to intervene in those situations; and (d) developing healthy and regular alternative habits.

E-coach: Within uMAT-R's in-app messaging feature, PPWP participants will be encouraged to directlycommunicate with a coach. Dr. Cavazos, a licensed psychologist and Dr. Szlyk, a doctoral-level licensed clinical social worker – both MPIs of this study – will oversee members of the research team directly involved with coaching participants. Zhuoran Zhang has a master's in experimental psychology and has accumulated valuable clinical experience over the course of the year as part of the e-coaching team. Elecia Worley is a masters-level social worker with remote and in-person clinical experience from her previous positions. They will assist Drs. Szlyk and Cavazos in managing and overseeing the coaching staff. Coaches will employ techniques from the Motivational Interviewing (MI) model. [20] MI is patient-centered and

strives to increase insight and awareness about risks related to unhealthy substance use and to heighten motivation for one tomove to a higher degree of readiness to change.[20] The MI model has been shown to reduce substance use,[21-24] and is especially conducive to digital therapeutics because it allows for flexibility in tailoring interactions and encourages an empathetic social listening style while soliciting individuals to reflect on their unique reasons for behavior change.

Goals Setting and Reminders: E-coaches can help to goals related to recovery in the app for participants based on needs expressed in messaging and in-app assessments. PPWP Participants will receive medication and upcoming appointment reminders.

Resources: uMAT-R e-coaches can provide information to participants on important resources, including local RCCs, suicide crisis lines and local St. Louis Narcotic Anonymous meetings. Other resources include where to seek support with housing and access to food and clothing, support with education/employment, and specific services for PPWP and child.

3.b Treatment Regimen

Participants will have access to uMAT-R for 1 month in this study. They will be encouraged to use all appfeatures during this time.

3.c Administration of uMAT-R

After consenting, participants will be provided with instructions on how to download uMAT-R.

3.d Technical Development of uMAT-R

Reconnect is a mobile health development company that has developed a digital platform comprised of proprietary software in communication with an online database that works to enable behavioral health providers to deliver digital content and interact with their clients. Reconnect has worked with behavioral health providers and organizations and has partnered with our research team to develop uMAT-R.

3.e Prior and Concomitant Therapy

All participants are also patients of addiction treatment facilities and will be receiving their standard treatment for both OUD or SUD and perinatal care.

E Study Procedures

E1 Screening for Eligibility

PPWP coming to a STR Treatment Agency, Federal Qualified Health Center, or another local substance use treatment center are provided with opiate and/or stimulant addiction treatment (counseling) and are closely supervised by their behavioral health team. The research team will meet with various groups that could be eligible for the study. A member of the research team will then go over the consent document in person or over the phone with the participant. If a client is not eligible for the intervention due to not having access to a cellphone, they will be asked if they want to complete the baseline survey. Prospective participants who have been referred by another participant or another community partner can reach out to our team via phone to complete the screener over the phone and can enrolled if they are eligible.

Specifically, for CARE Clinic at Washington University School of Medicine, the research team will view their Monday afternoon clinic schedule in EPIC to see when individuals are scheduled that could be eligible for the study.

E2 Schedule of Measurements

Table 1. Study Measures for Aims #1

Measure		Self-report assessments collected from participants	Data collected via other sources
Provider demographic characteristics survey	Providers complete brief survey that asks about demographic characteristics, current work details, and previous work history.	Collected a baseline via REDCap	

USE questionnaire	Participants will rate ease of use and learning (i.e., Efficiency), usefulness (i.e. Technical effectiveness), and likability (i.e., Satisfaction) ona seven-point Likert scale (1 = strongly disagree,7 = strongly agree), as well as open-ended itemsasking participants to list the most negative and positive aspects of *uMAT-R*.	X- collected after 1-week of app use	
Primary Outcomes			

Engagement with *uMAT-R*	1) Number of times logged into the app, 2) time spent in the app once logged in, 3) time difference between app logins, and 4) number ofinteractions with the coach Participants will provide feedback for the following: 1) uMAT-R app download 2) viewing of instructional video 3) daily app use 4) completion of daily assessments		Automatically collected within the app Collected from Epharmix messaging
MOUD uptake and adherence	8 questions about lifetime and current use, including reasons for not using MOUD; Urine screening results, obtained through participant medical records and the ModifiedMorisky Scale; self-reported assessment of medication compliance through 6 items that measure knowledge and motivation	X	
RCC engagement	On the app, participants will be asked to record their weekly engagement with the local RCCs (in-person or remote). For example: attended a peer support group (AA/NA), attended a Narcan training, met with a career counseling, attended a workshop on parenting/maternal health, attended workshop on healthy living, contacted peer counselor, or other.	X	
Attitudes	An 8-item tool to evaluate participants' attitudes towards MAT, modified from the Attitudes of Methadone Scale[37]	X	
Depression and anxiety	PHQ-9 and GAD-7 used to assess current depression and anxiety	X	
Suicide risk	Interpersonal Needs Questionnaire to assess connection, burdensomeness, and thwarted belongness- 3 factors related to elevated suicide risk	X	
Substance use history	Assessment of current opioid and other illicit drug misuse, including assessment of overdose history and cravings	X	
Opioid use	Self-reported recreational substance use (past 30 days)	X	
Barriers to treatment	Assesses both potential barriers to obtaining treatment prior to the study as well as actual barriers to obtaining treatment after the study	X	
Pregnancy and Postpartum			
Revised Prenatal Distress Questionnaire(PDQ)	Assesses stress originating from issues commonin pregnancy (e.g., medical care, physical symptoms, and infant's health)	X	
Postpartum Stress Scale.	Assesses stressors that may emerge during the postpartum period	X	
Parenting Sense of Competence Scale	Assesses the parent's sense of competency in taking care of their child.	X	
Unmet basic needs	Assessment of how confident the women are that they can find resources to help them meet their basic needs	X	
Healthy behaviors for PPWP.	We will measure participants' intent to breastfeed using the Infant Feeding Intentions (IFI) scale. Contraceptive knowledge and intentions will be measured using the Contraceptive Knowledge Assessment.	X	
Daily	Brief, 3 questions about their confidence in maintaining sobriety, having a healthy pregnancy and meeting their basic needs.		Collected within the app
Weekly	Assesses struggles in the past week relating to drug use, pregnancy and basic needs and if the app was useful in addressing these issues. Also assesses buprenorphine compliance for past week.		Collected within the app

Qualitative assessments. After 1 week and 1 month (PPWP only) of uMAT-R access, participants will be asked to complete 20-30 minute semi-structured interviews with a trained interviewer, in-person or virtually (phone call or via Zoom). Participants will be provided the option to complete it independently via RedCap link. During the 1 week interview, participants will be asked to discuss their experiences with uMAT-*R* in greater detail, including perceived benefits and challenges of participation and suggested modifications to improve specific components of uMAT-R. Complications/ technical glitches with the app, reactions to the online coaching, how it fared in regard to its ease of understanding, helpfulness, intuitive flow, presentation, pacing, and suggestions for improvement will also be assessed. During the 1 month interview, PPWP participants will be asked additional questions related to the usability and acceptability of uMAT-R, as well as questions related to recovery and other lived

experiences related to SUDs and mental health. The interviews will be conducted in-person, over the phone, or via Zoom and will be recorded, and transcribed verbatim for qualitative analysis if they are completed with a trained interviewer.

Research staff will record the interviews view a mobile device (e.g. hand-held recorder, mobile phone, or laptop). Video and audio will be collected based on how the interview is conducted (i.e., in-person, phone, or Zoom) and data from the recordings will be transcribed. Research staff will then immediately save the recording and transcribed interview on a HIPAA approved-WUSTL Box or the HIPAA approved-WUSM server. Research staff will immediately delete the recording and transcribed interview from the device (with 24 hours of the interview). Recordings and transcribed interviews will only be identified by the participants' designated study ID. Recordings will not be attached to any identifiable information. These steps are established as best practices by the WUSM Information Security office.

E3 Safety and Adverse Events

3.a Safety and Compliance Monitoring

We go to great lengths to protect the confidentiality of our subjects and are especially sensitive to data regarding substance use and substance use-related problems among a particularly vulnerable population.

Participant safety: Drs. Szlyk and Cavazos (MPIs), Ms. Zhang, and Ms. Worley will closely monitor all coaching interactions with participants. Their combined experiences and credentials make them qualified for this role and will ensure participant safety during this study.

Additional protections for pregnant women, fetuses, and neonates
Per Federal regulations: 1) no inducements will be offered to terminate the pregnancy 2) no member of the research team will have any part in decisions as to timing, method, or procedures used to terminate pregnancy, and 3) no member of the research team will have any part in determining the viability of the neonate.

Emotional discomfort: Participants who report discomfort as a result of participation will be reminded that their participation is voluntary. They can refuse to answer any questions that they are not comfortable with or discontinue the survey assessments/interview at any time.

HIPAA compliance: All project staff will have fulfilled Washington University's mandatory HIPAA training requirements. All aspects of the protocol and study implementation will meet the HIPAA requirements specified by the Human Studies Committee and the Privacy Office at Washington University.

Reconnect will host *uMAT-R* and all data collected within the app. Reconnect has partneredwith many health care providers to aid in patient addiction recovery, and Reconnect is HIPAAcompliant. Reconnect will comply with the rules on handling of Protected Health Information under the Health Insurance Portability and Accountability Act ("HIPAA") Standards for Privacy ofIndividually Identifiable Health Information, 45 C.F.R. Part 160 and Part 164, Subpart E ("PrivacyRule"), the HIPAA Security Standards, 45 C.F.R. Part 160 and Part 164, Subpart C ("Security Rule"), the HIPAA Breach Notification Regulations, 45 C.F.R. Part 164, Subpart D ("Breach Notification Rule"), and the federal regulations governing the confidentiality and security of substance use disorder information, 42 C.F.R. Part 2 (the "Part 2 Regulations") (collectively the "Requirements").

3.b Safety Monitoring

i Investigator only

The MPIs, Drs. Szlyk and Cavazos, will be responsible for routine monitoring of the study progress. This monitoring includes scheduled weekly meetings with study staff and review of all study-related documentation.

3.c Definitions of Adverse Events

Coaches and research team members will be trained to monitor for adverse events, including Serious Adverse Events (SAEs) would include occurrences that result in death, are life-threatening, or require hospitalization. The research team will report any potential adverse events immediately upon their identification to the PI. We will also monitor for adverse events at all follow-

up assessments and via all other communication with study participants. Any potentially adverse events will be evaluated by the PI within 72 hours. Any SAE will be queried and reported even if it appears that the serious unanticipated health event is unrelated to study participation.

3.d Data Collection Procedures for Adverse Events

Adverse event assessment, recording, reporting and investigation will be accomplished through structured/standardized assessments, reports from the facilities' representatives, and self-reported information provided in the in-app coaching feature. If any information that is disclosed indicating potential harm a participant or others within the mobile application and/or the surveys, will be disclosed to the facility. The surveys will ask participants questions pertaining to suicidal ideation and depression. If the participant answers 'yes' to current thoughts of suicide, the research team will call the participant as soon as possible to check in and determine if the participant needs a handoff to a crisis service. Afterwards, the team will document this phone call and notify the participant's treatment facility. Zhuoran Zhang, Elecia Worley, and other members of the e-coaching team (Jordan Michener and Emily Maranets) will follow-up with the participant. Zhuoran Zhang has a master's in experimental psychology and has accumulated valuable clinical experience over the course of the year as part of the e-coaching team. Elecia Worley is a masters-level social worker with remote and in-person clinical experience from her previous positions. Jordan Michener has experiences working with children, adolescents, and adults at a behavioral health hospital and holds certificates in Forensic Interviewing and Crisis Intervention. Emily Maranets has in-person and remote clinical experience working with a variety of clinical populations in both inpatient and outpatient settings.

3.e Reporting Procedures

The PI has ultimate responsibility for ensuring that AEs are detected and reported in a timely manner. AEs will be reported to the IRB in accordance with the IRB's policy.

3.f Adverse Event Reporting Period

A safety report will be generated monthly. Any AEs will be reported directly to the PI. As required by the Washington University IRB, the PI will subsequently report any adverse events to the Washington University IRB using methods specified by the IRB.

E4 Study Outcome Measurements and Ascertainment

Quantitative measurements: MOUD uptake and adherence, MOUD attitudes, RCC engagement, recovery capital, as well as mental health items will be assessed via self-report using online Research Electronic Data Capture (REDCap) surveys at baseline. Substance use history will also be assessed at baseline via self-report in this way. App usability will be assessed at one week also via self-report using online REDCap surveys. REDCap is a secure, web-based application designed to support data capture for research studies. Surveys will be formatted for use on either a computer or a mobile device.

Engagement with the uMAT-R app (e.g., number of times logged in, time spent in the app, time difference between app log-ins, and number of interactions with the coach) is automatically collected within the app platform (Reconnect).

For more information about specific quantitative measurements, see section E2 Schedule of Measurements.

Qualitative assessments. Participants will also be asked to complete a 20-30 minute semi-

structured interview with a trained interviewer after using the uMATR mobile app for 1 week and 1 month (PPWP only). The interviews will be conducted in-person, over the phone, or via Zoom and will be recorded and transcribed verbatim for qualitative analysis.

F Statistical Plan

F1 Sample Size Determination and Power

The primary purpose of this study is feasibility. We will receive information on uMAT-R with 64 PPWP participants; this sample size is feasible to recruit from various treatment facilities, is within the range of samples sizes for other pilot tests of digital therapeutics,[25-31] and is sufficient for data saturation for qualitative interviews.[32]

F2 Interim Monitoring and Early Stopping

Data that will be reviewed at the routine monitoring meetings include the number and type of participants enrolled, that all subjects meet eligibility criteria, the number and reasons for exclusions from enrollment, drop-outs and any protocol deviations, the number of participants using the app, and that the study is following the IRB-approved protocol. A summary of adverse events (AE) and an individual review of serious adverse events (SAE) will also occur in real-time as they happen and at these routine monitoring meetings. AEs or SAEs that raise concerns (significant change in mood or suicidality) will be immediately reported to the MPIs who will determine an appropriate course of action.

To facilitate participant safety, study participants must meet study inclusion and exclusion criteria. Once enrolled, follow-up protocols will assess the unanticipated health events at all clinic visits and follow-up contacts. Should either excessive risk and/or lack of measurable benefit to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or the lack of benefit.

F3 Analysis Plan

Quantitative assessments will be recorded using REDCap electronic data capture survey tool. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. App usability will be examined using descriptive measures (mean, standard deviation, median, range) on the efficiency, technical effectiveness, and satisfaction components of the USE questionnaire. Descriptive statistics will also be used to describe engagement with the app (e.g., median number of log-ins, time spent in the app, number of interactions with the coach, etc.), as well as the characteristics of our patient sample (demographics, mental health and substance use history). Descriptive statistics will also be used to examine MOUD uptake and adherence, MOUD attitudes, RCC engagement, recovery capital, pregnancy- and post-partum-related anxiety, confidence in meeting basic needs, and opioid or stimulant use within our sample. Team will also employ data science-informed approaches for text analyses using message data. Analyses will inform development of a future conversational agent to be paired with the mobile intervention.

Transcripts from interviews will be collected to assist with qualitative data management and coding. Inductive thematic analyses will be conducted by two research team members using the six steps described by Braun and Clarke[33] (getting familiar with the data, creating initial codes, looking for themes, reviewing and refining themes, defining and naming themes, producing the report). Other pilot studies of apps have used a similar approach to analyze the qualitative discussion of app content and/or user experience.[26,27] Feedback from the qualitative

interviews will help to refine app format, content, and coaching for future studies.

G Data Handling and Record Keeping

G1 Confidentiality and Security

Information collected in Reconnect (de-identified, aggregate engagement data and survey data from in-app assessments) will be downloaded by Reconnect staff, encrypted, and sent to the secure Washington University email address of a research team member. Research staff members will un-encrypt the data and store it on a dedicated, single-use partition of a server under direct control and management by a Washington University IT Specialist. This partition is not included as part of the routine server backup, and the data, in whole or in part, will not be stored or cached on anyexternal workstations, PCs, or other devices. This partition is not shared via networked file systems to other computers. Directory and file access permissions on the server are based on user ID and group membership. Each user is assigned a unique identification and password string.

G2 Training

The MPIs, Drs. Szlyk and Cavazos, and Ms. Montayne will be responsible for managing and overseeing the individuals involved with coaching participants in this study. Both Dr. Cavazos and Ms. Montayne have years of experience working with individuals struggling with substance use. The MPIs, Drs. Szlyk and Cavazos, will also be responsible for training the members of the staff prior to conducting the in-person or remote interviews with participants.

G3 Source Documents

All interviews will be recorded and transcribed verbatim unless completed via RedCap surveylink. Transcripts will be removed of all identifiers and only labeled with the Participant's ID number. We will be utilizing the InfoSec approved company Landmark for transcription services (see attached email).

All other participant assessments will only occur online using REDCap.

G4 Records Retention

All participant records are stored on a password protected server that is managed by Washington University School of Medicine. Only research team members listed on the IRB-approved team will have access to study materials. These materials will be stored for at least three years as required by the IRB.

H Study Administration

H1 Organization and Participating Centers

All study activities will take place at Washington University School of Medicine and consenting facilities.

H2 Funding Source and Conflicts of Interest

This study is funded by NIH & Washington University Psychology Department funds. There are no conflicts of interest to declare.

H3 Subject Stipends or Payments

Participants will be incentivized with gift cards after each survey assessment and will receive an additional set of gift cards for their completion of the interview.

H4 Study Timetable

	Year	**2022**			
	Quarters	1	2	3	4

Develop *uMAT-R* content (daily recovery tips, plain language materials)	X			
Develop and test new *uMAT-R* features	X	X	X	
Enroll 64 PPWP participants from various facilities		X	X	
Run interviews on *uMAT-R*		X	X	
Data analysis and dissemination of results via papers and presentations			X	X
Refine app content accordingly				X

I Publication Plan

Results from this study will provide critical information needed to refine uMAT-R and estimate effect sizes to plan a larger-scale, clinical trial that we will propose in next-step NIH

R mechanisms. Results from this study will disseminated through conference presentations and academic journals. Any results published from this study will not contain any participant identifiers.

J Attachments

J1 Tables

J2 Informed consent documents

J3 Patient education brochures

J4 Special procedures protocols

J5 Questionnaires or surveys

K References

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