A Pilot Study of Telehealth Treatment for Opioid Use Disorders

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REVISION HISTORY:

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Revision #	**Version Date**
2	8/24/2024
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Synopsis

Primary Objective Conduct pilot study to assess effects of enrollment in a comprehensive telehealth platform, RecoveryPad (RP) in adults with moderate or severe opioid use disorder.
Study Duration Approximately 2 years (1 year for study activities, 1 year for data analysis)
Study Design Single-arm, pilot interventional clinical trial.
Number of Study Sites One study site (Yale University) with multiple settings for remote recruitment.
Study Population Adults with moderate or severe opioid use disorder
Number of Participants Thirty participants.
Primary Outcome Variables The primary outcome is attendance at first appointment for medication for opioid use disorder at 30 days.
Secondary Outcome and Exploratory Outcome Variables Secondary outcomes include: ● engagement in first MOUD engagement at 90 days ● number of subsequent overdose events at 30 and 90 days Exploratory outcomes include: ● Feasibility of intervention, as measured by retention in study. ● Readiness and intention to engage in treatment, as measured by a 10-point Likert-type scale. ● Acceptability and satisfaction of intervention by participant, as measured by 10-point Likert-type scales. ● Comparison of MOUD engagement at 30 and 90 days with publicly available data from previous in-person studies.

Abbreviations

Abbreviation	**Explanation**
RP	Recoverypad:
MOUD	MOUD: Medications for Opioid Use Disorder
OD	OD: Overdose
OUD	OUD: Opioid Use Disorder
CPR	

API BNI NLP ML	CPR: Center for Progressive Recovery, LLC API: Application Programming Interface BNI: Brief Negotiated Interview NLP: Natural Language Processing ML: Machine Learning

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1 Introduction

1.1 Introductory Statement

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines, and according to CFR 21 Part 812, other applicable government regulations, and Institutional research policies and procedures.

2 Background

2.1.1 Device Preclinical Experience

The mobile application uses React Native to allow cross platform use (i.e., Android, iPhone and web browser). The API Server was built in node JavaScript utilizing token-based authentication to allow for secure transactions between client (mobile) and the API. The Brief Negotiation Interview (BNI) Chatbot was built in Python utilizing existing frameworks to help minimize development time along with an extension for the API to access its module. The Administrator Portal was also built in React Native, which will allow for reviewing analytics, like users' readiness and intentions to engage, and updating algorithms.

Regarding functionality, the mobile application explains to the user how the program works, and conducts screenings and assessments. If help is needed from the user, they can click on a button in the mobile application to connect them to the research coordinator via the RecoveryPad web application. The Application Program Interface (API) Server provides authentication and authorization, in addition to communication with the chatbot module. Analytical endpoints for the API server have been built to satisfy reporting needs of the administrator portal. Client text is inputted into a database to allow for the chatbot module to further its learning capability. Traditional chatbot architecture encompasses 3 components: design, build, and analytics.

Designing involves defining what the chatbot will look like and how it will interact with users. Building is creating the "brain" of the chatbot, i.e. its ability to understand input (e.g., BNI transcriptions) and generate output (e.g., questions). Analytics monitor performance and offer guidance on improvement.

The "Brain" of the chatbot was built using machine learning and natural language processing. Using Python, a preferred language for use in chatbot development, the development team utilized an

existing NLP framework (i.e., NimbleMiner) to implement study's NLP and machine learning (ML) components. We first used a semi-automated NLP approach to classify each response in the transcriptions into specific pre-defined categories based on our previous work (e.g., types of motivational statements) then split our dataset into training (700 encounters) and testing sets (300 encounters). Using the training set, we generated machine learning algorithms (including decision trees, support vector machines and recurrent neural networks) to predict answer categories for each question. We applied each one of the prediction algorithms on the testing set to identify the best performing algorithm. Algorithm performance metrics included sensitivity (or recall), precision and F-scores (a harmonic mean of precision and recall). Our goal was to achieve a system performance F-score of >85% for each response category. The best performing algorithm was used in the chatbot development to classify responses to questions and asking follow-up questions based on predetermined BNI logic.

The chatbot uses its "brain," much like a clinician using brief motivational interviewing would, by eliciting motivational statements around engaging in buprenorphine treatment from the user by asking questions and making reflective statements during each of the 4 steps of the BNI, namely: 1. Raise the Subject; 2. Provide Feedback; Enhance Motivation, and 4. Negotiate & Advise. These motivational statements are stored into the chatbots database through the API server so the chatbot module can provide reflections and reminders at certain times. While the platform informs users not to use it if they are in crisis or a life-threatening situation (e.g., suicidal ideation/intent/plan), CPR coaches and clinicians will search for keywords or phrases related to such crises and situations on the administrator portal (where all of the texts are stored), and, if any are found, will immediately contact the relevant user(s) with directions and support to contact 988 or other national suicide hotline phone numbers, and/or directions to go call 911 and/or to go to their nearest emergency department. If a participant expresses active suicidal ideation (SI) to the RecoveryPad chatbot or to a coach, the research assistant who reviews RecoveryPad output or the coach will contact the participant at the phone number that was provided by the participant to verify that the participant is experiencing SI. If the participant is experiencing SI, the research assistant or coach will contact 911 and direct the emergency service providers to the participant's location. If the participant cannot be contacted by the research assistant or coach, the emergency service providers will be directed to the participant's last known location. This process is consistent with established practices that are followed when an individual contacts a clinic or emergency department and reports SI.

The administrator portal allows the storage and review of client and usage data. Hosting consists of three environments: 1. Development, 2. Staging, and 3. Production. The development environment is used primarily for the construction of these modules. Staging environments typically mimic production and are to test functionality before being released into production. Production is a controlled live environment that will perform all functions.

2.1.2 Device Clinical Experience

The efficacy of BNI+bup. Building on our bup efficacy trials, our Yale Emergency Medicine (EM) group conducted a randomized clinical trial of 329 emergency department patients who were treated with either a referral, generic BNI, or a BNI focused on bup plus 1 dose of bup. Results demonstrated that the differences in treatment engagement at 30 days among the groups were statistically significant (79% engaged in bup for BNI+bup; 43% engaged in any treatment for generic BNI; and 37% in any treatment for Referral).

Developing technology-enabled BNI. Our EM group demonstrated that a tablet-based BNI for adults with alcohol use disorder, mild to severe, had good feasibility, usability, acceptability, and that a short message service (SMS)-based BNI for adolescents with high-risk alcohol and cannabis use, and a web-based BNI training program for healthcare providers with artificial intelligence components, had high satisfaction and and preliminary efficacy.

BNI Adherence Scale (BAS) for Practitioners. Dr. Pantalon has developed deep expertise in rating audio-recorded BNI encounters. Most recently, he found that higher adherence led to better outcomes.

RecoveryPad. CPR has developed a commercially-available text-based recovery coaching platform, called RecoveryPad (www.recoverypad.com) that connects recovery coaches, trained with CPR's web-based course, and individuals with substance use via asynchronous texting.

2.2 Background/prevalence of research topic

Approximately half a million Americans died from opioid OD in 2009-2019.[1] Between April 2020 and April 2021, drug OD deaths increased by 28.5 percent, surpassing a tragic record of 100,000 deaths—the highest toll recorded in a twelve-month period.[7] CT ranks in the top 10 among states with the highest rates of opioid-related OD deaths,[8] and the number of OD deaths increased by 285% from 2012 to 2020.[2] This problem has grown with the proliferation of deadly synthetic drugs like fentanyl.[7] Of the 1,372 overdose deaths in CT in 2020, 92% involved opioids; and 85% involved fentanyl.[9] During the COVID-19 pandemic, the incidence rate of OD deaths increased by 14.3% in 2020,[2,7] affecting non-Hispanic Blacks

most severely when compared to other race/ethnicities and the national population. Of note, the opioid-related OD death rate was third highest among non-Hispanic Blacks, and its increase exceeded all other racial and ethnic groups in the US between 2015-2016 (40% vs. 21%).[10-12] Drug OD is now considered a leading cause of fatal unintentional injury.[13] Although opioid use disorder (OUD) is pervasive among all populations, it is more frequently observed in vulnerable and marginalized populations.[14-17] Opioid use disorder intervention strategies fall short in equitable reach and impact for diverse populations at risk of OD.[18,19] Initiation and retention of medications to treat opioid use disorder (MOUD) that can prevent OD are disproportionally low among people of color.[20] Evidence shows buprenorphine treatment rates were lowest in areas with Black and Hispanic residents, but highest for highest income areas.[21] To address the worsening racial/ethnic disparities in opioid deaths and access to treatment for OUD, multiple strategies need to be explored to better redress barriers in engaging diverse populations.[22-25]

3 Rationale/Significance

3.1 Problem Statement

Since 1999, there has been a 400% increase in the rate of drug overdose (OD) deaths in the U.S., with over 70% of the deaths in 2019 related to opioids.[1] The opioid crisis continues to worsen in the State of Connecticut (CT) for all racial/ethnic, gender, and age groups, with the number of OD deaths increasing by 285% from 2012 to 2020.[2] While the deployment of first responders in the field for OD, including police, fire, and emergency medical services, provides life-saving resuscitation and naloxone, it is unknown whether other evidence-based interventions are available and being utilized. To date, we lack critical and actionable real-time data from individuals who have experienced OD and from first responders and emergency medicine providers, including whether a treatment referral was offered to individuals who have overdosed and also time from OD to treatment engagement. This data could assist local authorities in predicting rates, timing, and location of ODs, as well as the types of services needed.

3.2 Purpose of Study/Potential Impact

The proposed project study aims to use our Opioid Use Disorder (OUD) Telehealth Platform to reduce overdose events. Our telehealth platform will be pilot tested to evaluate its preliminary efficacy in terms of motivating engagement in medications for OUD (MOUD), which has been shown to reduce overdoses, as well as its feasibility, acceptability and satisfaction to both first responders/providers and participants. The primary outcome will be measured at the client level.

3.2.1 Potential Risks

Potential risks include psychological distress related to the BNI, as the study is related to OUD use and treatment. The other risk associated with the study is the possibility that confidential information obtained during the study will be disclosed. However, we will receive a certificate of confidentiality to help protect study data, and only study staff will have access to study data. Further, all records will be identified by code number, when possible, to minimize the inclusion of identifiers in analysis. Additionally, regarding chatbot information security and privacy, the Telehealth Platform user interface (via web browser) will be SSL and all communication will go through an API server using SSL transport layer. In other words, everything has to go through the API server which will provide authentication and authorization to the platform. SSL is using the standard security technology for establishing an encrypted link between a server and a client. The API server will be communicating with an internal chatbot service through a TCP interface that is not open to any external network other than the API server. The chatbot service will have access to an internal database that will store all data, but no outside service will have access to it. All data storage will be encrypted and HIPAA compliant where every row that contains sensitive personal information will be given a unique identifier.

3.2.2 Potential Benefits

There is no direct benefit of participation to the subjects, other than the satisfaction of an altruistic contribution to medical science, as findings could have broad implications for sustainability of technology adoption into first responder and ED staff practices. Additionally, potential benefits for the participants could include receiving treatment and recovery coaching for opioid use disorder.

4 Study Objectives

4.1 Hypothesis

- Hypothesis 1: Use of the RP will be effective in increasing engagement with medication for opioid use disorder at 30 and 90 days.

- Hypothesis 2: Use of the RP will help decrease overdose events at 30 and 90 days.
- Hypothesis 3: Deployment of RP will be feasible, as evidenced by participant retention in study at 90 days.
- Hypothesis 4: Ratings of acceptability, feasibility and satisfaction with the RB will be favorable among participants and individuals referring participants.
- Hypothesis 5: The RP will demonstrate similar outcomes for MOUD engagement at 30 and 90 days as compared to prior in-person research.

4.2 Primary Objective

Successfully deploy the RP among 40 study participants and obtain feedback on feasibility, acceptability and efficacy of the telehealth platform.

5 Study Design

5.1 General Design Description

This is a pilot study funded by a R61 grant, designed to prepare for a Phase II efficacy trial funded by a R33 grant. As such, we will only set out to recruit enough participants to establish a stable mean in order to get a preliminary sense of the outcomes for future power analyses. For this pilot study, a total of 40 participants will be enrolled in a single-arm interventional clinical trial.

5.1.1 Study Date Range and Duration

Participation in the study is 90 days from enrollment. The anticipated enrollment and follow-up period is from Spring 2023 - September 2025.

5.1.2 Number of Study Sites

Yale University will serve as the single study site and collaborating sites include the Center for Progressive Recovery, LLC (the small business concern [SBC] that is the subrecipient in this application applicant and that has developed the OUD Telehealth Platform) and City University of New York. Participants will be recruited remotely using harm reduction resources and discharge materials that are already being used by the Fairfield, Litchfield, New Haven, and New London counties' first responders (local police, fire, and emergency medical services) and select emergency departments.

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

The primary outcome will be measured by attendance (yes or no) at the first buprenorphine appointment within 30 days of referral.

5.2.2 Secondary and Exploratory Outcome Variables

Secondary outcomes include engagement in the first MOUD appointment at 90 days and self-report of the number of overdose events at 30 and 90 days. Exploratory outcome variables include feasibility of intervention, readiness and intention to engage in treatment, acceptability and satisfaction of intervention, and comparison of MOUD engagement with data from previous in-person studies.

5.3 Study Population

The study population includes adults with moderate or severe opioid use disorder who are not currently engaged in MOUD.

Rationale for population selection:

There is an urgent need to improve OUD treatment and reduce the rate of opioid -related deaths. This platform will provide individuals with moderate to severe opioid use disorder and at risk of overdose real-time access to an artificial intelligence-powered chatbot and providers who prescribe medication for OUD (MOUD), as well as other harm reduction services for high-risk individuals; and we hypothesize that it will remove many of the barriers to follow up that these individuals face.

5.3.1 Number of Participants

A total of 40 participants will be enrolled in this study.

5.3.2 Eligibility Criteria/Vulnerable Populations

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Can speak, read and write in English
2. Provision of signed and dated informed consent form
3. Adult aged $\geq$18 years
4. Screened positive for OUD, moderate or severe, based on the Diagnostic and Statistical Manual-5th Edition
5. Have a working cell phone number and working device that can access a web browser and receive texts (i.e., smartphone, tablet or computer) OR be willing to use a device provided by the study team

6. Can provide a working email address OR be willing to create one

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Current use of buprenorphine, methadone, or naltrexone for a substance use disorder
2. Pregnancy or lactation
3. Known current suicide risk based on participant self-report
4. On parole or incarcerated at time of enrollment based on participant self-report

Of note, if individuals with other major psychiatric and/or medical disorders request a referral for care for these disorders, they will be provided with the same written information about community resources that is currently being provided to patients who are evaluated in the Yale New Haven Hospital Emergency Department.

Additionally, if individuals wish to enroll in our study after attending inpatient detox/rehab treatment, the research assistant will contact the participant and the rehab counselor at the phone numbers provided on the release of information form that was provided by the participant. The metrics will be unchanged for this group of participants.

6 Methods

6.1 Treatment – Device

6.1.1 Intended Use for Device

The intended use of the OUD telehealth platform, RecoveryPad, is to enhance motivation and engagement in treatment for OUD, as an alternative to in-person BNIs.

6.1.2 Device Administration and Schedule

Following consent, participants will be assigned to receive the OUD Telehealth Platform, which will be delivered remotely by research staff, who can also walk them through the 1-minute registration process, give them instructions on further use (i.e., just click on the link) and answer any questions. Once the participant clicks on the link, whether at the time of recruitment or thereafter, they will complete the initial chat, which includes instructions for the entire platform. The chatbot will then guide the participant through multiple BNIs focused on the goal of MOUD engagement, with the following steps: 1) Raise the Subject/Establish Rapport; 2) Provide Feedback; 3) Enhance Motivation; and 4) Negotiate a Plan. The chatbot then reminds the participant of their reasons why they might engage in buprenorphine treatment based on their responses to Steps 2 & 3, and their negotiated plan, at choice times (e.g., just prior to the participants' MOUD appointments). The chatbot will electronically connect participants to a partner provider of telehealth buprenorphine or a referral to a

traditional ("brick and mortar") MOUD provider. Throughout the 30 days, participants will also be able to text with a human recovery coach to assist them in the process, as well as to discuss any other recovery-related issues, especially connecting them to other harm reduction services and recovery supports in the community.

6.1.3 Method of Assignment/Randomization

All study participants will receive the same intervention.

6.2 Assessments

6.2.1 Efficacy

Efficacy of the RecoveryPad will be measured by 1) engagement and interaction with the RecoveryPad to demonstrate feasibility and 2) differences in primary, secondary and exploratory outcomes outlined in this study.

6.2.2 Safety

There are no safety issues anticipated in association with the RecoveryPad. If any unanticipated safety issues arise, we will report them to the IRB as needed.

6.2.3 Adverse Events Definition and Reporting

All adverse events are reported using the Institutional Review Board (IRB) standard template for reporting adverse events. The PI reviews all adverse events, classifies the attribution of adverse events (e.g., definitely, probably, possibly related; unlikely or unrelated) and grades the severity of the event, utilizing the FDA's definition of serious adverse events, on a 6-point scale (0=no adverse event or within normal limit; 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=fatal). Serious unanticipated or anticipated adverse events will be reported within 5 days to the IRB. Adverse events will be reported in summary form at least annually to the IRB. The summary will include the number of subjects enrolled and a summary of graded adverse events to date, using the chart format included in the Yale University Data Safety and Monitoring Plan template. The PI will evaluate all adverse events and determine whether the event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (e.g., Risks to Subjects) or consent form (e.g., Risks and Inconveniences) are required.

6.3 Study Procedures

Enrollment and Randomization: Individuals eligible for participation based on inclusion and exclusion criteria will be offered participation and electronic informed consent will be obtained.

Note: While participants are financially responsible for their own healthcare, we will only refer them to treatment options that are listed as being covered by their health insurance.

Baseline Assessment: Demographics, source of referral to the study (e.g., field or ED) and all of the inclusion/exclusion measures noted above will be collected from the participant by our remote eConsent portal, which is 21 CRF Part 11-compliant (see sections 5.3.2 & 6.3, and Baseline Assessments Form). Readiness and intention to engage in MOUD treatment, and ratings of acceptability of and satisfaction with the telehealth platform will be assessed via the platform after first use.

One Month Assessment: At 30 days post-enrollment, we will collect the following data:

- **Participants:** Self-reported number of overdose events during the 30-day period following enrollment, treatment engagement, readiness and intention to engage in MOUD treatment, and ratings of acceptability and satisfaction of the telehealth platform.
- **RecoveryPad platform:** Attendance at the first MOUD treatment appointment (Yes/No)(NB. Treatment will occur via RecoveryPad or at a brick-and-mortar clinic).

Three-month assessment: At 90-days post-enrollment, we will collect the following data:

- **Participants**: Self-reported number of overdose events during the 60-day period following enrollment, treatment engagement, readiness and intention to engage in MOUD treatment, and ratings of acceptability and satisfaction of the telehealth platform.
- **RecoveryPad platform:** Continued attendance at MOUD treatment appointments (Yes/No).

Participant Payments: Participants will receive a maximum of $100 for participation in this study. Payment distribution is as follows:

- $25 gift card after the completing the initial chat
- $25 gift card following completion of the one-month assessment.
- $50 gift card following completion of the three-month assessment.

Gift cards will be mailed (physical gift cards) or emailed (electronic gift cards), depending on participant preferences.

6.3.1 Study Schedule

Following enrollment, participants will have access to the RecoveryPad for 90 days. During participation, they will complete three milestones: initial chat, one-month assessment and three-month assessment. During the 90-day period, they will have continued access to the telehealth platform, which includes the BNI Chatbot, telehealth buprenorphine, and recovery coaching. After completing the study, participants will no longer have access to the RecoveryPad but can continue with any treatment and/or providers they were connected with through the platform.

6.3.2 Informed Consent

An informed consent form has been submitted with this protocol, which describes in detail the study intervention, study procedures, and risks. The consent will be given to the participant online, but they can be provided a paper consent form upon request. Participants will be given as much time as needed to review the information and ask any questions they may have. Questions will be answered by the RA in a way that does not reveal, or ask the individual to reveal, any PHI. If the individual's questions have been satisfactorily answered or if they have no questions, then they are given the option of signing the consent form online or in-person if they request. If they sign the consent form, a copy of it will be emailed to them.

6.3.3 Screening & Recruitment

Individuals will be referred to the study primarily from three settings, including in the field with first responders and harm reduction staff, in clinical settings (ED, inpatient, and outpatient care), and from the YCCI database. Individuals referred from the field and clinical settings will receive information about the study by word of mouth, flyers, or via the standard harm reduction resources and informational materials that are already being used by our community and clinical partners, which include study team contact information, QR code, and website linking the patient to the same enrollment platform accessed by the QR code to learn more about the study. Study team coordinators will also use Epic on a secure Yale-supplied encrypted laptop or tablet to review the emergency department boards to identify patients who are likely to have an opioid use disorder related chief-complaint, such as overdose. Should the study coordinator identify a patient in this category, they will reach out to the responsible clinician of record caring for the patient to inform them that the patient may be eligible for this study and to send the QR enrollment code to the clinician via Mobile Heartbeat or via a text message on their mobile device. The clinician may choose to share this QR code with the patient, along with all other standard harm reduction resources and discharge materials that are already being provided to this patient; but the clinician will not play a formal role in the recruitment process.

In addition to receiving referrals from our partners in Connecticut, we will also receive referrals from partners in New York. We will extend our recruitment of individuals with opioid use disorder by reaching out to the communities participating in the NY HEALing Communities Study (HCS) with whom we have long-standing relationships. As part of HCS goals, our team members at CUNY SPH have been working closely with these communities by helping them to implement evidence-based interventions to reduce overdose mortality rates. These communities and partner agencies are located within the following 16 New York counties, several of which are proximal to Connecticut: Ulster, Columbia, Greene, Putnam, Orange, Suffolk, Sullivan, Broome, Chautauqua, Erie, Genesee, Monroe, Yates, Cortland, and Lewis. We will reach out to harm reduction and recovery organizations, peer support groups, hospital and EDs, and coalition members who were involved with HCS, as well as to other similar partners, in these communities to distribute the QR codes and website link to potential eligible patients.

In addition to the process described above, our research team will also reach out to community stakeholders who may be in contact with individuals with opioid use order by using different types of social media as appropriate (e.g., sharing tweets about the study, sending personal emails to colleagues, publishing press releases, etc.). These stakeholders can then choose to share our study information through their standard outreach materials or in other ways they deem to be appropriate but will not play a formal role in the recruitment process.
Individuals referring potential participants from the field or from clinical settings will not be involved in the consent process. Consent will be accomplished as by a research coordinator described in section 6.3.2. YCCI's REDCap will be used to obtain informed consent.
Finally, the study team will also use the following resources from the Yale Center for Clinical Investigation (YCCI) to assist with participant recruitment:

1. *Yale Center for Clinical Investigation (YCCI) Help us Discover Database:* YCCI has an ever-growing "Help Us Discover" database of more than 20,000 individuals who have expressed interest in research at Yale. Emails with study details and contact information are sent monthly to the group to maintain engagement and research interest. Researchers and study teams have found that communications have increased interest and clinical trial recruitment after each YCCI email campaign. Researchers and staff teams may utilize the "Help Us Discover" database to contact patients directly with the understanding that they will not contact volunteers more than three times.

2. *YCCI website:* YCCI maintains a searchable research studies website that allows participants to look for research studies based on disease area, gender, age range, keyword, or investigators. We will work with YCCI to list our study flyer on the website, yalestudies.org. A recruitment flyer that includes contact information for interested patients will also be posted in the clinics.

3. *Direct-to-Patient Messaging*: YCCI developed the Direct-to-Patient Messaging capability with the Yale New Haven Health (YNHHS) electronic health record system (EPIC) in MyChart to help further

identify potential participants. After the study receives IRB approval to use MyChart recruitment, YCCI's Joint Data Analytics Team (JDAT) will develop an Epic based query which aims to identify high-level matches based on eligibility criteria. In collaboration with JDAT, an automated MyChart message will be sent to potential participants through the participant's MyChart portal.account. The participant will also receive an email notification informing them that they have a new research study that may be of interest to them. Interested participants will self-identify through their MyChart. portal, phone, or email. Researchers will receive identifying information of only those individuals who indicate interest.

Once participants express interest in the study, either by contacting the study team or visiting the study link, all assessment of eligibility will be done online (via the study recruitment/enrollment website, NOT RecoveryPad) or over the phone or in person with the research team, depending on the participant's preference. YCCI's REDCap will be used to obtain informed consent.

Of note, RecoveryPad will not be offered in lieu of a standard-of-care in-person BNI; and no standard treatment will be withheld in the ED, field, or at any of the settings described above. Information about RecoveryPad will be provided with other standard harm reduction resources at discharge.

Our community partners may choose to refer potential participants to our QR that will be added to the standard harm reduction and discharge materials that are already being used, but the partners will not be asked to play a formal role in the recruitment process.

The following is a list that is representative of the range of our community partners:

Table 1 – Community Partners

Partners	Roles
Emergency Departments	Yale New Haven Hospital ED (includes Lawrence + Memorial Hospital & Westerly Hospital)
	Bridgeport Hospital - Emergency Department
	Bridgeport Hospital - Milford Campus
Police & Fire	Robert Lawlor - New England High Intensity Drug Trafficking Area
	Chief Wright - New London Police Chief
	Chief Curcio - New London Fire Chief
Local Public Health & Govt.	Maria Coutant Skinner – Litchfield County Opiate Task Force
	Mayor Passero - New London Mayor
	Jen Muggeo - Ledge Light Health District, New London
Harm Reduction Agencies	Kelly Thompson - Alliance for Living, New London
	Joanne Montgomery - Liberation Programs, Bridgeport

The following is a list that is representative of the range of our statewide community partners for brick-and-mortar referrals:

Table 2 – Brick-and-Mortar Referral Partners

Partner	Role
APT Foundation	Methadone & Suboxone Providers
Connecticut Counseling Centers	Methadone & Suboxone Providers
Liberation Programs	Methadone & Suboxone Providers
Chemical Abuse Services Agency	Methadone & Suboxone Providers
Root Centers for Advanced Recovery	Methadone & Suboxone Providers
South Central Rehabilitation Center	Medically-Observed Withdrawal Program (i.e., "Detox")
The Retreat Centers	Residential Treatment Program (i.e., "Rehab")

6.3.4 Enrollment

Once a participant provides consent, they will have full access to the study platform and be prompted to complete their initial chat and assessment.

6.3.5 On Study Visits

1. **Baseline assessment (up to 45 minutes)**
   - Instructions for using the Study platform (accessed via QR code or link emailed from RA)
   - Baseline assessment, including demographics, inclusion/exclusion measures, source of referral to the study (e.g., field or ED), readiness and intention to engage in MOUD treatment, and ratings of acceptability and satisfaction with the telehealth platform.
   - Chat: The RP platform will guide the participant through multiple BNIs focused on the goal of MOUD engagement, which include the following steps: 1) raise the subject/establish rapport, 2) provide feedback; 3) enhance motivation, and 4) negotiate a plan. The chatbot then reminds the participant of their own reasons for why they might engage in MOUD treatment based on their responses to steps 2 & 3, as well as their negotiated plan, at critical times (e.g., just prior to the participants' MOUD appointments). The RP will electronically connect participants to a partner provider of telehealth buprenorphine or with a referral to a traditional ("brick and mortar") MOUD (including methadone or Vivitrol, if that is preferred) provider depending on participant preference, and remote recovery coaching.
   - Participant payment ($25 gift card)

- Continued access to the RP platform for the entire study period, including the ability to text with a human recovery coach to assist them in the process, as well as to discuss any other recovery-related issues, especially connections to other harm reduction services and recovery supports in the community.

2. **30-day assessment (up to 15 minutes)**
   - 30-day assessment, including attendance at MOUD, readiness and intention to engage in MOUD treatment and ratings of acceptability and satisfaction with the telehealth platform.
   - Participant payment ($25 gift card)

3. **90-day assessment (up to 15 minutes)**
   - 90-day assessment, including attendance at MOUD, readiness and intention to engage in MOUD treatment and ratings of acceptability and satisfaction with the telehealth platform.
   - Participant payment ($50 gift card)

6.3.6 End of Study and Follow-up

Following completion of study procedures, the research team will review data for completeness and attempt to complete any missing data, as possible. If patients withdraw from the study early, investigators will retain data collected up until discontinuation of the study. After completing the study, participants will no longer have access to the RecoveryPad but can continue with any treatment and/or providers they were connected with through the platform. Additionally, semi-structured follow-up interviews will be held with participants who elect to do so and have completed the study. Data from these interviews will be used to inform the recruitment and enrollment process, and intervention delivery for the next phase of the study. Involvement in the semi-structured interview will be optional for all study participants and will not affect a participant's ability to remain in the study. Participants will be notified of the interview request via email or phone call depending on contact preference indicated during enrollment. Participants who wish to proceed with the interview will be reconsented verbally prior to the start of the interview which will be completed via phone call. Interviewers will also ask for permission to record the audio of the phone call and inform the participant that this is optional. If the participant does not wish to be recorded, no audio recording will occur, and we will proceed with interview while taking notes.

Interviews will last approximately 15 minutes and participants will be awarded a $25 gift card delivered via email upon completion. Interview transcripts will be anonymized and stored following the same storage procedures outlined in section 3.2.1 of this study protocol.

6.3.7 Participant Withdrawal

As noted in the consent form, participants can voluntarily withdraw at any point in the study. Upon discontinuation of the study, participants will no longer have access to the study platform and their account will be deactivated. Unless otherwise stated, researchers will keep all participant data collected prior to discontinuation of the study. To be clear, we would continue to have the participant complete assessments, use RecoveryPad, and collect their data for research purposes if they require additional treatment.

6.4 Statistical Method

6.4.1 Statistical Design

As a pilot study, statistical design and analysis will be largely exploratory and directed by outcomes outlined above. When appropriate, outcomes will be evaluated using a two-sided test with a type I error rate of 5%. Statistical analysis will be performed using R, SAS and/or SPSS statistical software. While adverse events are not anticipated, any adverse events that do occur will be described in the analysis as appropriate

6.4.2 Sample Size Considerations

As a pilot study, the study was designed based on feasibility and what the principal investigator estimates is a reasonable study population size to explore and understand study outcomes based on experience and research. As such, no power calculations were performed.

6.4.3 Planned Analysis

6.4.3.1 Primary Analyses

The primary study objective is to successfully deploy the RP among -40 study participants and obtain feedback on feasibility, acceptability and efficacy of the telehealth platform. The objective will be evaluated via the primary, secondary and exploratory outcomes outlined using basic statistical analyses outlined in this protocol.

6.4.3.2 Safety

As a low-risk study with established, safe clinical interventions, safety issues are not expected in relation to study participation. Should any safety concerns arise, however, any unanticipated adverse events will be reported to the IRB as outlined and reported in publications.

6.4.3.3 Analysis of Subject Characteristics

Basic analyses of participant demographics, opioid use habits and engagement in treatment will be reported.

6.4.3.4 Health economic evaluation

No specific analyses will be conducted to evaluate the health economic impact of the study interventions.

6.4.4 Subsets and Covariates

As a feasibility pilot study, calculations on confounding variables were not needed.

6.4.5 Handling of Missing Data

As a feasibility pilot study, all available data will be analyzed to maximize the potential for meaningful findings. For reporting purposes, the total number of participants with available data will be noted for each outcome described.

7 Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

In concordance with best practices and guidelines, consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant will sign the informed consent document prior to engaging in any study activities. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records.

In addition to safeguards outlined in this document to protect patient confidentiality, the study will also be issued a certificate of confidentiality by the NIH to provide further protection of patient information.

7.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.

The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year. A study closure report will be submitted to the IRB after all research activities have been completed. Other study events (e.g., data breaches, protocol deviations) will be submitted per Yale University's IRB's policies.

7.3 Subject Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All in-person research activities will be conducted in as private a setting as possible.

With respect to minimizing risk associated with a breach in confidentiality, all subjects will be assigned a unique study number that will be used on all data collection forms. All staff will be required to successfully complete HSPT and will be required to follow standard HIC practices when interacting with subjects or accessing their data. As the research staff will need to maintain certain records that identify subjects for follow- up, no forms containing study data will contain any identifiers other than the study number. Computerized subject data will be in password protected files in locked offices or on a secured server. To protect confidentiality, all electronic and paper study records will refer to subjects only by a study number. Once enrolled, subjects will be given a unique study number, to which only members of our research team will have access. Study data will be kept protected and treated as confidential at all times. Computerized subject data will be password protected. Data will only be reported in aggregate. During an audit or program evaluation, representatives from the Yale Human Investigation Committee may have access to subject data but will strictly follow rules of confidentiality. Upon completion of the study, all computerized subject datasets will be de-identified and stored in a password-protected study computer, to which only the PI,

investigators and study personnel will have access. All paper files with subject information will remain in locked files in the study offices of the PI, until they are destroyed, after all analyses are complete. Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with subject permission or as required by U.S. or State law. Confidentiality with regard to collected materials will be maintained via a numbered reference system maintained by the Principal Investigator. Subjects' names will appear only on a consent form and "key" form kept in a secured cabinet by the PI separate from the subject records. All collected materials will be kept in locked file cabinets in a secured office.

The study participant's contact information will be securely stored at the study site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or, if applicable, sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in secure HIPAA-compliant databases. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived in a password-protected study computer, to which only the PI, investigators and study personnel will have access.

7.4 Deviations/Unanticipated Problems

A protocol deviation is any noncompliance with the study protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. If the study team becomes aware of an unanticipated problem (e.g., data breach, protocol deviation), the event will be reported to the IRB per their policies.

7.5 Data Collection

Paper forms, including consent forms and any other case report forms, will be stored in a locked file cabinet in a locked room that only research team members have access to. Electronic data will be stored in a study database maintained on YCCI's REDCap, which is on an encrypted, HIPAA-compliant server. All conversations and information collected through the RP will be stored within the HIPAA-compliant app and exported to the REDCap database periodically. After retaining study data

for three years after enrollment per NIH requirements, the dataset will be de-identified and retained for future research.

7.6 Data Quality Assurance

The organizational structure used to ensure quality of data in this project include extensive training and close supervision of the RA in data collection, and preliminary review of collected data by the Principal Investigator and/or Project Manager for completeness and accuracy.

7.7 Study Records

Study records will include consent forms, communication logs, communications in the telehealth platform, data on attendance at treatment appointments, and survey assessments. To be clear, *RecoveryPad* clinicians will be contacting the brick-and-mortar clinical providers to verify treatment (See the Release of Information form that the participant would complete only if/when they requested services outside of *RecoveryPad*.) The duration of time that the study team can access the medical record will be capped at the 90-day engagement timepoint; that is, the study team will not access treatment information after 90 days.

7.8 Access to Source

Source data will be maintained per Medical Records policy in a password protected, secure, Health Insurance Portability and Accountability Act (HIPAA) compliant, web-based electronic database with a built-in audit trail. Only Institutional Review Board (IRB) approved research team members who have current HIPAA and Collaborative Institutional Training Initiative (CITI) Good Clinical Practice (GCP) and human subjects protection training will be authorized to access records.

7.9 Data or Specimen Storage/Security

Research data will be collected from study subjects by trained RA who have successfully completed all required HIC and HIPAA training, using the paper study forms approved by Yale HIC or via a secure electronic handheld device and wirelessly uploaded to a secure server. These forms will only include the subject's unique identifier, which is assigned to the subject at the time of enrollment, to which only study researchers will have access. All information that is obtained in connection with this study will remain confidential and will be disclosed only with subject permission or as required by U.S. or State law. Information about substance use and treatment history will be collected. All collected data will be stored in locked files, in the locked study-dedicated office of the Principal Investigator, with access granted only to the study research team. Paper data will be computerized (entered into a study database) and password protected, with access granted only to the study research

team. Data will only be reported in aggregate. Data will be deidentified prior to formal data analysis, making individual subject identification impossible.

All private and identifiable information that is collected will remain confidential. Patient's responses will not be connected to any identifying information when entered into a database created for the survey except for study ID. A log will be maintained separately that will link the patient name with the ID number for all subjects.

7.10 Retention of Records

In compliance with NIH guidance, it is the PI's responsibility to retain study essential documents for 3 years from study launch.

7.11 Study Monitoring - Data Safety Monitoring Plan

This is a high risk study. Consistent with the Data and Safety Monitoring Plan (DSMP) template of the Yale University School of Medicine, the DSMP includes provisions for data review and performance of safety reviews, as described below:

- The MPIs and co-investigators will draft and review on a weekly basis, measures to minimize the risk of adverse events to the participants. While our Telehealth Platform will connect participants to a partner provider of telehealth buprenorphine or to standard ("brick and mortar") MOUD providers, no study personnel will be prescribing or managing any medication treatment. That said, our Telehealth Platform and study personnel will ask the participant about their motivation for and engagement in (i.e., attendance at) meetings with their prescribers.
- The MPIs and co-investigators will meet on a weekly basis to discuss study progress and any adverse events.
- The data safety monitoring board (DSMB) will consist of the MPIs, and four other experts in the area of technology-enabled brief intervention and opioid use disorders, to be named by Yale University's committee on DSMBs or an external IRB.
- The DSMB will meet every two months to review interim data analyses and any adverse events as needed. In addition, IRB will review the study protocol at their discretion and will review/approve any amendments before they are made. Any adverse effects encountered will be reported promptly to the IRB and to the funding agency, according to current regulations.

Data and safety monitoring procedures in this study include computerized data collection and monitoring systems and an organizational structure of clearly defined tasks assigned to all research and clinical personnel involved in the conduct of this study. The computerized study tracking system consists of a database system that records research activities including recruitment and follow-up activities. The MPIs will use this database to monitor ongoing participant participation. Research Coordinators will computerize collected study data using specialized data entry software (e.g., SPSS). This will facilitate efficient data entry and allow for elimination of out-of-range values and double entry of data, which is likely the result of key punch errors. All error corrections will be fully documented in the research records.

All adverse events are reported using the IRB standard template for reporting adverse events as described below. Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (*Dr. Rebekah Heckmann*) according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

The following scale will be used in grading the severity of adverse events noted during the study per the IRB standard template:

1. Mild adverse event
2. Moderate adverse event
3. Severe

In addition to grading the adverse event, the MPIs will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

X All Co-Investigators listed on the protocol.
□ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
X National Institutes of Health
□ Food and Drug Administration (Physician-Sponsored IND #_____)
□ Medical Research Foundation (Grant_____)
□ Study Sponsor
X Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

The principal investigator (*Dr. Rebekah Heckmann*) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required. Adverse events will be reported in summary form at least annually to the IRB. The summary will include the number of subjects enrolled and a summary of graded adverse events to date, using the chart format included in the Yale University DSMP template. The MPIs will evaluate all adverse events and determine whether the event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (e.g., Risks to Subjects) or consent form (e.g., Risks and Inconveniences) are required.

Finally, we will adhere to standard Good Clinical Practice (GCP) and the applicable regulatory requirement(s) around quality assurance measures for subject recruitment, enrollment, enrollment targets, and for the validity and integrity of the data. Specifically, "All those planned and systematic actions that are established to ensure that the trial is performed, and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s)," will occur with regularity. Finally, as per Yale University's IRB requirements, all study personnel will be required to complete Good Clinical Practice training and all study procedures will be carried out in compliance with the principles and codes set forth in these guidelines.

7.12 Study Modification

The PI will be responsible for monitoring the data and conducting performance and safety reviews, at the specified frequency. Either the PI or the IRB have the authority to stop or modify the study. The monitoring by the IRB will occur annually at the time of re-approval. The PI will conduct data and safety review at least quarterly and at any time a serious adverse event occurs. During the review process, the PI will evaluate whether the study should continue unchanged, requires modification or amendment to continue, or should be closed to enrollment.

7.13 Study Discontinuation

Participants can withdraw from the study at any time by contacting the research team or Yale University IRB. Withdrawal from the study will have no impact on clinical care or treatment they were referred to or connected with as part of the study. Upon withdrawal, participants will no longer have access to the telehealth platform and their account will be deactivated. Unless otherwise stated, researchers will keep all participant data collected prior to discontinuation of the study.

7.14 Study Completion

This study duration will be approximately two years from IRB approval, which will allow one year for enrollment and study interventions and one year for data analysis.

7.15 Conflict of Interest Policy

All investigators on this study will be required to complete and maintain Conflict of Interest (COI) forms with Yale University. All but one of the current investigators have no COIs to disclose that are relevant to this study. However, Dr. M.V. Pantalon is a Yale investigator who has a conflict of interest with this study via his roles as co-founder/co-owner of, and investigator at, CPR, a subrecipient of the grant funding this project (i.e., royalties, or financial gain greater than the minimum allowable by their

institution, etc.). This conflict has been reviewed by Yale University with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All investigators will follow the applicable conflict of interest policies. Additionally, the DSMB will be informed of Dr. Pantalon's financial conflict of interest with CPR.

7.16 Funding Source

This study is federally funded by a National Institute on Drug Abuse R61 grant.

7.17 Publication Plan

Dissemination of findings will occur via presentations at relevant conferences and publications in peer-reviewed journals. All data reported on will be in aggregate and no identifiable information that could potentially identify participants will be shared. The study investigators will hold primary responsibility for sharing study results and staff involved with conducting the study, analysis and presentation/manuscript development will be recognized accordingly, where appropriate.