Human Subjects Research Protocol

The Common Human Subjects Protocol Cover Form **must** be completed and accompany this form. This Protocol form should be completed for any human subjects research proposal that does not have a specific "protocol," such as a grant application. This form must be submitted along with a copy of the complete grant proposal and all the information in this form **must** be consistent with that proposal. This protocol form, once IRB approved, will be the working protocol for that research. **When completing this document, do not refer to page numbers within your grant**. If revisions are necessary during the course of the research, amendments should refer to this protocol form, not the grant proposal. Enter responses for all sections. Check N/A if the section does not apply. All materials must be submitted electronically to the IRB via InfoEd. Proper security access is needed to make electronic submissions. Visit the InfoEd Resource Materials page for more information.

PROTOCOL SUMMARY

Project Title:	Protocol Version Date:
Emergency Department Initiated Buprenorphine Intervention for Opioid Use Disorder	04/07/2021

Principal Investigator: Scott Mackey, Sanchit Maruti, Dan Wolfson, and Roz Bidad

Grant Sponsor:	Grant Number:
Pilot grant from the Northern New England Center for Translational Research (NNE-CTR) grant awarded to the Maine Medical Center and funded by the NIH's National Institute on General Medical Sciences (NIGMS); SAMHSA; NIDA	SAMHSA: 1H79TI081515-01 NIDA: 1R21DA049859-01 Northern New England Center for Translational Research: U54GM115516

(For grants routed through UVM, indicate the OSP Proposal ID # located at the top of the OSP Routing Form)

Lay Language Summary: *(Please use non-technical language that would be understood by nonscientific IRB members to summarize the proposed research project. The information must include: (1) a brief statement of the problem and related theory supporting the intent of the study, and (2) a brief but specific description of the procedure(s) involving the human subjects. Please do not exceed one single-spaced 8 ½ X 11" page.)*

Opioid-related overdose deaths have quadrupled since 1999 making drug overdose the new leading cause of accidental death in the U.S.1 The current practice of providing emergency department (ED) patients who endorse opioid use disorder (OUD) with only a referral to local treatment programs, which often have long waiting lists, represents a tragic missed opportunity to engage patients in sustained medical care.2,3 We hypothesize that a novel intervention at the UVM Medical Center (UVMMC), which will 1) initiate buprenorphine treatment in patients presenting at the ED with OUD, and 2) guarantee enrollment in the UVMMC Addiction Treatment Program (ATP) within 24 to 72 hours, will address the acute crisis period when individuals are most vulnerable to relapse and lead to increased long-term participation in Medication-Assisted Treatment (MAT). This project is expected to generate immediate benefits for those enrolled and will provide proof of concept evidence for a new model of engaging individuals with OUD in long-term care.

Vermont has a lower rate of fatal opioid overdoses than the national average and a significantly lower rate than other rural New England states (e.g. 13.9 deaths per 100,000 in Vermont compared to 26.2 in New Hampshire in 2014).4 This situation has been attributed to the development of an effective "Hub and Spoke" OUD treatment system and proactive state-sponsored programs to increase access to emergency opioid overdose rescue kits and needle exchanges.4,5 Despite this, the number of drug-related fatalities in Vermont continues to increase in parallel with the alarming national upward trend, surging 37% from 2015 to 2016.6 Thus, the Vermont response to the opioid epidemic urgently requires further improvement to address a still growing problem. A key challenge in addressing OUD is that most individuals who would benefit from a medical intervention do not receive any assistance. Only 10.8% of the estimated 21.7 million people in the U.S. with a past year substance use disorder received specialized treatment.7 Consequently, the presentation of patients with OUD at the ED is a critical

opportunity to identify individuals in need and direct them toward long-term treatment programs. The current standard of care for individuals with OUD presenting to the ED provides management of acute symptoms and contact information for treatment programs, which often have long waiting lists.3 Here, we will compare the standard practice with a novel intervention that will provide 1) immediate initiation of buprenorphine treatment at the ED and 2) guaranteed placement in a specialized OUD treatment program (i.e. UVMMC Addiction Treatment Program -ATP) within 24 to 72 hours after discharge. The primary outcome measure will be opioid use at 1 week and 3 & 6 months after buprenorphine initiation.

Aim 1. To determine whether ED-initiated buprenorphine treatment coupled with enrollment in a bridge clinic that will supervise MAT until the patient is stabilized and placed with a local MAT provider will reduce illicit opioid use compared to ED-initiated buprenorphine treatment coupled with immediate referral to a local MAT provider. Hypothesis: Patients assigned to the ED-initiated buprenorphine plus ATP bridge clinic intervention will have significantly reduced illicit opioid use as determined by urine drug screen at 1 week, and 3 & 6 months than patients who only receive direct referral to a local MAT provider. .

PURPOSE AND OBJECTIVES

Purpose: *The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.*

The explosive increase in opioid use in the U.S. over the past two decades poses a formidable threat to the national welfare.10-13 In the last month, an estimated 400,000 individuals have used heroin and over four million individuals have used prescription pain medication for non-medical purposes.14,15 The latest estimates released by the CDC for the year 2016 indicate that a dramatic surge in opioid related deaths has produced a population level decline in average life expectancy.16 Opioid-related overdose fatalities have quadrupled since 1999.1 In 2016 alone, 63,200 Americans died of an opioid-related overdose, which represents a 21% increase over the preceding year. The rapid development of evidence-based approaches to manage the opioid epidemic is critical at this time. Here, we will examine whether an ED-initiated intervention will lead to lower rates of opioid use and higher enrollment in medical treatment for OUD.

Currently, the most effective treatments for opioid withdrawal are methadone and buprenorphine.17-19 Medication-Assisted Treatments (MATs), which prevent cravings and withdrawal, lower the rate of fatal overdoses and transmission of infectious disease through needle sharing and increase patient functioning and ultimately retention in treatment.20,21 However, most individuals who would benefit from a medical intervention do not receive any assistance. Only 10.8% of the estimated 21.7 million people in the U.S. with past year substance use disorder received specialized treatment.7 Thus, the presentation of patients with OUD to the ED represents a significant opportunity to identify and direct these individuals toward treatment services.3,22-24

Figure 1. Diagram of the Vermont hub and spoke model

Stakeholders in the Vermont health care system have pioneered the Hub and Spoke model to deliver MATs in the state (Figure 1).4 Since Vermont is a predominantly rural state, the Hub and Spoke model emphasizes local providers and distributed services, which lowers the barrier to treatment imposed by the necessity of travelling long distances to receive services.25,26 Each of five geographical regions in Vermont are serviced by one or more Hub clinics, which dispense and monitor treatment with methadone or buprenorphine. Patients with the greatest monitoring requirements are enrolled in the Hub clinics, while local providers (i.e. Spokes) who have received specific training in the prescription, monitoring, and diversion control of buprenorphine manage patients requiring a less intensive level of care. Referrals to the Hub and Spoke system are provided by services listed in the outer ring of Figure 1, e.g. pain management clinics, family services, etc. The innovative Hub and Spoke model in combination with proactive state-sponsored programs to increase access to emergency opioid overdose rescue kits and needle exchanges have been credited with driving the rate of fatal opioid overdoses in Vermont below the national average, and significantly lower than other rural New England states.4,5 Despite this, the number of drug-related fatalities in Vermont continues to parallel the national upward trend, jumping 37% from 2015 to 2016.6 Thus, the Vermont response to the opioid epidemic urgently requires further improvement to address a still growing problem.

Here, we will investigate whether ED-initiated MAT with buprenorphine and sustained clinical follow-up for patients presenting with OUD at ED lowers opioid use and increases retention in treatment Preliminary evidence suggests that ED-initiated MAT will produce positive short-term outcomes. In a randomized trial, opioid dependent patients receiving ED-initiated buprenorphine treatment with 10 weeks of supervised MAT were significantly more likely to be enrolled in a treatment program at 30 days after study recruitment than patients who only received a simple referral (i.e. 95% vs. 37%, respectively).8 Retention rates remained elevated at 2 months.9 However, these effects had completely disappeared by 6 and 12 months. We believe that the long-term failure of this intervention at 6 and 12 months was due to lack of opportunity for most participants to continue supervised MAT after the end of the study. The present study will examine whether ED-initiated MAT combined with sustained clinical supervision at ATP, which monitors patients until they transfer to long-term care, results in lower rates of opioid use. ED-initiated of treatment for OUD would mirror immediate treatment of other chronic life-threatening diseases presenting to the ED.

INNOVATION

- Integration of ED-initiated buprenorphine treatment with sustained treatment follow-up at ATP, a MAT bridge clinic.
- ATP will eliminate the treatment waitlist for study participants and effectively bridge the critical relapse period between the ED visit and entry into long-term treatment.

Impact: The ED initiated buprenorphine treatment and ATP intervention is expected to effectively bridge the risk of relapse in the critical period between ED presentation and integration into the standard Vermont Hub-and-Spoke system for monitoring long-term MAT. Opioid use disorder contributes to frequent re-admission rates in certain patients. Improving the chances that these individuals enroll in long-term care will reduce ED burden and free up resources for other patients. Positive findings on Aim 1 will support network-wide adoption of this intervention in Vermont.

References. *Include references to prior human or animal research and references that are relevant to the design and conduct of the study.*

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Objectives: *Clearly state the primary and secondary objective(s) of the study.*

The primary outcome will be urine specimens for illicit opioids at 1 week and 3 & 6 months after ED initiated treatment Urine specimens will be collected under observation of same-sex staff and immediately analyzed for opioids (buprenorphine, methadone, oxycodone, hydrocodone, hydromorphone, heroin, fentanyl) and other drugs (cocaine, amphetamines, benzodiazepines, cannabinoids) via enzyme multiplied immunoassay. Missing urine specimens will be considered positive for illicit opioids, consistent with an intent-to-treat approach.

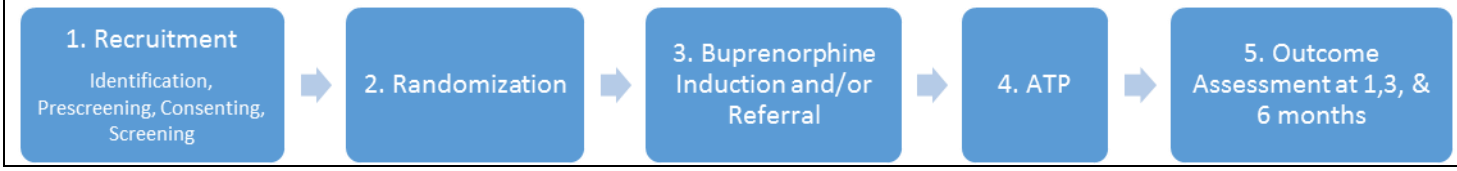
Secondary outcomes will include self-reported illicit opioid or other (non-opioid) drug use, treatment enrollment status and behavioral questionnaires (i.e. the GPRA Client Outcome Measures questionnaire the Treatment Effectiveness Assessment (TEA),43 and the Vermont Treatment Needs Questionnaire (TNQ)21).

METHODS AND PROCEDURES

Study Design: *Describe the research design, including a description of any new methodology and its advantage over existing methodologies.*

This pilot project will test whether ED-initiated buprenorphine treatment for individuals presenting to the UVMMC ED with OUD combined with a MAT bridge clinic leads to a reduction in illicit opioid use at 1 week, and 3 & 6 months compared ED-initiated treatment with a direct referral to a local MAT provider. The intervention and study design include 5 main stages (see figure below): 1) Patients admitted to the ED with indicators of OUD will be consented and screened for study eligibility; 2) Participants will undergo buprenorphine induction at the ED; 4) Participants enrolled at Central Vermont Medical Center and Porter Medical Center will be referred directly to a local MAT provider. Participants enrolled at UVMMC will be referred to the UVMMC ATP, a MAT bridge clinic that will supervise MAT with buprenorphine in all participants who enroll in the program until the individual is transferred to a long-term MAT provider, referred to a higher level of care or drops out of treatment --treatment duration at ATP is typically 8 weeks before referral of stable patients to primary care providers; 5) All participants will be contacted at 1 week, and 3 & 6 months after randomization to determine current illicit opioid use.

We expect to enroll 200 participants over 3 years.



Procedures: *Describe all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc. Include required screening procedures performed before enrollment and while on study. Please provide in table, list or outline format for ease of review. (describe and attach all instruments)*

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

Our project team (Drs. Maruti, Mackey, Barkhuff and Wolfson) includes clinical and research expertise required to undertake the study. Dr. Maruti is an addiction psychiatrist who heads the UVMMC ATP and Dr. Mackey is clinical research faculty. Drs. Barkhuff and Wolfson are UVMMC ED physicians. Ms. Bidad, RN and Ms. Mahler, LCMHC, LADC will coordinate research support at the ED Research Program and ATP, respectively.

The study consists of 4 parts: 1) Recruitment, 2) Buprenorphine Induction, 3) Referral, and 4) Outcome Assessment at 1, 3, and 6 months.

Recruitment, Randomization and Buprenorphine Induction or Referral all occur during the initial visit to the ED. The part of the protocol performed at the ED can be summarized in 11 steps. See also illustration of EMRAP staff structure in Informed Consent section.

Brief Summary Table Listing 11 Steps During Initial ED Visit

1. Recruitment

Step 1. Patients arrive at Emergency Department.

Identification

Step 2. Research Associates (EMRAP undergrad trainees) identify potential participants based on indicators of OUD in EPIC Electronic Health Records (EHR).

Step 3. Research Associates will notify an EMRAP Research Coordinator of potentially eligible participants. The Research Coordinators are full-time EMRAP research employees.

Prescreening

Step 4 Research Coordinator will confirm in-person or via telephone with ED physicians/nurses providing care for patient that approaching the individual is appropriate and will not interfere with service.

Step 5 Research Associate or Research Coordinator approaches potential participant and performs prescreen either in-person or via telephone. The prescreen text is attached to this application. Prescreening information is stored in REDCap. If a subject is found to be ineligible, data entered for that subject will be deleted from REDCap at that time.

Step 6 Based on answers consistent with opioid use disorder, proceed to next step otherwise thank individual and destroy prescreen answers.

Step 7 If patient declines continuing enrollment process, will be provided with informational wallet card describing research study, informing patients that they may return to the ED at a later date to reattempt enrollment

Consenting

Step 8 Participant is consented into the study by one of the Research Coordinators either in person or via telephone with coordination from ED care team to sign appropriate documentation. If eligible participant does not consent, individual will be thanked and prescreen information destroyed. Prescreening information is stored in REDCap. If a subject is found to be ineligible, data entered for that subject will be deleted from REDCap at that time. Consent may be completed via eConsent form. Printed copy of signed consent form will be provided to the consent after completing consent process.

Step 9 Research Coordinator confirms OUD diagnosis.

2. Buprenorphine Induction

Step 10 Participants receive induction treatment from ED physician who has been certified to prescribe Suboxone.

3. Referral

Step 11 Participants enrolled at Central Vermont Medical Center or Porter Medical Center are referred to a local MAT provider. Participants enrolled at UVMMC are refered to the UVMMC ATP, a MAT bridge clinic.

Step 12 Research Associate leads participant through behavioral questionnaire battery on ipad. (This step may occur before step 10 while the participant is waiting to see ED physician).

Note that Central Vermont Medical Center and Porter Medical Center are not yet prepared to start data collection. Details about procedures at these sites will be added by amendment as it becomes necessary. No protocol procedures will be performed at CVMC or Porter until these amendments have been reviewed by the IRB. We ask that the IRB approve the UVMMC site to continue enroll participants while the other sites are prepared.

Part 1) Recruitment.

Identification (Steps 2 and 3). Potential participants will be identified by indicators in presentation and medical history consistent with OUD, including presentation with acute overdose or symptoms consistent with opioid withdrawal (such as piloerection, diarrhea, tachycardia, cravings, and pupillary dilation), and EMS use of naloxone on scene or en route to the hospital as reported verbally to ED physician or nurse. Patients with abscesses, especially in the antecubital fossa and other areas consistent with injection drug use and patients with a history of endocarditis will be asked about opioid use and prescreened for enrollment. Research Associates or a Research Coordinator will screen health information of incoming patients on EPIC EHR system to identify study candidates. “Request for Partial Waiver of Authorization for Recruitment Purposes” is attached. In addition, ED physicians may alert ED research staff to patients with suspected opioid use disorder based upon physician’s observations in the course of ED medical care. Note: Research Associates will not access ambulance run sheets or Siren because these may contain information about new patients from sources for which the UVM IRB

does not monitor HIPAA compliance.

Prescreening (Steps 4 and 5). Research Coordinator will confirm with physician/nurses providing medical care to patient that it is appropriate to approach individual and will not interfere with ED service. Research Associate or Research Coordinator will perform prescreening following a written script (see attached prescreening script). Prescreening includes self-report questions on opioid use that could indicate OUD to determine eligibility. Since the prescreen contains PHI questions about opioid use "Request for Waiver or Alteration of Informed Consent/Authorization/Documentation" related to the prescreen is attached. Information shared during prescreen represents a minimal risk to the patient.

Consenting (Steps 7 and 8). Consent will be performed according to standard Emergency Medicine Research procedures. More information on this is outlined in the Informed Consent section of this protocol. Consent will be performed by a Research Coordinator who is paid employee of EMRAP. Consent form is attached.

Eligibility. English-speaking patients over the age of 18 presenting at the UVMMC ED with indicators of an OUD will be assessed for eligibility. Exclusion criteria will include: current participation in an alternate treatment program for OUD (Exception: Individuals recently released from correctional facilities or residential treatment programs who do not have a current prescription will allowed to participate
–Note: Parolees have the opportunity to join the study voluntarily. Participation is not a condition of their parole and thus they do not fit the definition of a prisoner under the OHRP guidelines which would require greater scrutiny.), inability to communicate, altered mental status, suicidality, medical extremis or requiring admission, prisoners, history of Suboxone injection in the past year, and hepatic impairment.

After consent, Research Coordinator will immediately confirm eligibility criteria including diagnoses of OUD by asking only the questions related specifically to OUD diagnosis in the Mini-International Neuropsychiatric Interview (MINI).[37,38] The remainder of the MINI will be performed in step 11. The Research Coordinator will also immediately assess suicidality by asking the question: "Are you thinking about suicide?" If the individual endorses suicidal ideation, the attending physician will be notified immediately and standard ED operating procedures for patients endorsing self-harm ideation will be followed. The Research Coordinator will also ask for locator information after the subject consents to participate in the study. The locator information form is attached. Research coordinators will have access to the locator form for the course of the study in order follow up with subjects at 1 week, 3 months, and 6 months.

Part 2) Buprenorphine Induction *(Steps 10 and 11)**.***

Participants will meet with an ED physician who will utilize rules for emergency prescription of Suboxone and who will have received training on buprenorphine induction from ATP. The physician will use the Clinical Opioid Withdrawal Scale (COWS) to assess level of withdrawal.

Note that besides Investigators Daniel Wolfson and Daniel Barkhuff other ED physicians waivered to prescribe Suboxone will not be listed as key personnel according to the following definition. Individuals who are Not Key Personnel: An individual who will be interacting with research subjects during the course of a research study, but only in his/her regular non-research employment capacity. That is, ED physicians will be interacting with participants of the study only in their clinical roles as ED care providers. Additionally, the requirement that physicians perform 4 hours of CITI training as Key Personnel would significantly limit the number of ED physicians willing to be associated with critical

research on ED best practices.

Participants will be given a 3-day Starter Pack containing 12 x 2/0.5 mg films of Suboxone for a total daily dose of 8mg of buprenorphine for 3 days (i.e. 4 x 2/0.5 films each day = 12 films).

Patients in withdrawal will be given an immediate dose of two 2/0.5 mg films of Suboxone (i.e. two Suboxone films containing 2mg of buprenorphine and 0.5mg of naloxone each) from the Starter Pack and instructions to take two more 2/0.5mg films at home the same day for a total daily dose of 8mg of buprenorphine. Patients not manifesting withdrawal, but with presentation and history consistent with moderate to severe OUD, will be instructed to take the first two films of Suboxone from the Starter Pack when experiencing mild to moderate withdrawal symptoms, and to take another two films if symptoms persist 1-2 hours after taking the first two films. Patients will be given a written explanation of the rationale for the induction process and the risk of precipitated withdrawal if Suboxone is taken when not experiencing withdrawal symptoms (see attached "Home Induction Instructions"). Participants will receive detailed verbal instructions in addition to a written self-medication guide.[44]

Participants will also receive in the Starter Pack Suboxone for two additional days of treatment (i.e. the remaining 8 films containing 2/.5mg Suboxone with instructions to take 4 films on day 2 and the remaining 4 films on day 3). The additional Suboxone doses will accommodate those entering the study on the weekend because the ATP only accepts new patients during week days (i.e. Monday to Friday). Participants are instructed to bring any extra doses with them to the first appointment at the ATP which will be incorporated into the maintenance prescription provided at the ATP. Research and clinical experience indicate that many patients will require daily doses of buprenorphine greater than 8mg to fully suppress craving and withdrawal, and for these patients dose escalation will be available under medical supervision when starting treatment at ATP. The initial 8mg dose limit is for self-administered doses only, to provide immediate relief of withdrawal symptoms and craving while limiting potential for excessive dosing or diversion.[44-48]

Potential for Medication Diversion. To reduce the potential for drug diversion, individuals will be allowed to enroll only once in the present study. Treatment initiation at ED will start with a dose sufficient to diminish withdrawal and craving but less than has been used in previous studies of linkage to treatment or home induction.[e.g. 45,49] Rapid follow-up including upward adjustment of dose if needed under medical supervision will be provided at the bridge clinic or the local MAT provider

The range of dates (i.e. week period around 3 and 6 months after randomization) for the last two follow-up visits will be written down and given to participants with other study materials at the initial ED visit. Participants will be told that they will be contacted in the week before the follow-up visits at 3 and 6 months to arrange the specific time and place of the follow-up visit.

Step 11. Collection of additional information will occur by phone within seven days of randomization. This will include psychiatric history assessed by the 15 minute Mini-International Neuropsychiatric Interview (MINI),[37,38] opioid use history (e.g. onset, duration of use, route of administration) assessed with the Pattern of Substance Use -Adult questionnaire in the PhenX toolkit, and the GPRA Client Outcome Measures questionnaire. Data will be collected on an iPad.

Part 4) Referral

Participants enrolled at Central Vermont Medical Center or Porter Medical Center are referred to a local MAT provider. Participants enrolled at UVMMC are referred to the UVMMC ATP, a MAT bridge clinic.

Addiction Treatment Program. The ATP is a part of the UVM Department of Psychiatry. Its mission is to expand treatment capacity and increase access to high-quality, evidence-based treatment for individuals with OUD in Vermont. The ATP team includes two fellowship-trained addiction psychiatrists, one general psychiatrist, and one family physician who are all experienced in treating OUD, as well as resident and fellow trainees from psychiatry, family medicine, and internal medicine, and licensed professionals in nursing, alcohol and drug counseling, mental health counseling and clinical social work. The staff is experienced in providing MAT to patients in all phases of treatment, in diverse settings and across levels of acuity, as well as in educating, training and supporting colleagues with varying levels of experience, training and comfort in addictions treatment. The ATP was selected by the State of Vermont to lead a state-wide Learning Collaborative Project to provide training and education to MAT practices throughout the state of Vermont.

ATP is housed in the UHC building on 1 South Prospect Street in downtown Burlington. The ATP offices are a five-minute walk to the UVMMC ED. Both ATP and ED contain meeting rooms where the PIs and study staff will be able meet to review recruitment targets, ongoing training, and other methodological issues which arise during the study. Successful participation in ATP is characterized by 3 stages (Figure 5).

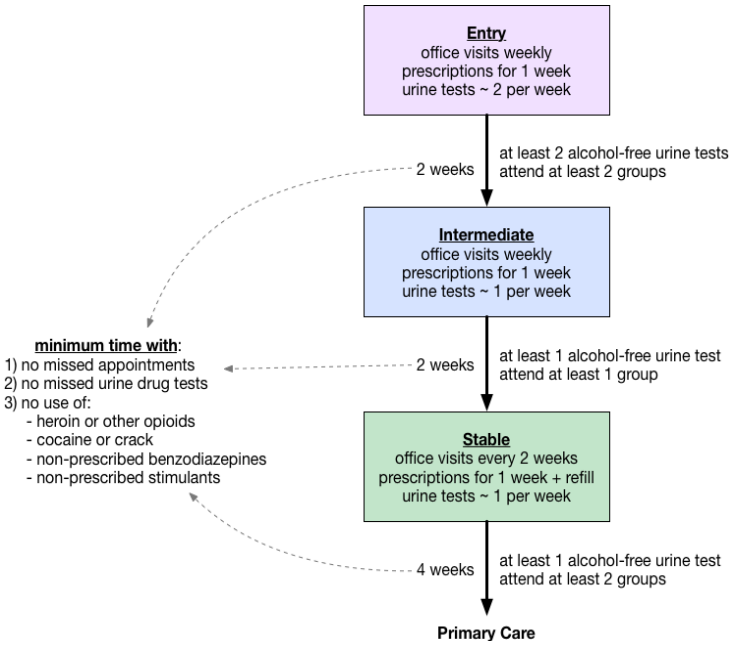


Figure 5. Flow chart typical 8-week program

Stage 1. Entry. This stage includes weekly follow-up with a physician and random urine drug testing 1-2 times weekly in addition to weekly individual or group counseling. Doses of buprenorphine/naloxone are adjusted as required to address persistent craving, withdrawal symptoms, or opioid use.

Stage 2. Intermediate. Includes weekly physician follow-up, once-weekly random urine drug testing, and ongoing counseling. Doses of buprenorphine/naloxone can be adjusted as in the entry period, though in practice this is required less frequently at this stage.

Stage 3. Stable. Includes physician follow-up every 2 weeks, once-weekly random urine drug testing, and ongoing counseling. Dose adjustments are rarely needed at this stage, and patients typically transition to primary care after approximately one month of stable-level follow-up.

Referral to primary care for continuation of MAT is initiated when a patient reaches the stable treatment level, and the transition typically occurs approximately 4 weeks later. Actual duration of enrollment at ATP varies depending on substance use, nonadherence such as missed appointments or urine drug tests necessitating treatment adjustments, as well as availability of appointments in primary care. Patients with ongoing substance use who are determined to require residential or Hub-level treatment are referred to those settings, and their treatment at ATP is continued while referrals are in process. Patients who complete residential treatment may return to ATP to resume office-based treatment if clinically appropriate. Since its formation in 2016, ATP has treated 248 patients of which 40 are currently enrolled in the program. Approximately 90% of patients treated at the ATP continue to remain in treatment with 70% of them receiving their treatment from Primary Care providers (Spokes). Of the patients treated at the ATP approximately 18% were referred back to the ATP for additional stabilization.

Note that if a participant withdraws or is withdrawn from the study, they will continue to receive services from ATP. Conversely, if a participant decides they no longer want treatment at ATP, they may continue to participate in the study.

Part 5) Outcome Assessment. The primary outcome will be illicit opioid use at 1 week and 3 & 6 months after buprenorphine induction. Consistent with standard ATP practice, urine sample collection and analysis will be performed by Aspenti Labs (https://www.aspenti.com/), a clinical drug testing service which is open Monday to Friday 7AM-7PM and has multiple locations throughout Vermont. Urine specimens will be collected under observation of same-sex staff and analyzed for opioids (buprenorphine, methadone, oxycodone, hydrocodone, hydromorphone, heroin, fentanyl) and other drugs (cocaine, amphetamines, benzodiazepines, cannabinoids) via enzyme multiplied immunoassay. Missing urine specimens will be considered positive for illicit opioids, consistent with an intent-to-treat approach. Additional outcomes will include self-reported illicit opioid or other (non-opioid) drug use, treatment enrollment status and behavioral questionnaires (i.e. the GPRA Client Outcome Measures questionnaire to track self-reported drug-use and life conditions). The Treatment Effectiveness Assessment (TEA)[43] will be included at 1 week, 3 months and 6 months to track patient perception of treatment progress. Additional follow-up questions based on the PhenX toolkit are attached.

Retention. Participating in OUD treatment has health advantages for the participants which is a motivation to remain in the study. Participants will receive a $25 gift card after answering questionnaires in Step 11. In addition, as an incentive to provide a urine sample and answer questions at follow-up, participants will receive a $25 gift card for answering questions by phone and a $50 gift card for a urine sample at each of the three outcome time points completed (i.e. 1 week, 3 and 6 months post randomization). In total, participants can earn up to $250 for their participation in the study. To avoid altering the motivation to stay in MAT, participants will earn payment for providing the urine samples and answering questions at each of the 3 follow-up time points, regardless of whether they are currently in treatment. Missing urine specimens will be considered positive for illicit opioids, consistent with an intent-to-treat approach.
Participants will be contacted by phone, text and/or email. A letter will also be mailed to participants (see attached). In the event the participant cannot be reached by any other means, a letter will be sent to the contact person provided by the participant at intake on the Locator Form. Contact information for phone, text and email will be collected at the initial ED visit. The dates (i.e. 1 week, 3 months and 6 months after randomization) for the follow-up visits will be written down and given to participants with other study materials during the initial ED visit. Participants will be contacted in the week before the follow-up visits at 3 and 6 months to remind them of the date and answer any question about where and how urine samples will be collected. Participants will also be reminded again the day before.

For research involving survey, questionnaires, etc.: *Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation. (describe and attach all instruments)*

☐ ***Not applicable***

Behavioral questionnaires will be used to assess participants at the following time points.

At baseline, participants will be assessed using the Locator Form, Referral, Suicidality, GPRA, MINI Neuropsychiatric Interview, Why are you enrolling in this program: Prevent overdose/Want to be sober/Family pressure/Legal pressure/Job pressure/Other. Total duration 1 hour.
At week 1, participants will be complete the MINI questionnaire Part II. Total duration 25 minutes.

At 3 months, participants will be assessed using a modified version of the PhenX drug use toolkit, the TEA and attached follow-up questionnaire and the GPRA. Total duration 25 minutes.

At 6 months, participants will be assessed using a modified version of the PhenX drug use toolkit, the TEA and attached follow-up questionnaire based on the PhenX toolkit Total duration 35 minute.

At 3 and 6 month follow-up:
1. Since you received buprenorphine (suboxone) in the ED have you taken any more buprenorphine prescribed for you by a doctor or other prescriber? (If No, skip to item 3)
2. If you answered yes to #1: are you currently (last 30 days) enrolled in treatment with a prescriber?
3. If you are not currently receiving suboxone from a prescriber, why?
4. Since you started receiving treatment in the ED have you experienced any of the following side effects of buprenorphine? (Constipation, diarrhea, stomach pain, nausea, vomiting, brain fog, sleeping too little, tiredness, sexual problems, feeling depressed or down, feeling anxious, headache)
If yes follow up with: How much discomfort did this cause you on a scale 1 to 5 where 1 is mild and 5 is severe?
5. Have you been doing more of any of the following since starting treatment in the ED:
Have you been eating more than before you started treatment?
Have you been drinking caffeine more than before you started treatment?
Have you been smoking more cigarettes or other nicotine products more than before you started treatment?
Have you been using more marijuana than before you started treatment?
Have you been drinking more alcohol than before you started treatment?
Have you been using other drugs more than before you started treatment? If yes, which ones?
Have you been spending more time online than before you started treatment?
Have you been gambling more than before you started treatment?
Have you been having more sex than before you started treatment?
Have you been exercising more than before you started treatment?
Any other activities? If yes, what are they?
6. How often over the last two weeks have you been bothered by not being able to stop or control how much you eat?
How often over the last two weeks have you been bothered by how much caffeine you drink?
How often over the last two weeks have you been bothered by how many cigarettes you smoke or use other nicotine products?
How often over the last two weeks have you been bothered by how much marijuana you use?
How often over the last two weeks have you been bothered by how much alcohol you drink?
How often over the last two weeks have you been bothered by how much other drugs you use? If yes, which ones?
How often over the last two weeks have you been bothered by how much time you spend online?
How often over the last two weeks have you been bothered by how much time spent gambling?
How often over the last two weeks have you been bothered by how much time spent having sex?
How often over the last two weeks have you been bothered by how much time spent exercising?

Individual questionnaire durations are as follows:
MINI Neuropsychiatric Interview takes approximately 15 minutes to complete.
Follow up questionnaire (attached) based on PhenX drug use history toolkit takes approximately 105 minutes to completeTEA takes approximately 5 minutes to complete
The GPRA Client Outcome Measures questionnaire takes approximately 30 minutes to complete.

Baseline questionnaires will be administered on an iPad by the EMRAP staff or the study RA in patient care areas or by phone.

At 1 week, 3 months and 6 months, questionnaires will be administered by the study RA by phone. Participants may be contacted in advance by text or email to arrange a time for the call that is convenient for the participant.

Questionnaires will be labelled with the participant's unique study ID number and stored separately from identifiable information (e.g. name, address, phone number etc).

Statistical Considerations: *Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.*

200 hundred individuals will be recruited to the study over the course of 3 years.

The primary outcome measure will be illicit opioid use at 1 week and 3 & 6 months.. Group differences (i.e. with or without the MAT bridge clinic) in opioid use will be assessed by logistic regression at each of the three time points. A power analysis using G*Power50 indicates that a medium effect size, e.g. 0.3, related to the comparison of illicit opioid use in the experimental and control groups will be correctly identified with a power of 0.93 in a total sample of 200 individuals. Statistical tests will be performed in SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp). Logistic regression will be one-tailed with significance defined as $p < 0.05$.

Risks/Benefits: *Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.*

Risks

Identifiable Information. Information that uniquely identifies individuals will be collected from participants. This will include name, phone number, email, and address to facilitate contact with the participant at study follow-up points (i.e. 1 week, 3 months, 6 months). This information will be kept separate from other study materials, which will be coded with a subject number based on order of entry into the study.

Demographic, Behavioral and Drug Use Information. Demographic information including age, sex, marital status, and occupation will be collected. Opioid Use Disorder will be assessed with the 15 minute Mini-International Neuropsychiatric Interview (MINI). Opioid use history (e.g. onset, duration of use, route of administration) will be assessed with the opioid related items on the Pattern of Substance Use -Adult questionnaire in the PhenX toolkit (https://www.phenxtoolkit.org/index.php?pageLink=browse.protocoldetails&id=510302). In addition, the Addiction Severity Index-Lite CF (ASI-Lite), the 12-item Short Form Health Survey (SF-12), the Treatment Effectiveness Assessment (TEA)43 and the Vermont Treatment Needs Questionnaire (TNQ) interviews will be conducted.

Biological samples. Urine samples will be collected at 1 week, 3 months, and 6 months. Urine specimens will be collected under observation of same-sex staff and immediately analyzed for opioids (buprenorphine, methadone, oxycodone, hydrocodone, hydromorphone, heroin, fentanyl) and other drugs (cocaine, amphetamines, benzodiazepines, cannabinoids) via enzyme multiplied immunoassay (Microgenics, Fremont, CA). Missing urine specimens will be considered positive for illicit opioids, consistent with an intent-to-treat approach.

Risks. The participants enrolled in this study have OUD. The most effective current treatment for the disorder is Medication-Assisted Treatment which will be provided to enrolled participants. The risks of participating in the study are weighed against sequelae of not seeking treatment, which include death due to acute overdose, birth defects in pregnant women and health risks related to needle sharing.

We will obtain careful informed consent to ensure that every potential participant fully understands all of the possible risks. In addition, we will not include individuals who we believe would not be able to tolerate the study procedures.

Medication related risks will be mitigated by medical supervision at the ATP who will train ED staff.

Risks from Buprenorphine (Suboxone):
Common side effects of Suboxone include:

- nausea;
- constipation or abdominal pain;
- sweating;
- tiredness or sleep other problems (insomnia);
- headache;
- redness, pain, or numbness in your mouth;
- feeling drunk; or,
- trouble concentrating.

Less common side effects of Suboxone include:

- vomiting
- mild dizziness;
- tingling
- muscle cramps;
- distress and irritability; or,
- fever.

Risk of Accidental Exposure in Children: There is an increased chance of child exposure to buprenorphine resulting from this medical intervention. However, this should be viewed in a wider health perspective. Most medications prescribed by ED (hypoglycemics, CCBs, BBs, cholchicine, other opioids, etc) are dangerous in exploratory ingestions and many of these are on the "one pill can kill" list for kids. It is likely the adults who will receive a Suboxone Starter Pack have opioids in the home already. In fact, the study is attempting to trade illicit use (e.g. heroin/fentanyl) for a safer opioid which should lead to improved adult supervision of children and reduce risk of parental death by overdose. The benefits to families of treating the disease appear to outweigh the risks.

Risks from Opioid Withdrawal: Opioid withdrawal symptoms which include tearing up, muscle aches, agitation, trouble falling and staying asleep, excessive yawning, anxiety, nose running, sweats, racing heart, hypertension, nausea and vomiting, diarrhea, stomach cramps, depression and drug cravings. Symptoms of withdrawal will be managed with buprenorphine. Participants will be educated about opioid withdrawal with a fact sheet that includes a brief list of coping strategies. If participants still experience opioid withdrawal after buprenorphine induction, research staff will cue the participant to use coping strategies. Clinical support will be provided by addiction psychiatrists at the ATP.
Risks from Research Assessments: The assessments being used in this study (e.g. measures of substance use, symptoms, information about patient history, and urine assessments) may cause some discomfort, boredom, anxiety or fatigue. Participants will be advised that they can take a break, refuse to answer question(s), or end the study session if they become uncomfortable in any way. Additionally, psychiatrists experienced in the treatment of addiction, will be present or rapidly available via pager for emergency consultation at any time.

Risk Related to Confidentiality: This research involves monitoring and treatment of patients who use illicit opioids. Participants may engage in other illegal drug use activities. Maintaining confidentiality is an area of utmost importance for this population.

Protections Against Risks
Clinical support for withdrawal will be provided by addiction psychiatrists at the ATP. Participants who receive ED-initiated buprenorphine treatment are guaranteed placement in the ATP. The ATP team includes two fellowship-trained addiction psychiatrists, one general psychiatrist, and one family

physician who are all experienced in treating OUD, as well as resident and fellow trainees from psychiatry, family medicine, and internal medicine, and licensed professionals in nursing, alcohol and drug counseling, mental health counseling and clinical social work. The staff is experienced in providing MAT to patients in all phases of treatment, in diverse settings and across levels of acuity, as well as in educating, training and supporting colleagues with varying levels of experience, training and comfort in addictions treatment. The ATP was selected by the State of Vermont to lead a state-wide Learning Collaborative Project to provide training and education to MAT practices throughout the state of Vermont.

Participant data will be coded to protect privacy. Each patient will be assigned a unique identification number. The list of participant names and identification numbers will be kept in a locked file cabinet separate from the database. Access to the computerized data system is carefully protected by a secured password entry system. Participants will be made aware of the various parties who will have access to their data in the informed consent document. Access to participants' data will be restricted to project investigators and other study staff on a need to know basis. Patient information, if reported, will be reported as group data. No patients will be individually identified.

To minimize risk of divulging confidential information regarding substance use or other illegal activities as well as other study information, strict attention to confidentiality will be maintained throughout every aspect of this research with standard policies and procedures, and protected by a Certificate of Confidentiality issued by NIH.

Individuals from vulnerable populations will not be included in the study.

Incidental findings will be reported to the participant by a study MD.

Potential Benefits

Participants enrolled in the study will either receive standard of care or buprenorphine MAT, which is the most effective current treatment for the disorder. Participants will be provided guaranteed access to treatment by specialized addiction psychiatrists at the ATP.

The proposed intervention will allow ED physicians to move beyond the mere treatment of the acute symptoms of the disorder toward treatments that will mirror the medical response to other chronic life-threatening diseases presenting to the ED, such as diabetes or cardiovascular disease. Similar to these other chronic conditions, the ED is a critical opportunity to connect patients who are not receiving adequate care with long-term treatment options. In addition, OUD contributes to frequent re-admission rates in certain patients. Improving the chances that these individuals enroll in long-term care will reduce ED burden and free up resources for other patients. This research is intended to provide pilot results to support an R01-funded research program to determine best practices for effectively engaging untreated individuals with OUD presenting to ED in MAT. Positive findings on Aim 1 will support network-wide adoption of this intervention in Vermont.

Therapeutic Alternatives: *List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.*

☐ ***Not Applicable***

Alternate Treatment.

Participants will be informed that they are free to leave the study at any time. The most effective current treatment for the disorder is medication-assisted treatment, which will be provided to enrolled

participants.

Alternate local treatment providers include: the Chittendon Clinic Hub, the Community Health Centers of Burlington, and Safe Recovery.

Data Safety and Monitoring: *The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/UVM Medical Center process for review of adverse events should be included in the DSMP.*

The PIs will monitor safety and review current literature throughout the study. The study team will meet for a full review of safety procedures and any adverse events every 6 months.

The PI will report adverse events directly to the University of Vermont IRB. In this study, we will use the FDA definition of serious adverse events (SAEs). The Principal Investigator will verbally report SAEs to the IRB immediately, followed by a written report to the IRB within one week

We will follow the guidelines established by the Committee on Human Research for reporting adverse events or unanticipated problems. We will use the FDA definition of serious adverse events (SAE). Adverse events reported to or noted by the study personnel will be reported to the key personnel within 24 hours. The guidelines established by the Committee on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The key personnel will verbally report SAEs to the IRB within 48 hours, followed by a written report to the IRB within one week. The key personnel will review all adverse events and other safety information semi-annually. Any unanticipated problems (protocol deviations, issues with confidentiality, or problems reported by the subject) that do not meet the definition of an adverse event that occur during this study will be reported by the key personnel within 24 hours. The key personnel will report the unanticipated problem to the appropriate university officials (IRB).

New safety information is not expected during the proposed intervention. However, in the event new safety information adversely affecting the intervention became available, it would be communicated immediately to the PI and Co-Is, and they will contact the IRB for further guidance including terminating the intervention to insure the safety of the participants.

We will obtain careful informed consent and insure that each participant fully understands the study procedures. We will not attempt to obtain consent from anyone with a legal guardian. Study participants may discontinue a study procedure at any time if they are uncomfortable or the study procedures appear to be causing exacerbation of illness.

Participants who are receiving buprenorphine will be monitored by specialized addiction psychiatrists at the ATP who are part of the study team. The ATP team includes two fellowship-trained addiction psychiatrists, one general psychiatrist, and one family physician who are all experienced in treating OUD, as well as resident and fellow trainees from psychiatry, family medicine, and internal medicine, and licensed professionals in nursing, alcohol and drug counseling, mental health counseling and clinical social work. The staff is experienced in providing MAT to patients in all phases of treatment, in diverse settings and across levels of acuity, as well as in educating, training and supporting colleagues with varying levels of experience, training and comfort in addictions treatment. The ATP was selected by the State of Vermont to lead a state-wide Learning Collaborative Project to provide training and education to MAT practices throughout the state of Vermont.

Electronic data will be kept in password-protected files and on secure servers and will be identifiable

by subject code number only. No one outside of the research group will have access to records identifying subjects' names at any time, except for the Office of Human Research Protections, the Institutional Review Board and other oversight personnel may be granted direct access to records as indicated in their oversight responsibilities. The information gathered will be used only for scientific, educational, or instructional purposes.

Adverse Event and Unanticipated Problem (UAP) Reporting: *Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the Committees on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/UVM Medical Center process for review of adverse events and UAPs to subjects or others should be included in the DSMP.*

The study team will follow the guidelines established in the committees on Human Research "Adverse Event and Unanticipated problems Reporting Policy".

Withdrawal Procedures: *Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).*

A subject may decline to join the study, or may withdraw from the study at any time. Subjects declining consent or withdrawing from the study will have all data deleted, with the exception of the logs that document the destruction. The study code assigned to the subject will remain in the database with "voluntarily withdrawn from the protocol" as the only information retained about the subject (patient identifiers will not be saved except on the study master list).

Note: Participants are not required to test negative on urine drug tests at the assessment time points of 1 week, 3 months and 6 months. It is expected that many will test positive. Although drug tests are part of the ATP treatment program, this is independent of observational urine drug tests performed for the study at 1 week, 3 months and 6 months which will be used to determine the success of the ED-initiated intervention. Individuals who decline or withdraw from ATP services are not automatically withdrawn from the research study. Additionally, individuals who withdraw or are withdrawn from the study may continue to seek treatment services from the ATP. Participation or not in the study will not affect medical care provided by ED or the ATP.

Sources of Materials: *Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.*

Urine samples, Questionnaires, Medical History

DRUG AND DEVICE INFORMATION

Investigators are encouraged to consult the UVM Medical Center Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

*Investigational Pharmacy Drug Service was consulted. They determined that IDS will not be involved in the current study because Suboxone is not be investigated as an IND. Rather, the research investigates a novel method to increase treatment enrollment with an already established use of Suboxone.

Drug (s) ☐ ***Not applicable***

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source. (attach investigational drug brochure)

Buprenorphine-naloxone (Suboxone). Sublingual film, FDA approved formulation available as 2 mg-0.5 mg, 4 mg-1 mg, 8 mg-2 mg, 12 mg-3 mg. Buprenorphine is a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist. The opioid agonist properties of buprenorphine are limited by a ceiling effect which occurs at higher doses. Naloxone is a mu-opioid receptor antagonist. When administered parenterally, naloxone produces opioid withdrawal symptoms in patients who are physically dependent on full opioid agonists. Naloxone is minimally active when administered orally. Buprenorphine in combination with naloxone for the treatment of opioid addiction reduces the possibility of parenteral misuse by producing withdrawal symptoms when injected.

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

Buprenorphine-naloxone sublingual films are commercially available, therefore further compounding or reconstitution is not required.

Storage and stability – for both intact and mixed products.

Store at a controlled room temperature of 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F).

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

Administer whole; do not cut, chew, swallow or move after placement. Place under the tongue near the base on the right or left side and leave under tongue until it is completely dissolved; proper administration techniques should be demonstrated for the patient.

If more than 1 film is needed to achieve the prescribed dose, place the second film SL on the opposite side as the first film, and minimize overlap as much as possible. If a third film is necessary, place it under the tongue on either side after the first 2 films have dissolved.

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Severe toxicity is rare. Ingestion of 88 mg of buprenorphine in an adult resulted in severe opiate withdrawal. Ingestion (oral instead of sublingual) of 112 mg of buprenorphine resulted in severe hepatitis/acute renal failure.

Respiratory depression has been associated with buprenorphine when administered intravenously. In many cases, coma and death have been reported in opioid addicted patients who have concomitantly taken benzodiazepines and misused IV buprenorphine. Buprenorphine should be used cautiously in patients with COPD, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or any preexisting respiratory depression. Patients who receive buprenorphine should be educated on the dangers of concomitant self-administration of benzodiazepines or other CNS depressants.

There is no specific known toxic dose with naloxone, though deaths have occurred in varying doses associated with its use. However, these case reports do not provide any direct evidence that the use of naloxone was solely responsible for mortality.

Interactions:
Drug-ethanol: Concurrent use of BUPRENORPHINE and ETHANOL may result in increased risk of respiratory depression and CNS depression.
Drug-food: Concurrent use of BUPRENORPHINE and GRAPEFRUIT JUICE may result in increased plasma concentrations of buprenorphine.
Drug-drug: Concurrent use of NALOXONE and OPIOID AGONISTS may result in decreased opioid efficacy and precipitation of opioid withdrawal. This interaction is unlikely to result in any adverse effects within this study as naloxone produces negligible antagonist effects when administered orally.

Is it FDA approved: (include FDA IND Number)

1. *in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.*
   Yes
2. *for the route of administration specified? If no, provide justification for route and describe the method to accomplish.*
   Yes
3. *for the intended action?*
   Yes

Device (s) [X] ***Not applicable***

Device name and indications (attach investigational device brochure)

Is it FDA approved: (include FDA IDE Number)

1. *for indication specified? If no, provide justification for proposed use and source of the device.*

Risk assessment (non-significant/significant risk) - PI or sponsor needs to assess risk of a device based upon the use of the device with human subjects in a research environment.

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: *Provide rationale for subject selection in terms of the scientific objectives and proposed study design.*

Subjects will be screened for inclusion if they present to the ED with signs of opioid use disorder (i.e. self-report or symptoms consistent with the disorder) Symptoms consistent with the disorder include: presentation with acute overdose or symptoms consistent with opioid withdrawal (such as piloerection, diarrhea, tachycardia, cravings, and pupillary dilation), and EMS use of naloxone on scene or en route to the hospital, patients with abscesses, especially in the antecubital fossa and other areas consistent with injection drug use and patients with a history of endocarditis.

Vulnerable Populations: *Explain the rationale for involvement of special classes of subjects, if any. Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).*

[X] ***Not applicable***

Number of Subjects: *What is the anticipated number of subjects to be enrolled at UVM/UVM Medical Center and in the case of a multi-center study, with UVM/UVM Medical Center as the lead, the total number of subjects for the entire study.*

We expect to enroll 140 participants at UVMMC and 200 participants in total.

Inclusion/Exclusion Criteria: *Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.*

Inclusion Criteria:
-Present to the UVMMC Emergency Department (and later after IRB review the Emergency Departments at Central Vermont Medical Center and Porter Medical Center)
-Endorse criteria for Opioid Use Disorder (OUD) as defined by the DSM-V
- Over the age of 18

Exclusion Criteria:
-Non-english speaking
-Current participation in an alternate treatment program for OUD (except recent release from correctional facility or residential treatment program and does not have a current prescription),
-Inability to communicate
-Altered mental status
-Suicidality
-Medical extremis or medical issue requiring admission
-Prisoners
-History of Suboxone injection in the past year
-Hepatic impairment

Inclusion of Minorities and Women: *Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.*

-Sex/gender will not be a selection/exclusion factor for the recruitment. In Vermont, women compose ~50% of the general population. Thus, we anticipate a similar proportion in the proposed research. However, participants will be recruited to the study because they present to the ED and are eligible. The predetermined randomization tables which include a stratification by sex will insure that equal numbers of women are sorted to the control and experimental groups.

Pregnant and nursing mothers will not be excluded. Opioids such the buprenorphine contained in Suboxone can cause birth defects. However, opioid withdrawal can be especially harmful during pregnancy, potentially resulting in preterm labor, fetal distress, or even miscarriage. Buprenorphine reduces opioid craving and alleviates withdrawal symptoms without the safety and health risks related to acquiring and abusing street drugs. Treatment with Suboxone is considered to be a lower clinical risk to the fetus than uncontrolled use of illicit opioids. In contrast to earlier recommendations about buprenorphine+naloxone, recent research is consistent with Suboxone being as safe or safer than buprenorphine monotherapy during pregnancy. This pilot project will inform practical aspects of the network-wide implementation of an ED-initiated intervention for OUD in Vermont including patients who are pregnant.

-Minorities. There will be no exclusion criteria concerning race or ethnicity. In Vermont, minorities represent approximately 5% of the general population. Thus, we anticipate a similar proportion in the proposed study. We will do all that we can to assure that minorities are represented in the research.

Inclusion of Children: *Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.* ***If children are excluded*** *then provide appropriate justification. Provide target accrual for this population.*

Individuals under the age of 18 are excluded. The minimum age limit is intended to exclude younger individuals who are under adult legal guardianship. Compared to the adult sample, the involvement of a guardian would significantly alter the motivational structure of seeking and staying in treatment to be tested.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

N/A

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

X	***Not applicable***

Recruitment: *Describe plans for identifying and recruitment of subjects. All recruitment materials (flyers, ads, letters, etc) need to be IRB approved prior to use.*

Participants will be recruited from patients presenting to the ED. Thus, there are no recruitment materials to be reviewed.

FINANCIAL CONSIDERATIONS

Expense to Subject: *If the investigation involves the possibility of added expense to the subject (longer hospitalization, extra studies, etc.) indicate in detail how this will be handled. In cases where the FDA has authorized the drug or device company to charge the patient for the experimental drug or device,* ***a copy of the authorization letter from the FDA or sponsor must accompany the application. Final approval will not be granted until the IRB receives this documentation.***
There are very limited circumstances under which study participants may be responsible (either directly or via their insurance) for covering some study-related expenses. If the study participant or their insurer(s) will be billed for any portion of the research study, provide a justification as to why this is appropriate and acceptable. For example, if the study involves treatment that is documented standard of care and not investigational, state so. In these cases, the protocol and the consent should clearly define what is standard of care and what is research.

The costs of urine drug screening at 1 week, 3 months and 6 months will be paid by the study

Payment for participation: *Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.*

	Not applicable

As an incentive to provide a urine sample and answer questions, participants will receive a $25 gift card after responding to questionnaires at baseline. They will also receive a $25 gift card for answering $50 gift card for each of the three outcome time points completed (i.e. 1 week, 3 and 6 months post randomization) up to a total of $250. To avoid altering the motivation to stay in MAT, participants will earn payment for providing the urine samples and answering questions at each of the 3 follow-up time points, regardless of whether they are currently in treatment.

Collaborating Sites*. When research involving human subjects will take place at collaborating sites or other performance sites when UVM/UVM Medical Center is the lead site, the principal investigator must provide in this section a list of the collaborating sites and their Federalwide Assurance numbers when applicable. (agreements may be necessary)*

X	***Not applicable***

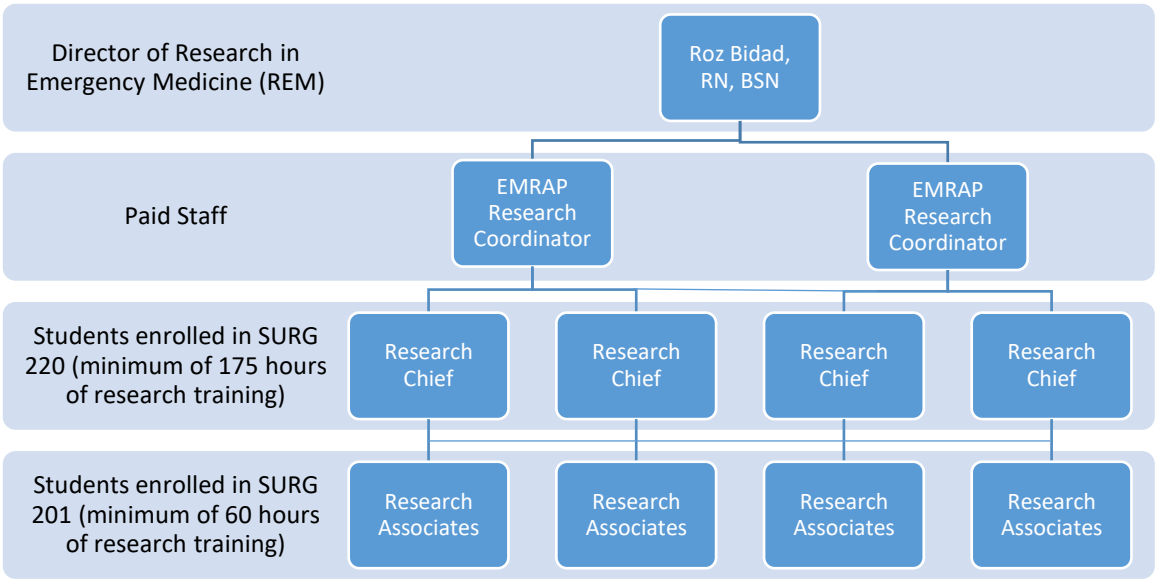
Note that Central Vermont Medical Center and Porter Medical Center are not yet prepared to start data collection. Details about procedures at these sites will be added by amendment as it becomes necessary. No protocol procedures will be performed at CVMC or Porter until these amendments have been reviewed by the IRB. We ask that the IRB approve the UVMMC site to continue enroll participants while the other sites are prepared.

INFORMED CONSENT

Consent Procedures*: Describe the consent procedures to be followed, including the circumstances under which consent will be obtained, who will seek it, and the methods of documenting consent. Specify the form(s) that will be used e.g. consent (if multiple forms explain and place identifier on each form), assent form and/or HIPAA authorization (if PHI is included). These form(s) must accompany the protocol as an appendix or attachment.*

Note: Only those individuals authorized to solicit consent may sign the consent form confirming that the prospective subject was provided the necessary information and that any questions asked were answered.

Informed consent will be obtained by Emergency Medicine Research staff with the support of the Emergency Medicine Research Associate Program (EMRAP). EMRAP is led by Dr. Daniel Barkhuff and Roz Bidad and is structured as follows:



Although Research Chiefs offer guidance and support to the Research Associates, it is paid staff and faculty that directly oversee the students. Students do not supervise other students. The research team are stationed in the clinical care area of the Emergency Department and remotely. The Research Associates will perform the task of screening for eligible subjects. They will utilize the EHR to identify patients they believe qualify for the study based on inclusion and exclusion criteria. Once they have identified an eligible patient, the Research Coordinator will contact a member of the ED clinical care team to confirm that they are appropriate and approachable for this study. At this point, a paid member of staff (Research Coordinator) will contact the patient for informed consent. Informed consent discussions will occur in the patient care areas of the Emergency Department with research staff in-person or via telephone. Informed consent discussions will NOT be performed in the waiting room, in triage or in the halls of the ED.

This study will utilize a prospective consent form. Consent will only be obtained from the patient and will include HIPPA authorization. The study team will document the process of informed consent using a form based on the UVM IRB's recommended template. Informed consent may be completed via eConsent on RedCap. Subjects will be provided with a printed copy of the signed consent form. Subjects may request the signed PDF be emailed to them, acknowledging that email is not a secure means of communication as UVM can't control the security of email or text messages once we send them. A field is included in the eConsent for subjects to indicate whether they would like their signed PDF emailed, acknowledging the understanding that these communications are not secure.

Information Withheld From Subjects: *Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.*

☐ ***Not applicable***

No information will be withheld from participating subjects

Attach full grant application, including budget information and/or any contract or draft contract associated with this application.

All materials must be submitted electronically to the IRB via InfoEd. Proper security access is needed to make electronic submissions. Visit the InfoEd Resource Materials page for more information.