Human Subjects Research Protocol

Project Title: Contingency Management to Improve Medication for Opioid Use Disorder Continuation After Discharge from the Emergency Department

Protocol Version Date: **7/22/2025**

Principal Investigator: Eric A. Thrailkill, Ph.D.

Check the type of the review:

X	Full convened meeting – The IRBs employ the convened meeting review process for review and approval of studies that are more than minimal risk.
	Expedited review – The IRBs employ the expedited review process for approval of studies that are determined to be minimal risk and only involves activities such as prospective collection of biological specimens for research purposes by noninvasive means (blood collection, salvia, nail clippings), collection of data through noninvasive procedures (ultrasounds, MRI, physical sensors) and research on behavior such as perception, cognition, motivation, identity, language and communication.

Federal regulations mandate that changes cannot occur until after IRB review and approval "except when necessary to eliminate apparent immediate hazards to the subject."

ALL modifications to the approved study materials (including Click forms) must be submitted to the IRB prior to implementation, regardless of the magnitude of change or effect on risk level.

PURPOSE AND OBJECTIVES

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

Annual opioid overdose deaths passed 100,000 in 2021 and opioid use disorder (OUD) remains an epidemic in the United States (Ahmad et al., 2024; Wilson et al., 2020). Medications for Opioid Use Disorder (MOUD) are effective for reducing illicit opioid use and overdose (Santo et al., 2021) but access to MOUD among US adults with opioid use disorder (OUD) remains low (27.8%; Mauro et al., 2021).

Given the high overdose rate, hospital Emergency Departments (ED) have become the front line for the opioid epidemic. Consistent with recent national efforts to increase access to treatment (Cao et al., 2020), the University of Vermont Medical Center ED began offering MOUD and referral to a community provider in 2023 with the Start Treatment and Recovery (STAR) program. The number of patients prescribed MOUD has increased and the method of facilitating treatment by utilizing the ED has potential for broader implementation which would save many lives. However, according to STAR program data, 51% of individuals who receive ED-initiated MOUD fail to attend their referral appointment to continue MOUD after discharge, which is consistent with findings from other states (Jennings et al., 2021). This is particularly concerning given the risk for overdose is markedly high after an ED visit, with over 20% of deaths occurring within the first 30 days after discharge (Weiner et al., 2020).

Contingency management (CM), wherein patients receive financial incentives contingent on behavior change (Higgins et al., 1994), is a standardized and highly effective intervention to promote behavior change (Lussier et al., 2006). Meta-analyses demonstrate that CM is effective at increasing MOUD adherence (Bolívar et al., 2021) but, to our knowledge, CM has not been tested as an intervention to increase treatment retention after discharge from the ED. Recently, there has been a call to consider modifications to CM protocols to address the overdose crisis more effectively (Khazanov et al., 2024). As such, this pilot project will adapt CM to improve MOUD continuation during the high-risk period following discharge from the ED.

The proposed pilot trial will assess the initial effectiveness and feasibility of CM for increasing engagement in outpatient MOUD treatment following discharge from the ED. The proposed CM protocol will utilize best practices and will be adapted to MOUD dosing schedules that differ between buprenorphine and methadone (described below). The primary outcome will be the proportion of participants that complete the initial outpatient clinic visit and receive a MOUD prescription following

discharge from the ED as verified in the EHR. The secondary outcome will be percent of scheduled MOUD clinic appointments attended in a 30-day period following discharge from the ED. Exploratory outcomes will be biochemically verified illicit opioid abstinence recorded at 30-day follow up, and rates of overdose and ED return visits obtained from chart review and self-report.

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

Ahmad FB, Cisewski JA, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

Bolívar HA, Klemperer EM, Coleman SR, DeSarno M, Skelly JM, Higgins ST. Contingency management for patients receiving medication for opioid use disorder: a systematic review and meta-analysis. JAMA psychiatry. 2021;doi:10.1001/jamapsychiatry.2021.1969

Cao SS, Dunham SI, Simpson SA. Prescribing buprenorphine for opioid use disorders in the ED: a review of best practices, barriers, and future directions. Open Access Emergency Medicine. 2020:261-274.

Higgins ST, Budney AJ, Bickel WK. Applying behavioral concepts and principles to the treatment of cocaine dependence. Drug and Alcohol Dependence. 1994;34(2):87-97.

Jennings LK, Lane S, McCauley J, et al. Retention in treatment after emergency department-initiated buprenorphine. The Journal of emergency medicine. 2021;61(3):211-221.

Lussier JP, Heil SH, Mongeon JA, Badger GJ, Higgins ST. A meta-analysis of voucher-based reinforcement therapy for substance use disorders. Addiction. 2006;101(2):192-203.

Mauro PM, Gutkind S, Annunziato EM, Samples H. Use of medication for opioid use disorder among US adolescents and adults with need for opioid treatment, 2019. JAMA network open. 2022;5(3):e223821-e223821.

Raiff BR, Jarvis BP, Turturici M, Dallery J. Acceptability of an Internet-based contingency management intervention for smoking cessation: views of smokers, nonsmokers, and healthcare professionals. Experimental and Clinical Psychopharmacology. 2013;21(3):204-216.

Santo T, Clark B, Hickman M, et al. Association of opioid agonist treatment with all-cause mortality and specific causes of death among people with opioid dependence: a systematic review and meta-analysis. JAMA psychiatry. 2021;78(9):979-993.

Weiner SG, Baker O, Bernson D, Schuur JD. One-year mortality of patients after emergency department treatment for nonfatal opioid overdose. Annals of emergency medicine. 2020;75(1):13-17.

Wilson N, Kariisa M, Seth P, Smith IV H, Davis NL. Drug and opioid-involved overdose deaths—United States, 2017–2018. Morbidity and Mortality Weekly Report. 2020;69(11):290.

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

The proposed pilot trial will assess the initial effectiveness and feasibility of CM for increasing engagement in outpatient MOUD treatment following discharge from the ED. The proposed CM protocol will utilize best practices and will be adapted to MOUD dosing schedules that differ between buprenorphine and methadone (described below).

The primary outcome will be the proportion of participants that complete the initial outpatient clinic visit and receive a MOUD prescription following discharge from the ED as verified in the EHR.

The secondary outcome will be percent of scheduled MOUD clinic appointments attended in a 30-day period following discharge from the ED.

Exploratory outcomes will be biochemically verified illicit opioid abstinence recorded at 30-day follow up, and rates of overdose and ED return visits obtained from chart review and self-report.

The research team for the planned study includes the STAR program staff and administrators that regularly conduct the STAR program in the ED. STAR staff will approach individuals deemed research eligible by the attending physician in the ED. STAR staff will conduct informed consent procedures, deliver study payment cards with use instructions, and provide study materials (baseline assessment) in the ED.

Once enrolled in the study, individuals will be assigned to either continue best practices in ED care delivered by the STAR program (BP) or to receive BP plus contingency management (BP+CM). We will measure adherence in the form of completing the outpatient clinic intake appointment and receiving MOUD, and MOUD prescriptions across the first 30-days post discharge from the ED.

We will randomize 30 adults who initiated MOUD in the ED to:

(A) BP alone: Best practices will consist of STAR program referral in ED to local outpatient services (Addiction Treatment Center at the University of Vermont Medical Center [UVMMC] or Chittenden Clinic) with reminders and support from STAR program staff.

(B) BP+CM: In addition to BP, participants will receive financial incentives contingent upon MOUD clinic attendance to receive an MOUD prescription. Incentives will be contingent on provider or electronic health records (EHR) verification of a filled MOUD prescription. Participants in the BP+CM condition will have the opportunity to earn a maximum of $485 over 30 days. The incentives will consist of a $15 priming incentive in the ED, $50 for attending the first outpatient visit, and the remaining $420 distributed evenly according to the number of scheduled clinic visits attended during the 30 days following discharge from the ED.

For example, participants who are prescribed methadone and visit the Chittenden Clinic to pick up their prescription daily will earn $15/per visit, while those prescribed buprenorphine and visit the ATC to pick up their prescription once every 3 days will earn $45/per visit. Note that individuals vary in the number of days between MOUD doses but we will adjust the payment so that the amount is equivalent to $15 per day. Individuals prescribed methadone and buprenorphine will have the potential to earn the same total amount but distributed according to clinical requirements for their respective prescribed MOUD. Participants in BP-alone and BP+CM conditions will receive $55 for completing assessments at baseline (in the ED) and 30-day follow up (in clinic), for a total of $110.

This two-arm pilot randomized clinical trial has two specific aims:

Specific Aim 1: Provide a preliminary test of whether BP+CM is more effective than BP alone at promoting MOUD clinic attendance after discharge from the ED.

Hypothesis 1.1: BP+CM will increase the proportion of participants who initiated MOUD in the ED that complete outpatient intake assessment and receive a MOUD prescription.

Hypothesis 1.2: Individuals in the BP+CM condition will complete a higher percentage of MOUD clinic appointments during the 30-day study period.

Specific Aim 2: Demonstrate feasibility of providing CM in the ED and outpatient MOUD clinic settings.

Hypothesis 2.1: The study team will successfully recruit and consent 30 patients in the ED who meet inclusion criteria.

Hypothesis 2.2: The CM protocol will prove to be feasible across both outpatient clinics by delivering incentives in response to all MOUD prescriptions, as confirmed by monitoring BP+CM participants' EHR.

Exploratory Aim: Explore the potential for BP+CM to increase illicit opioid abstinence and decrease harm.

Hypothesis 3.1: BP+CM will have a greater proportion of biochemically verified illicit opioid negative urine screens recorded at the 30-day follow up compared to BP.

Hypothesis 3.2: BP+CM will decrease the number of overdoses self-reported and recorded (as indicated by chart review) by participants during the 30-day study period compared to BP.
Hypothesis 3.3: BP+CM will decrease ED visits (indicated in chart review) during the 30-day study period compared to BP.

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

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

To assess whether incentives improve outpatient visits for individuals prescribed MOUD in the ED, participants will be individuals from the ED that receive MOUD prescription (methadone or buprenorphine) and referral to an outpatient clinic (Addiction Treatment Center and Chittenden Clinic) through the STAR program.

Vulnerable Populations: Explain the rationale for involvement of subjects (e.g., cognitively impaired, non-English speaking, prisoners, students). Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).

☐ Not applicable

Subjects will be individuals with OUD as documented by physicians and medical staff in the ED. This is a vulnerable group for which we plan to assess a potentially life-saving intervention. There is potential for undue influence created by impairment. We will follow standard procedures in the ED for determining capacity to provide consent. Specifically, STAR staff in the ED will consult with the attending physician in the ED to determine whether impairment precludes consent to enter the study. Per the existing STAR protocol, ED patients will only be approached after confirming with the patient's ED clinical team that the patient has the capacity to provide informed consent and is appropriate to approach.

Inclusion/Exclusion Criteria: Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined, by whom and how it will be documented in the research record.

Please note: Inclusion and exclusion criteria must be documented for all criteria (e.g., EPIC notes, eligibility checklist with associated source documents, notes to file). Participant reported information must be documented in the research record; a lack of documentation does not prove absence of a criteria.

Inclusion and exclusion criteria will be minimal to recruit a diverse population of individuals and to meet study goals for assessing the feasibility of the CM intervention in a hospital ED setting.

Inclusion Criteria
-STAR referral to outpatient clinic (Addiction Treatment Center and Chittenden Clinic) with prescription for buprenorphine or methadone.
-Age ≥18 years.
-Provide informed consent.

Exclusion Criteria
-Pending incarceration in the next 30 days.
-Plan to leave the area (Burlington/Chittenden County) in the next 30 days.
-Physical, health, or structural challenge that prevents attendance at outpatient clinic.

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.

We will do everything we can to include minorities and women in the study. Frequency of ED admittance will influence opportunity to enroll individuals from these groups.

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. Provide target accrual for this population. Identify whether children are wards of the state. **If children are excluded** then provide appropriate justification.

We will not include individuals aged <18 years as these individuals do not typically receive referrals to outpatient clinics to receive MOUD prescribed in the ED.

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

Will the SONA Psychology Pool be utilized? *Include documentation indicating permission to use this recruiting tool* Yes [ ] No [X]

METHODS AND PROCEDURES

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

This proposed two-arm pilot randomized clinical trial will randomize 30 adults who initiated MOUD in the ED to (A) BP + CM or (B) BP alone.

We will record clinic attendance as evidence that an MOUD prescription was dispensed as reported by a Chittenden Clinic or Addiction Treatment Center provider or as recorded in the participant's electronic health record (EHR) by the attending physician. This binary variable will be recorded for all participants for a 30-day period following discharge from the ED. Participants will complete a follow-up visit on day 30 which will consist of a urine drug screen and questionnaires (acceptability, self-reported abstinence, self-reported overdose). Participants will be allowed a 10-day window to complete the follow-up visit.

Procedures and Methods: Describe all procedures (sequentially) to which human participants will be subjected. Describe required screening procedures performed before enrollment and while on study. 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.

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.

Staff that coordinate the STAR program will identify eligible participants. The order of events are expected to proceed as follows:

In the ED:

1. **Standard STAR procedures:** (Note these procedures are described for informational purposes and are not part of this protocol; these all occur prior to consent for this study)
    - OUD diagnosis confirmed and Clinical Opioid Withdrawal Scale (COWS) completed.
    - Patient submits sample for Drug Screen 11, Urine (whenever possible).
    - Patients are provided with an initial dose of buprenorphine or methadone.
2. **Screening:** Patients identified as eligible by STAR research team are screened for study. STAR research staff in the ED explains the CM trial and, if interested, patient signs consent form. Patient also signs a HIPAA authorization for release of protected health information and multi-party release form for either the Howard Center Chittenden Clinic if prescribed methadone, or Addiction Treatment Center if prescribed buprenorphine.
    - **If they decline to participate,** they will continue to receive treatment as usual from the STAR program, including the STAR baseline survey
3. **Randomization:** Participants are randomized to BP condition or BP+CM condition.
    - All participants will receive a Focus Blue Visa card in the ED.
    - All participants will receive instructions on payment acknowledgement forms (PAF) and complete their first form in the ED on REDCap.

4. **STAR baseline survey:** Participants will be informed that approximately 25% of the STAR baseline survey questions are the same as the research baseline survey questions, so study staff will be documenting their responses to those questions twice: Once on a clinical form (for STAR) and once on a separate research form (for the research study). We will inform them each time a question applies to both the research study and the STAR clinical service. They will have the option to skip any question at any time or withdraw from the research study at any time and continue to receive clinical treatment. The baseline survey will be administered by interview and responses will be recorded on a study iPad into a secure REDCap form or by paper-and-pencil to be entered into REDCap later depending on participant preference and/or wifi connectivity.
    - Staff will document the ~25% of baseline questions that apply to both the STAR clinical service and the financial incentive research study twice, on separate forms. The research data will always be stored separately from the clinical data as Staff will recorded the data in a secure REDCap form. Staff will use a study iPad to enter data into REDCap research form at the same time as the clinical form, or later from paper-and-pencil depending on participant preference and/or wifi connectivity.
5. ED Staff submits EPIC referral.
6. Depending on type of MOUD prescribed, referral will direct participants to services at the Addiction Treatment Center (ATC) or Chittenden Clinic. The consent process in the ED is expected to take 1-2 hr.
    - **For Buprenorphine:**
        - Patient provided with Buprenorphine in the ED per STAR workflow.
            - Note this medication is administered as BP per STAR procedures. This protocol does not alter or supersede ongoing STAR program activities in the ED.
            - Buprenorphine in the ED by STAR is an initial “bridge” prescription to span the time between ED discharge and the scheduled outpatient clinic intake. Bridge

prescriptions consist of take-home doses for buprenorphine until the date of the scheduled outpatient clinic intake.
- Patient given instructions to come to ATC promptly at 10:00am the following business day + reminder of incentive that will be earned if in BP+CM condition.

- **For Methadone:**
  - Patient provided with Methadone in the ED per STAR workflow.
    - Note this medication is administered as BP per STAR procedures and is not part of this protocol.
    - Per STAR protocols, methadone bridge prescriptions consist of daily doses of methadone from the ED until the date of the scheduled outpatient clinic intake.
    - The present protocol does not supersede BP that are ongoing in the ED as part of the STAR program.
  - ED provider refers them directly to Howard Center Chittenden Clinic and provides info sheet on walk-in hours @ 7:15am + reminder of incentive that will be earned if in BP+CM condition.

Outpatient Treatment Provider:

1. Study Staff in will monitor MOUD prescription via EHR or by receiving attendance data from provders at the Chittenden Clinic/Howard Center or Addiction Treatment Center/UVMMC. Number of prescriptions is experimental data.
2. Participant attends clinic, prescription is dispensed and entered into patient EHR by dispensing physician.
3. If prescription is confirmed and patient is in BP+CM condition, Study Staff will contact patient (patient preference of text message/email/phone call) to deliver a notice of incentive delivery and deliver link to complete PAF on REDCap.
   a. Note that Addiction Treatment Center and Chittenden Clinic Staff will notify Study Staff of participant attendance by marking a checkbox next to participant code in a REDCap form. While Addiction Treatment Center and Chittenden Clinic staff provide data via REDCap surveys, they will not have access to participant research data or the REDCap projects. Study Staff will administer PAF and payment to participants at each clinic.
4. Study Staff monitors REDCap form and supports participant in case of trouble accessing online form.
5. Once PAF is completed, Study Staff transfers incentive to participant's Focus Blue Visa card and sends message to notify participant of incentive delivery.

30-day Follow up and Study Termination:

1. As part of standard protocol, STAR staff will contact participants each week.
2. For participants enrolled in the study, STAR will include a reminder to come to the clinic to complete a 30-day follow-up survey and urine drug screen administered by the study staff in UHC.
3. All participants that complete this survey will receive $55 in compensation delivered to the Focus Blue card (with completed PAF). The follow-up survey is experimental data.
4. Participants will have a 10-day window to complete the 30-day follow-up appointment.

Assessments:

Clinical Opioid Withdrawal Scale (COWS) – Tool to assess signs and symptoms of opioid withdrawal [ClinicalOpiateWithdrawalScale.pdf] – Administered in ED by STAR staff. Study staff will have access to these measures and coded data will be recorded in REDCap.

Baseline Survey: Demographic and substance use questionnaire administered at study intake in the ED [Baseline_questionnaire_3-10-25.docx]. Administered by STAR staff on an iPad. Study staff will have access to these measures and coded data will be recorded in REDCap.

Follow up survey: Items on number ED visits and overdoses in the past 30 days. *Did receiving payments influence whether you can to the clinic?* Treatment acceptability items (Raiff et al., 2013) - Responses to individual questions using a 100-mm visual analog scale (1 = lowest satisfaction, 100 = greatest satisfaction). 1) overall satisfaction; 2) acceptability of receiving payments; 3) belief that program needs were met (response options: did not meet my needs at all, only met a few of my needs, met most of my needs, met almost all of my needs); 4) satisfaction with the program (Quite Dissatisfied, Dissatisfied, Mildly Satisfied, Very Satisfied); 5) willingness to participate again in the future (Definitely Not, Probably Not, Probably So, Definitely So). Administered by clinic staff at 30-day follow-up visit. Coded data will be recorded in REDCap.

Treatment:
Usual Care – All participants (BP and BP+CM conditions) will receive standard outpatient care at their clinic.
Study Compensation - Once consented, eligible participants will be issued a study Visa card (FocusBlue, US Bank). All compensation will be administered to this card.
Incentives – Participants assigned to the BP+CM condition will be eligible to receive additional incentives delivered to their Study Visa card by study staff.

TYPES OF PROCEDURES (Please do not use the "other" option unless the procedure is not listed.)
Check all that apply

X	Survey (mail, telephone, in-person, on-line)		Blood drawing:	Vol.		Over days, weeks?	
X	Medical exams/history					Type & Amt.	
	Deception ***see below**		Surgery		X	Collection of Urine and/or Feces	
	Observation		Drug Administration			Communicable Disease Testing	
	Photographs		Device Use			Ultrasound (e.g., echocardiogram)	
	Audio Recording		Exercise			Imaging (e.g., CT scan, DEXA, mammogram, PET scans, SPECT)	
	Video Recording		Diet			Use of Radiation treatment	
	Interviews in person or by phone		Pathology Specimens (retrospective)			Use of Radioactive substances (e.g., radiolabeled antibodies, drugs, or contrasts)	
	Focus Groups		Genetic Materials (DNA)** **see below**			MRI (for treatment studies)	
	Review of prospective data	X	Questionnaires			MRI (not for treatment studies)	
	Review of retrospective data		Diaries			Tissue (obtained for clinical purposes)	
X	Recording of Identifiable Data		Pregnancy Tests			Tissue (obtained solely for research)	
	Electrocardiograms						
X	Sensitive Data (criminal or sexual conduct, drug or alcohol conduct or use)						

(specify): Individuals enrolled in the study will be in outpatient treatment for opioid use and receiving medications for opioid use disorder Drug use information is involved since all participants are prescribed MOUD. Procedures therefore involve personal health information that is related to a substance use disorder and subject to 42 CFR Part 2. The main risk is breach of confidentiality. We have taken steps to mitigate this risk. Risk for breach of confidentiality is very low (<10%).

****If genetic information is being collected, GINA language must be added to the consent form.**

*Deception typically involves withholding information from the potential subject and would require an alteration to

the consent process.

If you are requesting Radiology services (equipment and professional needs) you will need to contact the Radiology Research Coordinator John.Little@uvmhealth.org and complete this form.

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.

Outcomes to be measured and analyzed. The primary outcome data will be daily MOUD prescription dispensing for each participant. Staff at Addiction Treatment Center and Chittenden Clinic will enter attendance data into REDCap survey forms. Once participants complete the study, we will conduct a retrospective chart review and record overdose and ED admission during the 30-day study period for all participants. All data (baseline questionnaire, prescription dispensing, follow-up surveys, chart review, urinalysis) will be entered into REDCap will be coded for further analysis.

Statistical methods. Baseline participant characteristics, including sociodemographic information, will be compared between the two conditions using analyses of variance for continuous, and chi-square tests for categorical variables. Differences between conditions at baseline will be considered as potential covariates in subsequent analyses. Our primary analysis will include all randomized participants. Missing survey data will be imputed using multiple imputation.

The proportion of participants who receive an MOUD prescription following discharge from the ED is the primary outcome of interest. A secondary outcome will be the proportion of participants who remained in outpatient MOUD treatment at the end of the 30-day study period between BP+CM and BP conditions. An exploratory outcome will be biochemically verified illicit opioid abstinence during the 30-day study period. Comparisons will be made using logistic regression and ANOVA. Analyses will be performed using SAS Statistical Software V9.4 (SAS Institute, Cary, NC). Statistical significance will be determined based on $p<.05$ for all analyses.

Sample size justification. This is a pilot trial and intended to provide an estimate of effect size upon which to base future power analyses. Planned sample size is based on previous pilot trials using CM conducted by our group. Meta analyses (Lussier et al., 2006; Bolivar et al., 2021) suggest about twice the outcome in the CM condition. We expect an effect size to be consistent with these prior meta-analyses: Cohen *d*=0.32 [95% CI, 0.15–0.47] to Cohen *d*=0.58 [95% CI, 0.30-0.86].

Risks: Describe any potential or known risks. This includes physical, psychological, social, legal or other risks (including breach of confidentiality, which is always a risk when collecting identifiable information). 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.

Breach of confidentiality – Study data include contact information, socio-demographic characteristics, medical history, and opioid use information. The risk of a breach of confidentiality is low and we will take precautions to minimize this risk as described below in the Protection Against Risks section.

Opioid withdrawal – Participants who succeed in transitioning to MOUD may experience withdrawal symptoms (i.e., anxiety, depression, difficulty concentrating, hunger/weight gain, insomnia, irritability and restlessness).

Protection Against Risks

Risk for breach of confidentiality will be addressed by utilizing staff in the UVMMC and Chittenden Clinic/Howard Center that possess credentialed access to electronic health records (EHR). Study staff will monitor REDCap and EHR for provider entries that indicate the participant has received their prescription. Once identified, staff will notify participants of payment pending completion of a REDCap PAF. Study staff will send a link to complete the form online or arrange a meeting with the participant to complete the form. Once the PAF has been completed, staff will administer the incentive to the study Visa card using the Focus Blue platform. Breach of confidentiality is unlikely (0-10% chance) due to trained study staff managing identifiable information.

Participants will be informed about possible AEs related to MOUD in the consent form. At study onset, participants will be provided with a phone number and e-mail to report any AEs that are urgent. We will withdraw participants who have an FDA-defined serious AE (SAE) that are likely or probably related to the study procedures. Traditional methods of collecting AEs can be insensitive, thus we will instruct participants to contact research personnel if they experience a severe AE. We will encourage participants to contact research personnel if they have questions about withdrawal symptoms or believe any withdrawal symptoms require treatment, which is part of Best Practices care that MOUD patients receive.

Potential participants are free not to participate in this study and participants are free to withdraw at any time and still receive Best Practices care. Potential participants who screen ineligible or do not consent to participate will be provided with Best Practices care as conducted by the STAR program within the ED, this includes, but is not limited to, resources to access OUD treatment, including MOUD, outside of this study.

Benefits: 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.

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

Benefits

The potential benefits to the subjects include reduced risk of mortality due to opioid overdose. Participation in this study could increase the chances of illicit opioid cessation and prevent long-term morbidity and mortality from illicit opioid use. This research also stands to provide scientific benefit by improving understanding of incentives to promote outpatient clinic attendance. Further, the intervention tested in this research has the potential to benefit public health by decreasing the substantial personal and societal costs associated with illicit opioid use in the United States. Thus, we believe the risks to participation in the proposed research are reasonable in relation to the anticipated benefits.

Therapeutic Alternatives

Referral to outpatient clinics with follow-up calls from STAR staff is the standard procedure in the STAR program operated in the ED. Best Practices is offered to every MOUD-eligible patient in the ED, as well as included in each study condition (BP+CM and BP).

Data Safety and Monitoring: *Please note that this is not the same as the Data Management and Security Plan that will be uploaded as a separate document.*

Describe the data and safety monitoring plan (DSMP). This should provide for a regular review of accrued research data and other relevant information to ensure the validity and integrity of the data and that there is no change to the anticipated benefit-to-risk ratio of study participation. In addition, there should be an ongoing review of study procedures to ensure that the privacy of research subjects and the confidentiality of research data has not been violated.

The specific design of a 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.

Patient eligibility and status

All intake data collection will be conducted online using a secure platform (e.g., REDCap). The PI and trained IRB-approved research personnel will review intake data as needed to determine eligibility. Research personnel and the PI will review the status of all active participants during weekly study meetings.

Rigorous data management/Quality assurance

All data will be collected via secure, HIPAA-compliant software (e.g., REDCap). All data will be collected using self-report questionnaires and EHR. All participant data will be directly loaded from the secure online surveys (e.g., REDCap) to the secure UVMMC server. Participants' identities will be disguised using ID numbers keyed to a master list. Identifying information such as telephone number and email address will be stored in a separate, secure, and password protected data file. All data will be accessible to only the PI and IRB-approved research personnel. The IRB approved biostatistician and PI will consult regularly to discuss ongoing data management and any problems that arise.

Data and safety monitoring plan

Weekly monitoring of data quality and integrity will be conducted by the study team and evaluated monthly by the PI. The study Medical Monitor, James Whitledge, MD will provide independent feedback and monitoring of the quality and safety of the study measures.

The study team will meet each week to monitor and evaluate the 1) study progress and 2) safety of the proposed pilot trial. With regard to study progress, screening, recruitment, and retention, data will be reviewed on a regular basis to assure that the study can be completed in a reasonable time frame to be of significant clinical relevance. With regard to safety, interim safety data for the trial will be reviewed on a regular basis in order to assure the continuing safety of participants. Of note, all serious adverse events, study or non-study related, will be reported to the IRB by the PI within 72 hours of the PI learning of the event. Any study-related IRB actions will be reported to the NIGMS by the PI within 72 hours of the PI learning of the action.

Participants will be informed about possible AEs related to MOUD in the consent form. At study onset, participants will be provided with a phone number and e-mail to report any AEs that are urgent. We will withdraw participants who have an FDA-defined serious AE (SAE) that are likely or probably related to the study procedures. Traditional methods of collecting AEs can be insensitive, thus we will instruct participants to contact research personnel if they experience a severe AE. We will encourage participants to contact research personnel if they have questions about withdrawal symptoms or believe any withdrawal symptoms require treatment, which is part of Best Practices care that MOUD patients receive.

Auditing procedures

The PI and study personnel will meet weekly to review any problems related to the quality of data collection and any AEs or SAEs that occurred during the past week. In addition, we will conduct an interim analysis of AEs halfway through data collection as well as interim analyses of AEs required by the DSMB. We will present findings from all interim analyses to the DSMB.

Define criteria to be used for decision making regarding continuation, modification, or termination of the entire study (not individual participation) (i.e. stopping rules).

Continuation will be determined based on the status of participant recruitment. Modifications will be made in response to Unanticipated Problems (UAPs) and otherwise at the discretion of the study PI. Termination criteria include sudden discontinuation of ability to conduct study (e.g., participant payment can no longer be delivered; change in rules regarding PAF; discontinuation of STAR program in ED).

What will be the frequency of the review? Please note that the frequency of reviews should be commensurate with the risk of the study. At a minimum, a review of the data should be conducted annually at time of continuing review. These reviews must be conducted at the frequency indicated below and must be documented in the regulatory binder or files.
Forward copies of data and safety monitoring board reports to the IRB via a modification.

- [ ] Monthly
- [ ] Quarterly
- [ ] Bi-annually
- [x] Annually
- [ ] Other (e.g., by dosing level, no. of subjects enrolled):

Will the sponsor be conducting data monitoring visits for this study?

- [ ] Yes
- [X] No
- [ ] NA

If yes, how often?

Adverse Event, Unanticipated Problem (UAP), Reportable New Information (RNI): 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 "Section 18: Reportable New Information" of the IRB Policies and Procedures will be followed.

UAPs will be evaluated and reported to the IRB by the study PI. Correspondence regarding modifications to the protocol will be handled by the study PI or designated staff. Guidelines established in "Section 18: Reportable New Information" of the IRB Policies and Procedures will be followed.

Withdrawal Procedures: Define the precise criteria for PI withdrawal of subjects from the study. Include a description of study procedures for when a subject withdraws themself from the study.

Since our primary measure is the proportion of participants who receive an MOUD prescription following discharge from the ED, study withdrawal is a primary outcome in this study. If a participant discontinues outpatient clinic attendance, we will not attempt to contact them.
Participants may be withdrawn from the study based on the judgement of the PI following consultation with study staff and/or clinicians.

DRUG INFORMATION

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

Drug (s) [X] **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.

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

Storage and stability – for both intact and mixed products.

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

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.

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.
2. for the route of administration specified? If no, provide justification for route and describe the method to accomplish.
3. for the intended action?

FINANCIAL CONSIDERATIONS

Describe all potential research related expenses to subjects:

Study payments will be conducted via online form. Participants may encounter costs associated with data charges from their cell phone provider. There will be no additional cost to participants for any aspect of this research study.

Compensation 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

Figure 1.
Schedule of payments for each study condition.

Treatment Day	ED	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	FU	Total $
Contingency Management (CM) condition																																
Methadone visits	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Voucher $	$15	$50	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15		$485
Assessment $	$55																														$55	$110
Total $	$70	$50	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$15	$55	$110
Bup visits	x	x							x							x							x							x		
Voucher $	$15	$50							$105							$105							$105							$105		$485
Assessment $	$55																														$55	$110
Total $	$70	$50							$105							$105							$105							$105	$55	$595
Usual Care (UC) condition																																
Voucher $	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0		$0
Assessment $	$55																														$55	$110
Total $	$55	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$55	$110

Key
ED = emergency department
CM = contingency management
Bup = buprenorphine
TAU = treatment as usual
VCBM = voucher-based CM
FU = follow-up

Note. This schedule shows maximum possible payment for individuals prescribed methadone and buprenorphine under idealized conditions.

Figure 1 shows a diagram of the possible payments earned during the study. Participants randomized to the BP+CM condition have the potential to receive $595 in compensation. Those randomized to the BP-alone condition have the potential to receive $110 in compensation for completing assessments in the ED and in the outpatient clinic at 30-day follow up. The figure is intended to illustrate the flexibility of the payment schedule for delivering incentives according to the different frequencies of clinic attendance that characterize buprenorphine and methadone treatment.

Compensation During the Study

All participants will receive study compensation via a US Bank Focus Blue Visa card. Once enrolled in the study in the ED, study staff will issue participants a Focus Blue card along with instructions on how to access the card balance via the web or phone and how to contact study staff to replace a card if lost or

damaged. Upon receipt, the card will be loaded with compensation for the study screening and consent ($55) to account for additional time spent completing questionnaires and eligibility assessments.

All participants who complete the follow-up assessment on Day 30 will be compensated $55 to account for additional time spent completing questionnaires and debriefing.

BP-alone condition: In the ED, participants in the BP-alone condition will receive clinic referral materials along with their prescription. Study staff will make contact with each BP-alone participant on a weekly basis to increase chances of retention at 30-day follow up.

BP+CM condition: In the ED, participants in the BP+CM condition will receive clinic referral materials and instructions on the payment schedule and notified of the $50 intake incentive to be delivered upon completion of the first outpatient clinic visit. Their card will also be preloaded with the ($15) incentive for their first prescription pickup in the ED (the total amount loaded upon receipt of the card will be $70).

Each subsequent outpatient clinic visit completion (as communicated by Clinic staff to Study staff through REDCap) will be compensated. The incentive amount delivered to the card will depend on the number of days since the last verified attendance such that the amount increments by $15 each day (Figure 1). STAR program data show that approximately half of individuals referred to MOUD treatment in the ED receive prescriptions for methadone and half receive prescriptions for buprenorphine. Methadone prescriptions are typically filled at the outpatient clinic each day whereas buprenorphine prescriptions can be filled once every 3-5 days. The study is designed to address this natural variation in clinic attendance frequency by matching the total incentive amount across participants prescribed buprenorphine and methadone. As shown in Figure 1, a daily incentive value ($15) will be possible and otherwise allowed to accumulate each day between visits (e.g., buprenorphine outpatient visit on Friday had last visited on Monday receives 4x$15 = $60).

Payment Administration

Coordination of payment will involve **ED STAR staff** (entering information into REDCap and distributing Focus Blue cards), **Study Staff with access to medical records** (monitoring participant REDCap to verify attendance, monitoring completion of PAFs, administering payments, replacing lost Focus Blue cards), and the **Participants** (receiving payment notifications via study texts and/or emails, completing PAFs).

ED STAR staff. At study intake, staff will issue all participants a US Bank Focus Blue card and will deliver instructions on how to access their balance on the US Bank website. Instructions will include how to contact study staff to report and replace a lost card. Instructions will include how to contact study staff in case of barriers to accessing online PAF or other problems arise. ED Staff will enter participant ID, note of study participation condition (BP+CM or BP alone), and standard referral information into a REDCap form.

Study Staff with access to EHR. UVM/UVMMC study staff in UHC will maintain secure REDCap forms with the randomization list corresponding to study condition (BP alone or BP+CM). Study also have credentialed access to 42 CFR Part 2 health information in the UVMHN Epic system. Study staff in Chittenden Clinic have access and training specific to the Howard Center EHR system. Study Staff will have access to all study payment cards through the US Bank Focus Blue platform and be able to cancel cards if reported lost and issue new cards. Study Staff will keep a record of card numbers and corresponding participant identification codes (ID) in a secure REDCap form.

Incentive delivery: Study staff will monitor EHR of each participant for prescriptions received. Once the record indicates a prescription receipt and depending on participant study condition (BP alone or BP+CM), Study Staff will calculate the amount of money to allocate to the participant card based on their study condition and last recorded attendance. This amount will be entered into a REDCap PAF, and a link to complete on REDCap will be created and sent via text and/or email to the participant. Once completion of PAF has been confirmed in REDCap, Study Staff will use the US Bank Focus Blue online platform to allocate funds indicated on PAF to the corresponding participant card. Payments will be tracked on a REDCap form and adjusted to reflect the amounts determined by the study incentive procedure described above.

Participants will receive weekly text messages and/or emails from STAR staff. Participants will complete PAF on REDCap and acknowledge the amount of money to be received. If a card is lost, the participant will be able and encouraged to contact study staff immediately to arrange receipt of a new card. Participants at risk for unreliable access to internet via cell phone or other device will be provided resources (e.g., pre-paid phone) on a case-by-case basis by study staff. Participants will not be reimbursed for travel or other expenses.

Research Data Management Plan: The Research Data Management and Security Plan form must be completed. The form, along with guidance, can be found in our forms library and must be submitted with your initial application.