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To Whom it may Concern,

This is a copy of the IRB-approved protocol for the clinical trial registered under NCT04562779. This is the latest version, approved on July 24, 2021. It underwent 'Continuing Review' with no changes in August 2021 and August 2022.

Sincerely,

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Protocol #: **20-2008**
Project Title: Single-dose interventions to reduce re-admissions for hospitalized patients with refractory alcohol use disorder: A randomized pilot feasibility study.

Principal Investigator: Dale Terasaki
Version Date: **07/24/2021**

I. Hypotheses and Specific Aims:

Every year, alcohol use disorder (AUD) generates millions of emergency department (ED) visits and hospital admissions, costing the U.S. health sector over $90 billion.[1] These hospital admissions are critical opportunities to start patients on addiction pharmacotherapy, but factors like medication non-adherence and post-discharge relapse contribute to frequent re-admissions. Two single-dose interventions are well suited to facilitate treatment retention and prevent re-admissions due to their prolonged, adherence-independent effects: extended-release (XR) naltrexone injection and intravenous (IV) ketamine infusion. These have not been thoroughly investigated in the hospital setting among high-utilizer, safety-net populations. Therefore, we aim to:

1. **Test the feasibility of randomizing hospitalized patients (n=45-60, age 18-65) with multiple AUD-related admissions to treatment with either extended-release (XR) naltrexone, intravenous (IV) ketamine, or no single-dose medication, all with enhanced linkage to care.** Feasibility outcomes such as recruitment rate, patient acceptability, post-discharge follow-up rate, and adverse events will help to identify key lessons for a future comparative effectiveness study.
2. **Estimate the 30-day re-admission rate for patients randomized to treatment with XR naltrexone, with IV ketamine, or no single-dose medication, all with enhanced linkage to care.** We hypothesize that the re-admission rate will be lower for each of the two single-dose medication groups than for the “linkage-alone” group.

II. Background and Significance:

Alcohol use disorder (AUD) generates approximately 5 million U.S. emergency department visits every year, leading to 2 million hospital admissions and collectively costing the health sector over $90 billion dollars annually.[1] Because addiction treatment is seldom accessed,[2] hospital admission represents a major opportunity for linkage to care[3,4] and initiation of oral (PO) naltrexone,[5] a first-line medication shown to improve outcomes such as number of drinking

days,[6] drinks per day,[6] and health care utilization.[5,7] Denver Health (DH) provides a dedicated addiction consult service (ACS) to assist in these efforts, and the ACS sees hundreds of new consults per month. Yet alcohol-related admissions at DH – estimated at nearly 2,000 per year[8] – show a higher 30-day re-admission rate than the hospital-wide average (Figure 1). This is consistent with a nationally reported re-admission rate for alcohol-related disorders of 21% compared to 14% overall in 2014,[9] ranking it 4th among common diagnoses.[9] Additionally, there is low post-discharge treatment engagement for these patients: one sample of hospitalized DH patients with AUD demonstrated an 11.8% follow-up rate at addiction clinic (chart review).

These sub-optimal transitions of care underscore the limited benefit of oral naltrexone for high-utilizer, safety-net populations who may have social contexts that compromise medication adherence.[10] Different tools are needed that can facilitate post-discharge treatment engagement and reduce re-admissions, goals in line with the DH Center for Addiction Medicine (CAM) and upcoming Hospital Transformation Project[11] application.

The following two pharmaceutical options are well-suited to the hospital setting and complementary to the myriad behavioral strategies to improve treatment compliance and linkage to care:[12]

1. An extended-release (30-day, “XR”), intramuscular injection of naltrexone (Vivitrol®). Studies on XR naltrexone have shown better long-term medication continuation compared to oral naltrexone[13] and reduced heavy drinking days compared with placebos.[14] Additionally, one meta-analysis showed a trend toward fewer admissions compared to oral naltrexone.[15] One ongoing clinical trial[16] is directly comparing oral to XR naltrexone for AUD in a safety-net hospital in Boston, and it is expected to evaluate the results in late 2020. Regardless, data from multiple centers and regions are needed, and our study uniquely targets high-utilizer patients.
2. A single infusion of intravenous ketamine, a dissociative anesthetic used in general anesthesia and pain management. At sub-anesthetic doses, ketamine provides rapid effects on mood that extend weeks beyond administration,[17,18] and in 2019 the FDA approved an intranasal formulation for treatment-resistant depression.[19] For AUD, treatment with ketamine decreased cravings and drinking at 10 days post-infusion in a human laboratory study that excluded patients with depression.[20] In a recent randomized trial, AUD patients were given one ketamine infusion and subsequently showed a higher rate of abstinence at 21 days beyond treatment and better attendance at the final study visit compared to the control group (100% vs 74%, respectively), with no serious adverse events reported.[21]

Both single-dose interventions hold great potential for improving AUD post-hospital transitions and reducing immediate re-admissions, but more data on feasibility and effectiveness are needed.

III. Preliminary Studies/Progress Report:

There have been no preliminary studies. However, an initial Tableau query showed that at Denver Health, patients admitted to the hospital with an alcohol related diagnosis had a 30-day readmission rate of between about 10 and 40 percent (see Figure 1). This is notably an underestimation, given that patients may have had readmissions at hospitals outside of Denver Health, which would not have been captured in those data.

There is also low outpatient treatment engagement following discharge for these patients. I reviewed a cohort of 17 patients that I cared for in August and September 2019, all of whom I referred to outpatient addiction clinic for treatment of alcohol use disorder. Only 2 presented within the following month. Among the 9 who were prescribed oral naltrexone, only 1 presented.

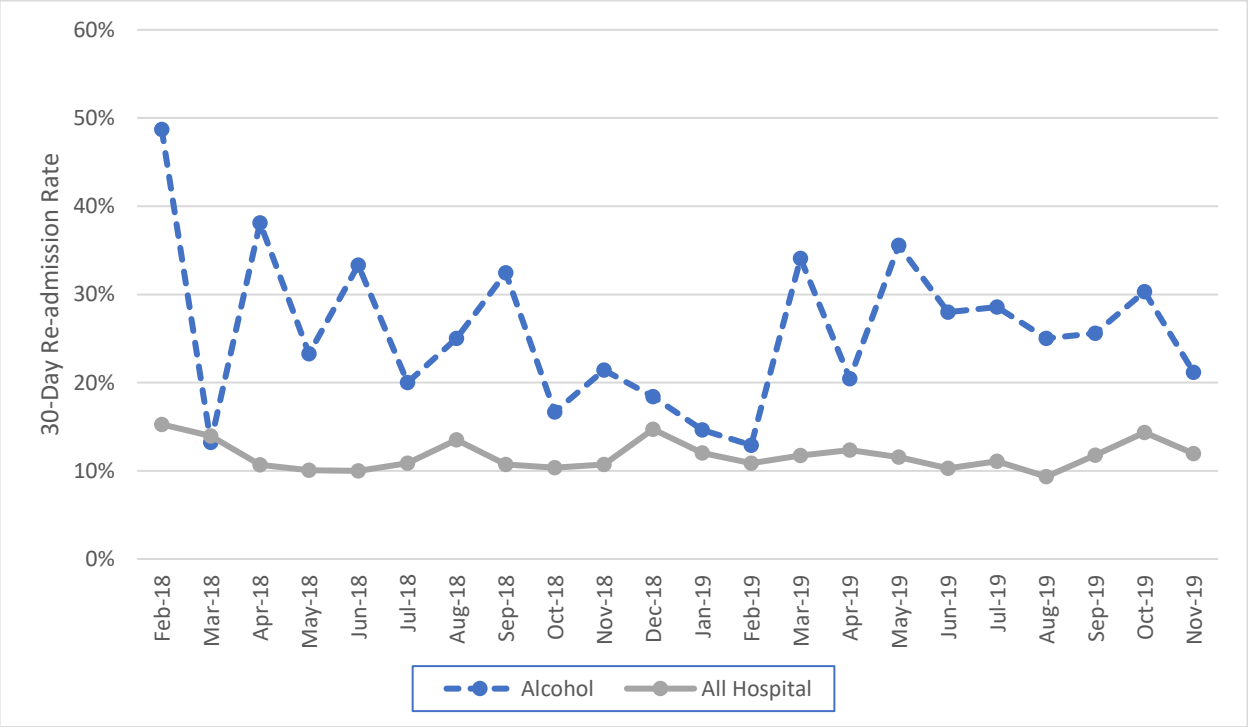

Figure 1 DH hospital re-admissions. Obtained via Tableau with assistance from Mara Prandi-Abrams. Alcohol admissions based on All-Patients-Refined-Diagnosis-Related-Groups (APR-DRG) 775 and 280.

IV. Research Methods

A. Outcome Measure(s):

See table 1 for primary and secondary outcomes. In brief, our primary outcomes will be those related to feasibility as well as risk of 30-day all-cause hospital re-admissions. Secondary outcomes include risk of 30-day all-cause emergency department visit,

differences in readiness-to-change, and likelihood of having an alcohol metabolite (EtG) in the urine at follow-up.

Table 1 Primary and secondary outcomes

	Study Aim	Description	Instrument(s)
1' feasibility outcomes	**1**	**Recruitment rate (# enrolled / month), follow-up rate, patient acceptability, adverse effects**	**Chart review, questionnaires**
1' clinical outcome	**2**	**Risk of 30-day all-cause hospital re-admissions**	**Chart review**
2' clinical outcomes	2	Risk of 30-day all-cause ED visits	Chart review
	2	Within-subject difference in readiness-to-change[22]	Questionnaire
	2	Laboratory(+) for alcohol at SUDS	Urine EtG
	2	Percent of binge drinking days[23] since discharge	Questionnaire

B. Description of Population to be Enrolled:

See Table 2 and 3 for inclusion and exclusion criteria. Rationales are also listed.

Table 2 Inclusion criteria

	INCLUSION criteria	Rationale
	Age 18-65	Limiting study scope to adult patients
	1+ alcohol-related* admission(s) OR 2+ alcohol-related ED visits in past 12 mo. *Admission diagnoses includes any of following: - alcohol use / intoxication - alcohol withdrawal - alcohol use disorder / dependence - seizure thought to be related to alcohol withdrawal - encephalopathy thought to be related to alcohol - pancreatitis thought to be related to alcohol - liver disease thought to be related to alcohol - cardiac arrhythmia or heart failure thought to be related to alcohol - gastrointestinal bleed thought to be related to alcohol	Limiting study scope to high-utilizer patients
	Has insurance (public or private)	Can follow-up at SUDS clinic
	Seen by addiction consult	Part of recruitment plan

Table 3 Exclusion criteria

	EXCLUSION criteria	Rationale
	Known or suspected active COVID-19 infection	Staff safety and ability to immediately follow up at SUDS clinic

	Hepatic: AST/ALT >5x upper-limit of normal, decompensated liver failure	Naltrexone can rarely cause hepatotoxicity. 5x ULN used by study by Collins et al (2015)
	Renal: Glomerular filtration rate <30ml/min	Naltrexone not recommended in renal failure
	Cardiovascular: History of acute coronary syndrome, cerebrovascular event, hypertensive crisis, known cardiomyopathy	Ketamine can transiently raise blood pressure
	Known elevated intracranial pressure	Ketamine can transiently raise blood pressure
	Thrombocytopenia (<50/microliter)	Naltrexone can potentially worsen thrombocytopenia
	Active moderate/severe withdrawal (based on hospital withdrawal protocol)	May need acute care that would interfere with intervention and discharge planning
	Active delirium (alcohol-related or otherwise)	Ketamine's dissociative effects could theoretically worsen delirium
	Already enrolled in study	A-priori decision to only enroll patients once
	XR naltrexone or IV ketamine in last 30 days	Prior administration could affect ability to distinguish effect of current intervention. Recent receipt of intervention would also be evidence that intervention not effective for them.
	Known intolerance to naltrexone or ketamine	Avoid harm to patient
	Other active severe substance use disorder (tobacco, cannabis excluded)	Limiting study scope to AUD
	Pregnant or breast-feeding, or planning.	Risk of harm to fetus not well established for naltrexone or ketamine
	Opioids: physical dependence or anticipated use in the next 30 days	Naltrexone is an opioid-antagonist
	Unstable psychiatric illness (active psychosis, active suicidality)	Ketamine's dissociative effects could worsen psychiatric decompensation
	Moving from region within 30-days of discharge	Cannot have immediate follow up at SUDS
	Discharge to acute/residential treatment	Cannot have immediate follow up at SUDS
	Involuntary hold	Cannot have immediate follow up at SUDS

C. Study Design and Research Methods

We propose an open-label, pilot feasibility trial (n=45-60), randomizing hospitalized patients to receive XR naltrexone, IV ketamine, or neither prior to hospital discharge, along with enhanced linkage to care. The primary clinical

outcome compared across each of the groups will be 30-day re-admission rates ascertained by chart review (Table 1).

To reduce variability, all participants will undergo a standard addiction consultation that includes behavioral components such as supportive therapy and motivational interviewing. They will also receive enhanced linkage to care (hereon "linkage") which includes being met by a staff member while in the hospital to begin the clinic intake process and assign a follow-up appointment date. Linkage will also include a contingency management[24–26] (monetary incentive to follow-up) in their post-hospital transition and receive standard case management and counseling at Substance Use Disorder Services (SUDS) clinic.

ACS team members will identify patients meeting inclusion criteria (Table 2), and – after conducting their usual consultation – approach them about the study. Approximately 900 patients met similar inclusion criteria in 2019 (Query by Josh Durfee). After screening for exclusion criteria, informed consent will occur, and initial baseline data will be obtained by "Treatment on Demand" (TOD), a grant-funded team of counselors who are already linking hospitalized patients to addiction care. Consented patients will then be randomized, and the ACS will work with the primary team to order and administer the assigned intervention close to discharge. Meanwhile, a TOD counselor will work to establish a follow-up date within seven days post-discharge. Additional data will be collected immediately after the intervention (for those in one of the two medication groups), at SUDS follow up, and 30-days post-discharge by chart review.

Medications

XR naltrexone is produced by Alkermes. Due to the cost (~$1300 on GoodRx for one dose), we will receive samples from Alkermes in a process that has been pre-arranged between DH inpatient pharmacy and their Colorado-based representative, Chris Thurnauer. We received preliminary approval on 12/3/19 from DH Pharmaceuticals and Therapeutics Committee to use these samples in the hospital for this purpose.

IV ketamine is currently utilized at DH at sub-anesthetic doses for pain control, with guidance from PolicyStat[27] #5253340. Its use in pain management is currently limited to ICU settings and utilizes boluses and infusions titrated to pain. According to discussions with inpatient pharmacy, approval for an infusion dose modeled after randomized trials[18,28–30] may be granted for use on floor units with specific contingencies: physician/investigator will be present at bedside during the infusion and nursing staff are educated on the protocol. This was discussed at Denver Health's Medication Administration Forum (MAF) meeting on 3/5/20.

Data Collection

Data will be primarily collected at four time-points (Table 4). Data will be entered by staff into a REDCap database on tablet computers in the hospital and at SUDS clinic. Data collected at enrollment will primarily be descriptive, including demographics, recent drinking history,[31] readiness to change, and various contributing factors to drinking. Immediately after intervention, vital signs,

symptoms, and acceptability will be recorded. Data collected on post-discharge arrival to SUDS clinic will include most 2' clinical outcomes. We will obtain re-admission rate (1' clinical outcome) through chart review, conducted by research team members at 30-days post-discharge.

Table 4 Patient flow and data collection points

Step	Who	Notes	Data collected – staff entered
Patient identified on consult list	ACS	Quick screen that meets inclusion criteria	
↓			
Addiction consult performed	ACS	Evaluation, withdrawal management, medication (though if patient consents to study, will not be prescribed an addiction medication at discharge), brief therapy, referrals, disease screening/harm reduction	
↓			
Screen, consent, randomization	ACS	Formal screen to identify any exclusion criteria. Simple randomization by algorithm	• E-Consent (should include consent to see records in "care everywhere" – some hospitals require permission – when checking for ED visits and re-admissions) • Screening documentation (inclusion and exclusion criteria) • Alcohol-related admissions in last 12 months (date, location, top 3 diagnoses) • Assigned group
↓			
Baseline data, referral to SUDS **[data collection point #1]**	ToD	ToD collects baseline data first, then performs "biopsychosocial intake" and sets up SUDS appointment within 1 week of discharge. Discharge date is not always predictable;	• Demographics • Baseline clinical data • Depression symptoms baseline (PHQ9 2 wks) • Drinking History 7-days prior to admission (TLFB) • Readiness to change (SOCRATES-8A) • ACE Questionnaire

		ACS to review active hospitalized research participants and contact ToD/update date in RedCap as needed.	
↓			
Intervention administered **[data collection point #2]**	RN, ACS	For 'linkage-alone' group, data to be entered following consult. For NTX group, intervention administered prior to discharge (could be same day as consent). Vitals immediately preceding and 40 min post- injection. Data collected after administration. For KET group, intervention administered prior to discharge (could be same day as consent), though should have no food for at least 3 hours (~50% gastric emptying). Vitals immediately preceding, after completion, and 2 hours following end of intervention.	• Vital signs (HR, BP, O2): linkage-alone group- baseline only, recorded *after* consult. NTX group- baseline, 40 min after administration. KET group- baseline, end of administration (~40min), 2 hours after end of administration. • Most recent AST, ALT • UDS-5 data • [for KET] Dissociative symptoms (CADSS) after administration (40 min) • [for NTX and KET] Acceptability of intervention (10-point Likert) after administration • [for NTX and KET] Readiness to change (SOCRATES-8A) after administration (40 min) ORDER: CMP (if not already obtained), UDS-5 (if not already obtained) ORDER in discharge orders (outpatient): CMP, UDS-5, urine EtG (if not already ordered)
↓			
Presentation to SUDS, data entered, contingency management reward administered **[data collection point #3]**	SUDS staff	Upon presentation, staff to collect study data. After completion, will receive contingency management reward. Then patient to complete standard intake/follow-up visit, if willing.	• Drinking History since discharge (TLFB since discharge) • Depression symptoms (PHQ9 modified to read "since discharge.") • Readiness to change (SOCRATES-8A) • [for KET] Dissociative symptoms (CADSS) • Adverse Events (Modified PRISE) • Acceptability of intervention (10-point Likert)

		Staff to instruct patient to present to the clinic laboratory (e.g. pav G) for CMP after the visit.	• Contingency management feedback (10-point Likert, open ended)
↓			
30-day chart review **[data collection point #4]**	Research staff	Should check encounters tab as well as “care everywhere” for Denver Metro region.	• Admissions (up to 5) within 30 days of discharge date (date, location, up to top 3 main diagnoses based on documentation available). • ED visits (up to 5) within 30 days of discharge date (date, location, up to top 3 main diagnoses based on documentation available). • AST, ALT obtained at SUDS f/u (if available) • Urine EtG obtained at SUDS f/u (if available)

Screening: The addiction consult team will attempt to screen patients meeting the inclusion criteria during inpatient admission. We anticipate 10 patients will meet inclusion criteria weekly. They will be assessed for clear exclusion criteria documented in the chart, and if none are noted the patient will be asked if they would like to join the study and complete the screening. If still no exclusion criteria are met and the patient expresses interest, they will be engaged in informed consent. The primary team will be notified by the addiction medicine team. Each combined process of screening and consent is anticipated to require 15 minutes at the end of a typical consultation. The screening window is anticipated to last 5 months.

Randomization: Patients will undergo a simple randomization algorithm to one of three arms.

Intervention:

- **Arm 1:** Receive a single dose of XR naltrexone (380mg) prior to discharge.
- **Arm 2:** Receive a single infusion of IV ketamine (0.5 mg/kg over 40 minutes) prior to discharge.
- **Arm 3:** No single-dose medication
- *All groups will receive enhanced linkage to care that includes contingency management, initiation of biopsychosocial intake, and appointment scheduling. This aspect alone surpasses the current standard of care.*

Contingency Management: Patients will receive a debit card prior to discharge from the hospital. We will utilize a pre-existing system - ClinCard by Greenphire. Participants will receive $10 upon completion of baseline data, and $20 upon completion of follow-up data (at SUDS clinic).

Follow up: Patients will be assigned a follow-up within 7 days of discharge at the outpatient addiction clinic (Denver Health SUDS clinic in pavilion K).

Standard of care: Current standard of care for alcohol use disorder in the hospital includes offer of medications (usually oral naltrexone) and addiction medicine consultation which can result in brief counseling and referral to SUDS clinic or other treatment program.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Table 5 Overview of risks and justifications of procedures and data collection tools

Procedure/Tool	Description, Risks	Justification
Injection of IM medication (naltrexone)	Risks include minimal pain and discomfort at the injection site which will occur on the lateral thigh or the buttock. One study suggested that the discomfort of an injection itself deterred a large number of participants.[32] If that is the case for our study, this decision will be honored with no repercussion aside from not enrolling in the study. More serious risks such as infection, blood clot, bleeding and/or allergic reaction are rare.	These risks are justifiable as there is very little risk of serious or permanent harm, and potential benefits in terms of preventing the consequences of heavy drinking are almost certainly greater.
Medication-related risks of naltrexone	Risk of opioid withdrawal if the patient is taking opioids concurrently (an exclusion criteria); Liver injury can be seen, but is usually mild and self-limiting. Patients with AST/ALT >5x ULN, hepatic failure, or decompensated cirrhosis will be excluded. Nausea, sleepiness and headache are the other most common medication side effects.	These risks are justifiable as there is very little risk of serious or permanent harm, and potential benefits in terms of preventing the consequences of heavy drinking. It is a single dose which limits exposure.
Medication-related risks of ketamine	Risk of unpleasant dissociative symptoms, delirium, hallucinations; high blood pressure which could lead to adverse cardiac events if patients are not screened carefully; initiation of ketamine abuse after discharge.	These risks are justifiable as there is very little risk of serious or permanent harm, and potential benefits in terms of preventing the consequences of heavy drinking. It is a single dose which limits exposure. Patients who experienced delirium during hospital stay will be excluded. Patients with known cardiovascular disease will be excluded. The most recent randomized trial using ketamine found no initiation of ketamine “abuse” following administration.[21]
Data collection tools – questionnaires, urine Etg	All questionnaires have the potential to bring up unpleasant memories of their use and strong emotions related to their motivations to change. Gathering re-admission data from insurance claims has	These risks are justifiable as strict precautions to safeguard protected health information will be applied.

	the potential for a breach of confidentiality. However, precautions to safeguard protected health information in accordance with international standards for human subjects research will be applied.	

E. Potential Scientific Problems:

One potential limitation is the small sample size. As a pilot study, our main aim is to test feasibility. A more robust, precise demonstration of clinical effectiveness will be pursued in a future project with data used from this study to inform sample size estimates as well as timelines.

Secondly, patients may be re-admitted to hospitals that do not show up in our medical record system (Epic). Insurance claims data would be ideal, but at this stage the added value does not justify the costs required for acquisition. Notably, Epic "Care Everywhere" can detect admissions in the University of Colorado Health system (12 hospitals in Colorado), SCL Health (5), and Centura Health (17). This network of hospitals provides high coverage based on our population, many of whom are homeless and located in a small regional geography.

Another potential limitation is a low follow-up rate at SUDS. This is one major reason for including contingency management[26] as part of our enhanced linkage to care. Regardless, the primary quantitative outcome (hospital re-admission) will not require data from SUDS attendance to measure.

Alternative designs were considered but deemed beyond the scope of this proposal:

- *"Double dummy" placebos*, which can minimize bias in both researcher and participant. However, this would be personnel and time-intensive, and due to ketamine's unique psychoactive effect, patients are unlikely to be successfully blinded.
- *2x2 factorial design*, which could gain information on combinations of multiple interventions, but would unnecessarily weaken inferences and complicate statistical analysis due to interactions in this small sample.
- *30-day in-person evaluation*, which would facilitate additional longitudinal measurement. However, we are not confident that enough patients would show up (or be reachable by telephone) to allow for meaningful analysis.

F. Data Analysis Plan:

Participants' demographic and baseline clinical data will be tabulated, and differences between groups will be assessed using a Fisher's Exact Test for categorical variables and a two-sample t-test for continuous variables. These tests

will help evaluate the effectiveness of randomization. Feasibility outcomes (Aim 1) such as adverse events and acceptability (Likert scale)[33] will be compared for each group using a Fisher's Exact Test and Wilcoxon-Mann-Whitney Test, respectively. Overall recruitment rate and follow-up rate will be tallied at the conclusion of data collection.

For Aim 2, all-cause hospital re-admission within 30-days of discharge will be recorded as a binary outcome. Rates of the two medication intervention groups (XR naltrexone or IV ketamine) will be compared against the group that received enhanced linkage to care alone.

This pilot study may not be sufficiently powered for robust hypothesis testing. By one crude estimate, we could have approximately 80% power to detect a difference between a medication group and the linkage-alone group with about 60 participants assuming a re-admission rate is 25% vs 15%. A larger effect size would increase our power and/or reduce the number of participants required. Regardless, this will provide parameter estimates that can inform a future sample size calculation in a larger effectiveness trial.

For further descriptive purposes, a secondary utilization outcome is risk of 30-day all-cause ED visits. This will be evaluated in a similar manner as hospital re-admissions. Additionally, we are interested in the within-subject difference in readiness-to-change. For those who follow-up, a mean of pre/post differences will be calculated, and a paired t-test will be used to determine if the null hypothesis (H_0: difference = 0) can be rejected. Drinking behavior will be measured using the Timeline Follow Back method.[31] Binge drinking will be defined as 5+ drinks for men, 4+ for women,[23] and the proportion of binge drinking days since discharge will be calculated for each group. Proportions of positive urine ethyl glucuronide (EtG) will also be tabulated for each group.

Data will be analyzed in SAS.

F. Summarize Knowledge to be Gained:

We hope to demonstrate feasibility of two single-dose interventions given in the hospital setting and estimate their effects in terms of hospital readmissions. The knowledge gained will help inform a future, larger comparative effectiveness study. The data will also help CAM staff related to tracking and incentivizing transitions of care for patients with AUD.

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