Emergency Department Initiated Extended-Release Naltrexone and Case Management for the Treatment of Alcohol Use Disorder

NCT04094584

Study Protocol
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Treatment of alcohol use disorders with extended-release naltrexone and tele-addiction assessment initiated in the emergency department.

I. Scope of the Problem:

Alcohol use disorders are common and represent a significant public health problem. In the United States 88,424 deaths annually and 1 in 10 deaths of working-aged adults age 20-64 can be attributed to excessive alcohol use [1,2]. This represents 2.5 million years of potential life lost and an annual cost of $249 billion [3]. Over the past 9 years, alcohol- related visits to the emergency department (ED) have increased by 47% with an annual cost increase of $4.1 billion to $15.3 billion [4]. During this time the number of people using alcohol in the United States and the total amount of alcohol consumed has not changed, suggesting that this increase in alcohol-related ED use may be due to increased consumption among a subset of frequent ED users [4].

ED visits can be leveraged as teachable moments to intervene with patients in times of crisis, and because of the large proportion of alcohol-related ED visits relative to other medical specialties, emergency providers are well-positioned to offer interventions that address substance use, such as Screening Brief Intervention and Referral to Treatment (SBIRT) and pharmacotherapy [7]. Further, EDs commonly employ social workers alongside medical providers to help link patients to outpatient services, including treatment for drug and alcohol use disorders. In addition, many patients with alcohol use disorders are marginalized from traditional primary care settings or have difficulty accessing effective treatment in non-ED settings. As a result, EDs are often the primary point of contact with the healthcare system for individuals with alcohol use disorder [7].

Screening, brief intervention, and referral to treatment (SBIRT) has demonstrated efficacy in reducing risky alcohol use and reducing net healthcare costs. SBIRT is strongly recommended for use in the emergency department by the CDC, the US Preventive Services Task Force, and the National Institute on Alcohol Abuse and Alcoholism [10]. Despite these recommendations, SBIRT is rarely utilized due to numerous barriers to implementation including time and cost [11]. Emergency department use of SBIRT paired with facilitated referrals where ED staff ensure eligibility, insurance clearance, and assist in scheduling and transportation to follow up visits has demonstrated feasibility and may reduce the barriers to accessing treatment [7].

Even though pharmacotherapy is recommended as the standard of care for alcohol dependence, fewer than 1 in 4 dependent patients receives treatment with an approved agent [6] and its use in EDs is virtually non-existent. Of the four drugs approved for treatment of alcohol dependence, extended release naltrexone (XR-NTX) has been found to be superior at reducing healthcare utilization, increasing detoxification facility use, and reducing total cost [5]. It may also be perceived by providers as a more feasible treatment to administer [6]. While there is a growing body of evidence supporting the efficacy of ED-initiated, medication-assisted treatment (MAT) of opiate use disorders [7], little research exists on ED-initiated MAT for alcohol use disorders. We propose to address this knowledge gap via a pilot study to examine the feasibility of ED-initiated XR-NTX paired with telemedicine SBIRT for frequent ED users with alcohol use disorders. Enrolled patients will receive up to 3 consecutive months of XR-NTX. A dedicated research case manager will be available for all participants. The research case manager will

outreach to the participants in the community to coordinate monthly injections. An addiction specialist from a community organization familiar the drug will administer the XR-NTX.

This study aims to address CARESTAR's Funding Priority to "support nonprofit health advocacy organizations, state and local agencies, providers of care and community partners in the development and implementation of meaningful, impactful and sustainable health related initiatives that improve care and expand access to emergency and trauma services, particularly with vulnerable populations."

II. Study Design and Procedures:

Overview of Design:
This is a phase 4 open label feasibility study of extended release naltrexone (Vivitrol, Alkermes Pharmaceutical), case management and tele-addiction medicine for treatment of alcohol use disorders in the ED. The planned study period is 2 years. During this time we will conduct necessary department staff training and recruit 25 patients. Each patient will be followed for 12 months from index visit by our study staff, with case management provided by a full-time research case manager. Patients will be enrolled consecutively, 24 hours a day, 7 days a week. Recruitment will take place in the UCSF Emergency Department, Parnassus campus. Follow up visits may occur in the UCSF ED or an outpatient setting agreed upon by the patient and the research case manager. Patients who drop out of the study will be replaced with new patients; enrollment will end once 25 patients have been retained in the study or at the planned end date.

Initial Screening:

All adult patients presenting to the University of California San Francisco ED during the study period with will be screened for frequent ED utilization (defined as 3 or more ED visits in the past 12 months including the index visit) by electronic medical record review conducted by the treating physician or member of the research team. UCSF, San Francisco General, and several other academic and community emergency departments in the San Francisco Bay Area share an electronic platform called the Emergency Department Information Exchange, or EDIE, that documents dates of ED visits and diagnoses. UC emergency providers can view visits at each of these sites, and ED visits to any hospital will be counted towards this 3-or-more threshold.

Determination of Eligibility:

An ED provider or staff (including physicians, advanced health practitioners, nurses, social workers, and case managers) may alert the PI or research study staff of potentially eligible patients based on the initial screen. The research team member will then determine eligibility as described below.

The PI Dr. Raven, research fellow Dr. Murphy or study staff (the research case manager) can all determine study eligibility. Initial eligibility will be determined based on chart review during the time of an ED visit. During study hours, the above mentioned faculty and staff will examine the

ED trackboard to determine if any patients currently in the ED at UCSF have made at least 4 ED visits in the past 12 months to UCSF or a combination of UCSF, ZSFG, or other hospitals based on shared data in our emergency department information exchange platform. If an individual is determined to be eligible based on these criteria, the faculty or study staff will review the chart for the most recent lab results including liver function tests (AST, ALT), platelets, and urine or serum pregnancy tests and urine toxicology testing specifically the presence of opioids including fentanyl (see exclusion criteria for specific cut off values). They will also review the past medical history and allergies in the electronic medical record to determine if the patient has cirrhosis or a document allergy to naltrexone or inactive ingredients contained in naltrexone XR. When a patient is determined to meet criteria inclusion by electronic record review, a study staff member will discuss the case with the ED provider caring for the patient to confirm the patient is willing to be approached, is clinically sober, and medically stable. The ED provider will then introduce the patient to the research staff who will discuss the study with the patient. The research staff member will assess the patient's willingness to participate. If a patient expresses interest in participating the research staff member will confirm the accuracy of information obtained from the medical record review that pertains to inclusion and exclusion criteria. If no discrepancies are found the research team member describe the study in detail and will perform a capacity assessment using the University of California San Diego Brief Assessment of Capacity to Consent to Research (UBACC) if there are any concerns about the participant's capacity to consent, such as ongoing alcohol or drug intoxication or withdrawal.

Capacity Assessment:

The UBACC is a validated 10-item questionnaire used previously in this population [16,17]. It rates the basic elements of capacity (understanding, appreciation, reasoning, and ability to express a choice) to identify subjects with questionable capacity to consent to a specified research project. Administration of the UBACC will occur after informing the patient about the study. The consenter will review each page of the informed consent document with the patient, pausing to reassess comprehension throughout the process. Then they will administer the UBACC. Once the patient's understanding is confirmed by the UBACC, the consenter will request the patient's signature and provide the patient with a copy of the signed consent document. If the consenter doubts the patient's comprehension of the study procedures the patient will not be enrolled at that time, but may be eligible in the future. Once capacity is established the patient will be asked to provide informed consent.

Consent:

Patients deemed to be eligible for enrollment after electronic record review may be approached by a member of the research team to assess willingness to participate. For patients interested in participating consent will occur only after the patient is clinically sober as judged by the treating ED provider and their capacity to consent has been established by the consenter, using the UBACC if necessary. The consenter will provide patients with information about the study, including risks and benefits of treatment with extended release naltrexone both verbally and in print. If the patient wishes to enroll in the study they will be consented by a member of the research team (research case manager, PI, research fellow) and sign the consent document.

With the exception of the research case manager, all members of the research team are practicing Emergency Medicine Physicians who frequently obtain informed consent for a variety of procedures performed while caring for patients in the emergency department and have completed required human subjects research training.

The research case manager will be trained in obtaining informed consent by completing the required training modules for UCSF human subjects researchers and be trained in the teach back method and use of the UBACC by the study PI, Dr. Raven.

Enrollment:

Patients identified as frequent ED users will undergo an alcohol use disorder screening conducted by the research case manager, PI, or research fellow using a validated screening tool, the Alcohol Use Disorder Identification Test (AUDIT) which constitutes the screening component of SBIRT. The AUDIT places patients into one of four categories: low risk, risky, harmful, and severe. Brief intervention and pharmacotherapy have previously been shown to be most effective in those with harmful or severe use disorders [12]. Patients found to have at least harmful alcohol use based on the screening will be offered enrollment (AUDIT score ≥ 8). Enrollees will have blood and urine samples collected to screen for active opiate use including fentanyl, platelet counts, pregnancy, or significant liver disease (see exclusion criteria below) if no results are available in EHR. With the exception of urine pregnancy screening these tests are done as part of the routine care of emergency department patients with alcohol use disorders who are interested in accessing treatment. The results will be used to confirm inclusion/exclusion criteria are met. Patients meeting all criteria will be enrolled into the study and will receive 380mg of extended-release naltrexone as an intramuscular injection in the ED.

Naltrexone training and administration:

Study staff will compose and send e-mail before the start of the study, with input from UCSF ED nursing leadership, to all ED RNs informing of the intent and responsibilities of the study. Subsequently, during RN sign out (twice daily at 7am and 7pm) study staff will remind ED RNs about the study protocol to ensure as much staff as possible is aware of RN involvement and responsibilities. The shift-change information session will be performed for a two week run in period to assure all RNs are oriented.

The ED is staffed by clinical pharmacists 12-16 hours per day and will be present during study enrollment hours. They will be trained on the specifics of the study protocol by our Zlatan Coralic, an ED pharmacist at our Parnassus ED. RNs will be able to consult Zlatan or any of the other ED pharmacists on the specifics of medication procurement, administration, and monitoring during the study period. Similarly, ED resident physicians and attending physicians will be informed of the study protocol and will receive didactic teaching about physician involvement and responsibilities via email and during resident conference and the monthly Department of Emergency Medicine faculty meeting.

Medication storage and distribution:

We will work with UCSF Investigational Drug Storage (IDS) to store all drug doses. The initial dose will be given in UCSF ED and for all doses, we will create a study-specific link in our electronic medical record system (Apex) for order entry, which will link to the study supply. Our study team will verify consent prior to verification and the study consent to be uploaded into Apex. IDS will generate an Rx form that can be used to request the subsequent clinic or other community-based doses ("clinic supply) drug for an enrolled subject.

The clinic supply will be labeled for the subject and picked up from UCSF IDS by study staff for transport to clinic or community site for administration. The clinic supply will be given 7-day expiration at room temperature from time of dispensing per FDA labeling. (Store unopened kit at 2°C to 8°C (36°F to 46°F). Kit may be kept at room temperature of ≤25°C (77°F) for ≤7 days prior to use; do not freeze. Following reconstitution of the suspension, administer immediately) and the drug will be transported at ambient temperatures. Insulated cooler to be used if ambient temperature are expected to exceed 25C. If the clinic dose is not used, unused study drug will be returned to UCSF IDS for accountability and disposal.

Index ED visit:

The case manager will obtain baseline data using a HIPAA compliant database REDCap used for multiple ongoing research studies at UCSF. Baseline data will be collected for the purposes of the study and for ongoing case management including information on where the patient lives or stays (if unhoused), contact information (phone numbers, family member contacts, email, etc.) and preferred mode of communication. Those without cellphones who choose to enroll and who agree will be provided with a cell phone at the time of enrollment for the purposes of maintaining touch with research case manager and research team. We will track the rate of cell phone issuance, loss, and use for study purposes as one of our feasibility metrics. The case manager will also use REDCap to collect a detailed substance use history using validated questions from the Addiction Severity Index (ASI), and assess social, occupational, and psychological alcohol related problems using the Short Inventory of Problems (SIP-2R). Alcohol use will be quantified using the timeline follow back method [18,19].

Index visit follow up:

The research case manager and the patient will coordinate a follow-up plan for the next injection visit. ED social workers routinely refer patients to case management and other outpatient services including drug and alcohol treatment programs. The facilitation of referral to ongoing care by the study case manager will simply represent a new option for securing outpatient follow-up for enrolled patients. This coordination of follow-up care will be outlined in the informed consent document and explained as a part of study enrollment.
Prior to leaving the ED after the index visit the research case manager will provide the patient with a medical bracelet or wallet card that identifies them as study participant using extended release naltrexone and provides the contact information for the PI and research case manager.

The medical bracelet or wallet card will alert providers that opiate dosing adjustments may be necessary to adequately treat acute pain should the patient require treatment during the study period. It will provide information about the added precautions necessary should that patient require opioid pain management. Specifically, as the amount of opioid required to achieve adequate analgesia may be increased any resulting respiratory depression may be deeper and more prolonged. Therefore a fast acting agent is preferred and the amount of opioid analgesic should be titrated to the clinical effect in a setting equipped for cardiopulmonary resuscitation. The PI will be available by phone for emergency consultation at any time.

Visit 2-3 study procedures:

Patients will receive a monthly intramuscular injection of extended release naltrexone for up to 3 consecutive months during visits for which the research case manager will outreach to the participants in the community. Injections will be administered in an outpatient setting by an addiction community provider familiar with XR-Naltrexone, or in the UCSF ED depending on patient preference. A 20-dollar gift card incentive will be used to encourage follow-up at the time of each injection. We will follow participants for 12 months from the time of enrollment (an additional 9 months after the final dose of XR-NTX administered on behalf of the study). Specimens for alcohol biomarker testing will be collected at follow up visits.

At each of the monthly follow up visits we will collect data on a) feasibility measures and b) study outcomes. During the follow-up period, the research case manager will track all participants and we will continue to collect data on study outcomes using REDCap including ED and inpatient hospital use, substance use, readiness to change, and engagement in substance use recovery/rehabilitation via community treatment programs, as well as subsequent doses of XR-Naltrexone administered. This data will be collected by administering the same validated questionnaires used in the index visit (AUDIT, ASI, SIP-2R). The PI and research fellow will also query the EDIE system and UCSF EHR monthly in order to identify any emergency department visits that could be related to the study procedures.

Follow up procedures after visit 3:

Following completion of the 3rd injection visit the patient will no longer receive XR-Naltrexone through the study. They will be encouraged to continue engaging with other community health providers to continue treatment, but are not required to do so. During the 9 months after the final injection visit the patient will contacted by phone approximately once a month by a member of the research team to collect outcome data as well as to discuss any ongoing treatment or changes in their health that occurred after the completion of the treatment period. At the end of the 12 month study period a data analyst will conduct a final review of the EHR and EDIE network to complete the collection of outcome data.

Case management services between study visits 1-3:
Between injection visits, the research case manager will be available to participants to assist with their needs including being connected to longer term case management services, connection with a primary care provider, or other services they may need related to food, clothing, and shelter. If participants who have chosen to follow up with community providers are having difficulty

making appointment, for example because they cannot find transportation, the research case manager can facilitate transportation to appointment. Participants can also choose to switch from following up in the UCSF ED to community providers of XR-NTX at any time. In such cases, the research case manager will coordinate referral to an alternative provider in San Francisco who can administer XR-NTX. Participants will be able to contact the study case manager by phone or meet in person depending on the case manger's availability.

Transition to ongoing care:

Patients who wishes to receive treatment with XR-Naltrexone after completing their 3 injections or after dropping out of the study will have the following options:

1. If the patient has been receiving injections during the study from a community provider they may continue treatment after the 3rd injection or choosing to drop out of the study.

2. If the patient has been receiving injections during the study in the UCSF ED they can be referred to a community site that administers XR-Naltrexone to establish treatment.

Handling of missed injection visits:

Patients who miss scheduled follow up injection visits will be contacted and asked to reschedule their injection visit as soon as possible. If they are able to reschedule within 2 weeks then no changes to study procedure are necessary. If they are able to reschedule within 2-4 weeks then they will be asked if they have used any opiates (including fentanyl) in the past 7 days. If they have not used opiates in the past 7 days then they will resume treatment, provided they are not endorsing any signs or symptoms of liver injury. If they endorse signs or symptoms of liver injury they will undergo screening as outlined above. If they endorse using opiates then they will not be allowed to resume treatment through the study. If a patient is unable to reschedule a missed injection appointment within one month they will not be allowed to continue in the study. If a patient is unable to resume treatment through the study then they will be provided with alternative follow up options (see transition to ongoing care).

Participant Payment:

A 20-dollar gift card incentive will be used to encourage attendance at the 6 monthly follow up visits required for XR-Naltrexone injections. Gift cards will be given at each of the six visits. The total value of gift cards available to each participant during the study period is $120.00. Gift cards will be issued for locations that do not sell alcohol (e.g. Starbucks coffee).

Study Subjects:

The target population is patients with frequent ED visits for alcohol related complaints who may benefit from ED-initiated XR-NTX. The accessible population is all people in the San Francisco Bay Area presenting to the ED with an alcohol related complaint. The study sample will be adult

patients presenting to the UCSF ED with active hazardous or high risk alcohol use and ≥4 ED visits in the past 12 months for alcohol related complaints.

Inclusion Criteria:
- Age ≥ 21
- AUDIT score ≥ 8
- Frequent emergency department visits, defined as: At least 3 emergency department visits for in the past 12 months, including the index visit.

Exclusion Criteria:
- Opioid use: currently receiving opioid analgesics, self-report of opioid use in past 7 days, current physiologic opioid dependence, patients in acute opioid withdrawal, urine toxicology screen positive for opiates including fentanyl
- History of hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent
- LFTs > 5x upper limit of normal or known cirrhosis
- Platelets less than 100,000 per cubic mm
- Acute condition at the time of enrollment that necessitates medical therapy with opioids
- Pregnant
- Incarcerated

Management of acute alcohol withdrawal:
XR-NTX is not a treatment for acute alcohol withdrawal. Acute alcohol withdrawal management will be left to the discretion of the treating physician.

Patients admitted to the hospital:

Hospital admission will not exclude an individual from study participation. The study medication will be delivered in the ED and the research case manager will follow the patient while he/she is an inpatient, and coordinate a follow-up plan with the admitting team at the time of hospital discharge.

III. Safety:

Adverse Events:
Serious adverse events have been reported to occur in ~5% of those treated with XR-NTX, which is similar to placebo [15]. Adverse events tend to be mild or moderate, with injection site pain, nausea, headache and fatigue being the most frequent.

The research case manager will collect information about adverse events at each monthly follow up visit and enter the data into RedCap data collection forms. Any unanticipated problems related to the study activities identified by the research team will be entered into the RedCap form as well. This data will be reviewed quarterly by the PI, who will determine if the event was expected, the severity of the event, and the likelihood that the event was related to the research study activities. Any serious adverse events will be reported to the PI immediately by the

research case manager, or any member of the research team who identifies a serious adverse event. The PI will report all serious adverse events resulting in death or possible life threatening events to the UCSF IRB immediately. All other adverse and unexpected events will be reported using the iRIS adverse event reporting forms within 5 business days of the PI becoming aware of the event.

Risks and risk minimization strategy:

Injection site pain, mild swelling, and possible ecchymosis are possible. The smallest acceptable needle size will be used and patients will be treated with non-narcotic oral analgesics as needed for bothersome injection site pain

XR-Naltrexone carries the risk of inducing opiate withdrawal in patients with opiate dependance. Urine drug screening and direct questioning about opiate usage will be used to exclude any patients with possible active opiate use disorders.

XR-Naltrexone is an mu-opioid receptor antagonist and thus may limit the analgesic efficacy of these medications should the patient require them for an unexpected acute medical or surgical condition. The antagonist effect can be overcome by increasing the dose of opioid analgesic. This confers a theoretical increased risk of respiratory depression. Participants will be provided with a medical bracelet and/or wallet card that carries relevant clinical information for providers as well as contact information for the PI and research team (see previous description under Index ED visit)

XR-Naltrexone carries a risk of drug induced hepatitis. Patients will be screened with liver function tests, questioned about medical history of liver disease, and have their medical record reviewed by the emergency medicine provider to screen for history of liver disease. Patients with cirrhosis or aminotransferase levels (AST, ALT) greater than 5x the upper limit of normal will be excluded. Participants will be questioned at subsequent XR- NTX administration visits about signs and symptoms of liver injury (upper abdominal pain, abdominal bloating, vomiting, yellowing of the skin or eyes, severe fatigue/weakness, joint and muscle pain). Answers to these questions will be reviewed weekly by the PI and clinical research fellow. If the PI and/or fellow believe the participant is exhibiting evidence of liver injury, they will arrange a follow up visit at the UCSF ED within one week. At that visit if the PI or fellow feels there is sufficient clinical concern for liver injury, then laboratory testing of liver function will be conducted during the visit. Any liver function testing that occurs as a result of the PI/fellow's concern for liver injury will be considered research specific testing and outside routine clinical care. The results of any laboratory tests done to evaluate for XR-NTX induced organ injury will be followed up by the PI or clinical research fellow. Subsequent injections of XR-NTX will not be given until the PI/clinical fellow have the results and confirmed that it is safe for the patient to continue treatment. If the liver aminotransferase concentrations rise to >5 times the upper limit of normal the study medication will be discontinued and the aminotransferases will be repeated in one week. If on repeat testing the amiotransferase elevation is again above 5 times the upper limit of normal the patient will be referred for Hepatology evaluation.

XR-Naltrexone is a deep intramuscular injection and additionally carries some risk of lowering platelet counts, typically by less than 20,000 per cubic mm. Patients with platelet counts below 100,000 per cubic mm. will be excluded in order to minimize the risk of bleeding.

As with any medication, XR-Naltrexone intramuscular injection carries a risk of allergic reactions including anaphylaxis. Patients with known allergy to naltrexone or any of the inactive ingredients of the injection will be excluded.

Data collected for this study includes details about alcohol and recreational drug use as well as information about employment and housing status. These topics may be sensitive to discuss, but are part of routine medical interviewing. Information collected by the research team will be take place in a private room and data stored securely (see data management plan).

No EDs in San Francisco administer Naltrexone, so there is no concern that a patient will receive extra doses during ED visits at locations other than UCSF. There are community sites, such as the San Francisco sobering center, SF street medicine and Health Right 360, where XR-Naltrexone is available and is administered to patients. These community sites are key stakeholders in the treatment of patients with AUD. One of the aims of this study is to establish a robust referral network for ongoing treatment of AUD once patients are discharged from the hospital/ED by mobilizing key stakeholders. We will coordinate with leadership and staff of community organizations that treat AUD throughout the study timeframe by forming a stakeholder committee that includes representatives from SF Street medicine, Health Right 360, and UCSF providers about both facilitators of and barriers to continuity of care after the initial ED visit and throughout the study. The committee with also serve as a venue for stakeholders to express any safety concerns, and will review any adverse events. The committee will meet quarterly and will record meeting proceedings and create a meeting summary.

Risk/Benefit balance:

XR-Naltrexone is FDA approved for the treatment of alcohol use disorders and has an excellent established safety profile. The serious adverse drug event rates are low and the drug is generally well tolerated. Based on available evidence, it is the most effective pharmacotherapy for alcohol use disorders. The benefits to participants of receiving a safe, established, effective treatment for their alcohol use disorder include reduction in total alcohol consumed, reduction in heavy drinking days, and increased success with achieving sobriety if desired. Based on current research literature, reduced days of heavy drinking and total alcohol use can be reasonably expected to lower the risk of alcohol related disease and alcohol related trauma. These are associated with significant cost, both personal and financial, to both patients and society.

IV. Analysis, Measurements, and Outcomes:

Because this is a feasibility study, primary outcomes of interest are recruitment (consent) rate, time required to complete initial tele-medicine assessment in the ED, time needed to administer XR-NTX in the ED, total ED length of stay, time to first follow up after the initial ED encounter, number of cell phones issued by the study, retention and follow up rates over the 3-month study

period, retention rate with other providers in San Francisco, number of doses of XR-NTX received during the study period and intervals between doses, and barriers to and facilitators of follow-up after the initial ED visit.

We will also collect pilot data on the following for statistical analysis:

Predictor Variable: Multi-modal treatment with Extended Release Naltrexone and case management

Primary Outcome: Change in the number of Emergency Department visits for alcohol-related complaints. [(# of ED visits for alcohol related complaint in 12 months after enrollment) - (# of ED visits for alcohol related complaint in 12 months before enrollment)].

Secondary Outcomes: number of standard alcoholic drinks consumed per week, number of days of heavy drinking, overall substance use severity (change in AUDIT score), change in alcohol-related social/occupational/psychological problems identified on SIP-2R, change in PEth, and change in urine ethyl glucuronide

Cost analysis: This study will not provide precise estimates of efficacy or costs. However, we will use our results to perform a basic cost analysis to guide future research. We will estimate: overall cost and cost per patient (medications, case management, follow-up visits), cost per avoided ED visit, cost per avoided hospitalization, program cost vs expected medical cost saved. All costs will be estimated at the societal perspective

Potential confounding variables or covariates, justifications:

There are several potential confounders which we will measure such as number of doses of XR-NTX received, willingness to change, engagement in other, baseline substance use severity, housing status, psychiatric and medical comorbidity, and basic demographic variables such as age and sex. The primary strategy employed to combat these cofounders is the selection of the primary outcome. Since the outcome is a change from the patient's baseline ED usage from the prior year each patient serves as their own control. Thus they are matched for many of the possible confounders.

The risk of bias is substantial given that all enrollees are to be treated with XR-NRT and the study is not randomized or blinded and the population of interest is at high risk of being lost to follow up. We intend to conduct both an intention to treat analysis and a per protocol analysis, though our sample size may limit the utility of this approach. We will employ an independent data analyst to collect the ED visit counts and perform the final statistical analysis.

Statistical issues:

Statistical Test: Paired T Test

Hypothesis:

ED initiated Treatment of alcohol use disorders with multi-modal therapy reduces alcohol related ED visits in patients with frequent ED visits for alcohol related complaints

Sample Size:
We will enroll 25 patients. As a feasibility study our sample size was chosen as it represents a reasonable patient load for a single case manager. Because this population is difficult to retain in treatment, we anticipate the drop-out rate will be significant. Patients who drop out of the study (either withdraw or are lost to follow up) will be replaced with new enrollees until 25 patients have been recruited into the study. The goal of this practice is to maximize the benefit to the patient population, avoid wasting donate study medication, and to allow the research team to optimize recruitment and retention strategies.

Last year 42 patients presented to the UCSF Emergency Department at least 4 times for an alcohol related complaint. Of this group the mean number of visits was 8.49 with a SD of 8.58. The median number of visits was 6. The number of visits ranged from 4-47. After excluding 2 outliers (40 and 47 visits, each > 3SD above the mean) the mean was 6.78 visits with a SD of 3.5 visits.
We estimate a standardized effect size of 0.584 would represent 2-5 emergency visits for alcohol related complaints. This equates to a 29-59% reduction in ED utilization, which is clinically relevant.

Data management plan:

The research case manager will use a tablet device to enter data into data entry forms in REDCap. The research case manager will also maintain a back-end Microsoft Access database. The REDCap data collection system is secure will be accessible only to members of the study team. The back-end Access database will be maintained on MyResearch in a folder accessible only to members of the study team. REDCap and MyResearch are on secure servers and are backed up regularly. When data are exported to STATA for statistical analysis, patients will be identified by a SubjectID that has no meaning external to the database. No dates will be exported.

Interim analysis:

We will conduct a qualitative analysis after 10 enrolled patients to
assess **enrollment** (enrollment rate, number of patients who do not meet inclusion criteria, unanticipated barriers to enrollment), **retention** (study retention rate, unanticipated barriers to retention, proportion of follow up visits in ED vs at patient's home or in the community), and adverse events that might be related to the study at that time including adverse reactions to the study drug. We do not anticipate adverse events occurring as a result of this study, because of the safety profile of the study drug and the fact that we are offering new, additional services to assist patients with treatment for alcohol use disorder, which are low-risk activities.

V. Personnel, resources, and partnerships:

UCSF will provide a full-time research fellow (board eligible Emergency Medicine physician), as well as other board certified Emergency Medicine physicians, RNs, and pharmacists, to assist with screening and enrolling patients, administering and storing medication, coordinate follow up, and perform data analysis.

Procedures other than injection of the study drug carried out as part of routine care during the index visit and with community healthcare providers services occurring after the index visit will be charged to the participant's insurance.

The cost of procedures done for research purposes only including urine drug screening, urine fentanyl screening, and repeat liver function testing for participants with suspected liver injury will be paid for by the study.

The study will pay for all doses of the study drug administered as part of this study (up to 3 per participant).

VI. Brief Proposed Timeline:

- May-July 2019- Submit for IRB approval and grant proposals
- October 2019-December 2019 hiring and training of research case manager and Emergency staff
- March 2020-June 2021 enrollment and data collection period
- June 2021-August 2021- data analysis
- September 2021- Begin writing manuscripts, submitting abstracts, developing proposal for follow up randomized control trial

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