Pilot Test of a Substance Use Treatment and Recovery Team (START) for Medical Inpatients with Opioid and Alcohol Use Disorders

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PROTOCOL SUMMARY

Purpose and Knowledge to be Gained	• The purpose the research is to conduct a pilot test of a substance use treatment and recovery team (START) for medical inpatients with opioid and alcohol use disorders • If the aims of the research are achieved, we hope to improve Medication-Assisted-Treatment (MAT) initiation and linkage to follow-up care and clinical outcomes, and, ultimately, reduce 90-day readmission rates for inpatients with OAUDs
Research Procedures	The primary research procedures are • Baseline interview with patient • 1-month follow-up interview with patient • Provider interviews
Subject Population	• Inpatients at CSMC 18 or older who screen positive for moderate to severe OAUDs
Duration	• The study includes 2 visits (Baseline interview, 1-month follow-up interview). • The total study duration is 1 month

GENERAL INFORMATION

CSMC Co-Investigators	Waguih Ishak, MD Teryl Nuckols, MD Bradley Rosen, MD Rebecca Hedrick, MD Responsibilities include consenting of subjects and delivery of intervention.
Sponsor/Funder	NIDA (National Institute on Drug Abuse)
Collaborating Institutions Involved in the Research	Allison Ober, MSW, PhD, Behavioral Scientist (PI at this site) RAND Corporation, 1776 Main Street, Santa Monica, CA 90407; 310-393-0411 ext. 6639, No research activities will be conducted at this site. All research activities will be conducted at CSMC.

1.0 BACKGROUND, RATIONALE

- There is a large unmet need for substance-use disorder (SUD) treatment in the U.S. In 2015, 20.4 million adults in the U.S. (8.4 % of all adults) needed treatment for an illicit drug or alcohol use problem; of these, 18.1 million did not receive it. [1] The consequences of untreated SUDs are enormous: premature death, billions of dollars in avoidable health care and criminal justice costs, decreased economic productivity, individual suffering, and long-term harmful effects on families and communities. [2-6] Opioid and alcohol use disorders (OAUDs) are of particular concern because of high rates of morbidity, mortality, hospitalizations and readmissions, [7-10] and because of the increasing incidence of opioid-use disorders (OUD) and associated consequences from the non-medical use of prescription opioids.[11] Medication-Assisted-Treatment (MAT) is available for OAUDs, but less than a quarter of publicly funded treatment programs[12] and fewer than half of private sector treatment programs offer MAT.
- Despite high prevalence, few inpatients with OAUDs receive evidence-based treatments while in the hospital.[13-15] Most physicians and other providers in acute hospital settings are not trained to assess or manage patients with OAUDs, [16] contributing to low rates of OAUD identification

and treatment initiation.[17-21] Pharmacotherapies to address AUDs (acamprosate, oral and injectable naltrexone, and disulfiram) and OUDs (buprenorphine/naloxone, methadone, and oral and injectable naltrexone) are effective for use across medical settings[22-28] but are seldom administered in hospitals or recommended as part of follow-up care. [29,30] New research demonstrates that initiating buprenorphine/naloxone in the emergency department with follow-up in primary care for patients with OUDs can increase SUD treatment entry and abstinence,[31] and that inpatients with complications from OUDs are amenable to initiating medication in the hospital and being linked with follow-up care.[32] The current standard of care for hospitalized patients with OAUDs is screening, brief intervention outcomes for people with moderate to severe AUDs or for people with OUDs.[33,34,16,35] Two possible reasons are that SBIRT does not incorporate MAT initiation or address the needs of those needing more than a brief intervention prior to referral. Barriers to initiating MAT for hospitalized patients may include lack of OAUD treatment expertise on the medical team and absence of a patient-centered, measurement- and population-based system for assessing and treating patients with OAUDs. Embedding a collaborative care team (START) for inpatients with OAUDs within an existing hospital consultation-liaison psychiatry service could improve MAT initiation and linkage to follow-up care and clinical outcomes, and, ultimately, reduce 90-day readmission rates.

- Collaborative care is a systematic approach to organizing and coordinating care for patients with complex conditions.[36] Based on the Chronic Care Model developed by Wagner et al.,[37] collaborative care addresses barriers to assessing and providing comprehensive, patient-centered care and leads to improved care and patient outcomes.[38,39] Collaborative care has four core attributes: (1) Team-driven: a behavioral health team is integrated into the medical team to provide coordinated care and develop patient-centered care plans; (2) Population-focused: the team provides care to a defined group of patients; (3) Measurement-based: The team 1 of 12 uses systematic, patient-reported measures to drive clinical decision-making; and (4) Evidence-based: the team facilitates use of evidence-based practices in the clinical setting.[40-43] Collaborative care approaches have enhanced integration of specialized care for depression and other chronic diseases into busy medical practices where providers do not have time or expertise to fully assess or manage care for patients with complex chronic conditions,[36] but they have not been tested for OAUDs in the inpatient setting. Moreover, recent research on the experience of medical inpatients identified with SUDs suggests the importance of access to MAT while in the hospital and coordinated care post-discharge.[44]

2.0 STUDY OBJECTIVES

Primary Objectives:

Test if embedding a collaborative care team called START the substance use treatment and recovery team (START) for inpatients with OAUDs within an existing hospital consultation-liaison psychiatry service could improve MAT initiation and linkage to follow-up care and clinical outcomes, and, ultimately, reduce 90-day readmission rates.

Secondary Objective:

In a larger study, subsequent to the pilot, we will test 90-day readmission rates and whether lower readmission rates are mediated by MAT initiation and linkage to follow-up care.

3.0 STUDY POPULATION

3.1 SELECTION OF THE STUDY POPULATION

CSMC inpatient population. Approximately 80 patients will be enrolled over the course of 5 months. Additionally, we will conduct semi-structured in-person or remote (telephone or

video) interviews with up to 10 physicians, 10 nurses, and 10 social workers from within the hospital who treat START patients during the pilot period, as well as up to 10 telephone interviews with follow-up providers who received patients referred from the hospital during the pilot period.

3.2 INCLUSION CRITERIA

1. Inpatient at CSMC
2. Age 18 and older
3. Screens positive for moderate to severe OAUDs based on the alcohol and opioid questions on the World Health Organization (WHO) Alcohol, Smoking, and Substance Involvement Screening test (ASSIST).[45] Patients with scores >10 for alcohol or >3 for opioid use will be eligible for the study
4. Speaks English as primary language
5. Willing to participate in, and able to provide contact information for, telephone follow-up calls and follow-up interview
6. Able to provide informed consent

3.3 EXCLUSION CRITERIA

1. Currently receiving FDA-approved medication treatment for an opioid or alcohol use disorder
2. Life expectancy of <6 months

3.4 SUBJECT SCREENING AND ENROLLMENT

- Data for screening will be procured using a daily data extract of potentially eligible subjects (variables include demographics, alcohol and/or opioid history and screenings).
- The Principal Investigator, Co-Investigators, and approved study staff will have access to these records.

3.5 SUBJECT RECRUITMENT

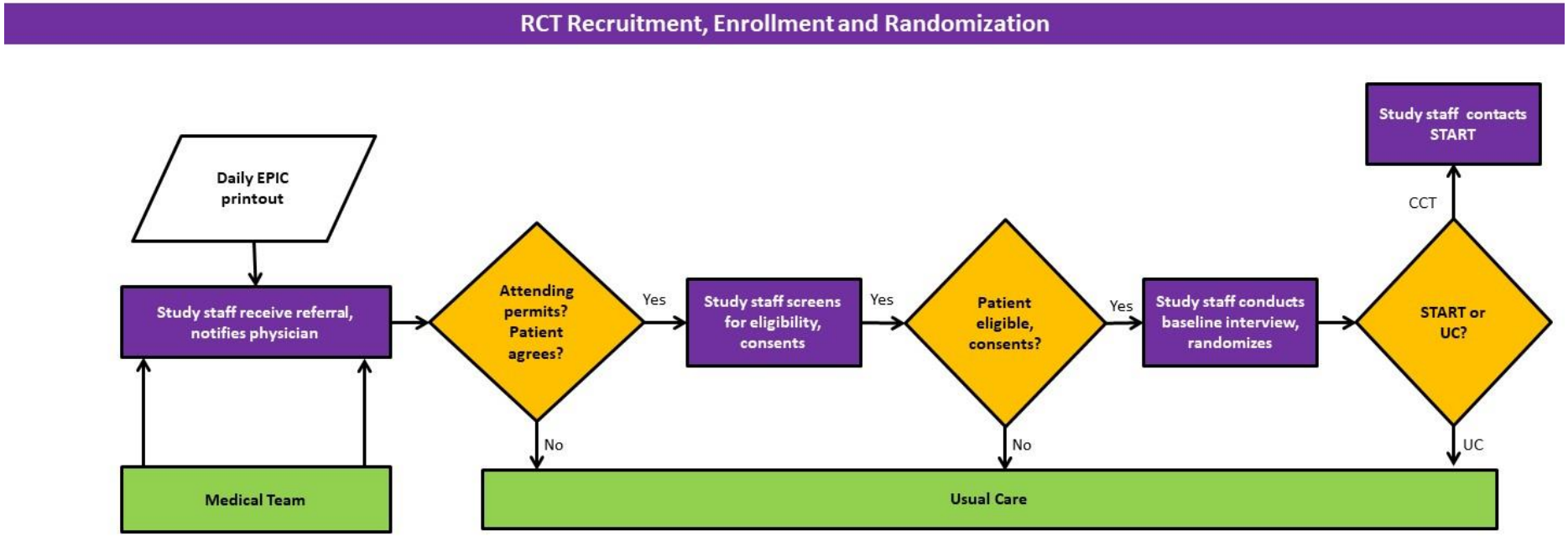
The study will recruit adults with moderate to severe OAUDs who are admitted to the inpatient medical center. Patients will be identified through physician referral, or through review of an existing daily EPIC workbench report of opioid and alcohol misuse (Daily Report). The approved CSMC study staff will identify patients with probable moderate-to-severe OAUD through a daily printout from EPIC or by direct provider referrals from physicians and social workers (see Figure 1 below).

- The CSMC approved study staff will identify patients with probable moderate-to-severe OAUD through a Daily Report or by direct provider Medical Staff referrals.
- Once a potential patient is identified, someone from the study team will contact the attending physician, briefly explain the study, and ask the physician for permission to contact the patient.
- If the attending physician agrees, the physician or someone from the medical team will explain the study to the patient and ask for their permission to be visited by study staff.
- Advertising and recruitment materials:
  For providers:
  - Study Physician Flyer
  - Physician Screening Card
  - Physician Recruitment Letter

For patients:

- Physician to Patient Letter (Dear Patient Letter) to be provided by the treating physicians to patients deemed eligible for the study.

Figure 1: Recruitment, Enrollment, and Randomization Diagram



4.0 STUDY DESIGN AND METHODS

- Eligibility screening - Assessments, demographics (conducted in person or remotely)
- Informed Consent, if eligible (to be obtained in person either on paper or electronically using an approved platform or remotely using an approved platform)
- Enrollment - the CSMC study staff will enroll consented, eligible patients.
- Baseline interview - after enrollment, the CSMC approved study staff will conduct an in-person or remote 30-40-minute baseline interview. Interview data will be recorded on a tablet or computer into a web-based survey system (REDCap). Patients will be compensated with a $50 Forte payment card (given in person or mailed).
- Randomization - following consent and the baseline interview, the CSMC approved study staff will randomize the patient to the START or UC arm using REDCap.
- All patients will be given patient education materials on alcohol and/or opioid use disorder, as well as harm reduction materials (OUD only). If the visit is remote, the research team will give these materials to a member of the medical team to deliver to the patient or place them in the patient's room.
- 1-month post discharge follow-up interview - the CSMC approved study staff will conduct a follow-up interview by telephone 1-month after the patient is discharged from the hospital. Patients will receive $50 loaded onto their existing Forte payment card for participation.

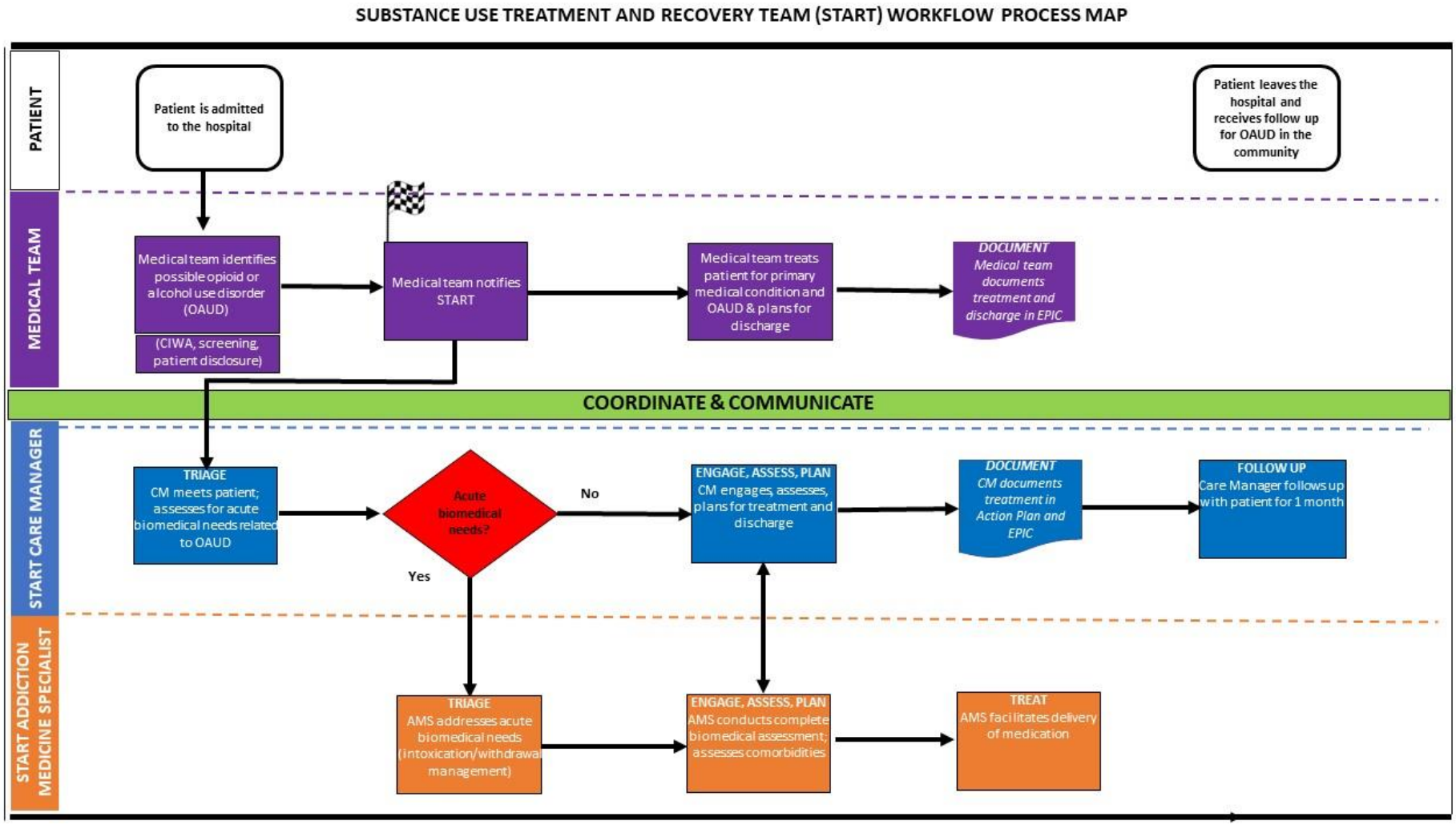
The components of the START workflow process are as follows (also shown in Figure 2):

1. Triage (Care Manager CM and Addiction Medicine Specialist AMS):
   The CM assesses the patient for acute biomedical needs related to the OAUD. The AMS addresses acute biomedical needs (e.g. facilitates withdrawal management).
2. Engage, assess, plan (CM and AMS) (conducted in person or remotely based on circumstances):
3. If there is not an urgent need for medical intervention or after the urgent medical need is addressed, the CM and/or AMS:
   - engages with the patient (CM and AMS)
   - conducts a diagnostic and biopsychosocial assessment (CM)
   - conducts a complete biomedical assessment and addresses comorbidities (AMS)
   - delivers the brief negotiated interview (BNI), an evidence-based intervention, to assess to increase readiness and develops a plan for initiating evidence-based treatment for OAUD (MAT) and/or psychosocial treatment) during and after the hospital stay (CM)
   - ensures the patient understands the follow-up plan and addresses barriers (CM).
4. Treat (AMS) The AMS:
   - facilitates MAT initiation
     - facilitates psychosocial treatment for the substance use disorder, if indicated and available.
5. Communicate and Coordinate (CM, AMS)
     - The CM and AMS communicate with each other to continue care through one-month (or more) after the patient is discharged.
     - The CM and AMS communicate with the patient and medical team, and, when appropriate, the patient's family and outpatient providers.
6. Follow-up (CM):

- The CM calls the patient once a week for 1 month after the patient is discharged from the hospital to assess whether the patient is following through with the discharge plan.
- The CM may also call outpatient providers to determine if the patient linked to care and has encountered barriers.

7. Monitor (AMS):
    - The AMS continues to monitor the patient after discharge through the CM's follow-up work.

Figure 2: START Workflow Diagram



INNOVATION

- This proposed study identifies the inpatient hospital stay as a new opportunity to initiate MAT and link patients with follow-up care for their OAUD. Hospitalization is an opportune time to initiate MAT and provide linkage to follow-up care for patients with either an OUD or AUD.[16] To our knowledge, no experimental studies have focused on initiating MAT and providing focused discharge planning and follow-up monitoring for hospitalized patients with either an AUD or OUD.
- The study offers a new model—a consultation-liaison service-based START—for improving care processes for hospitalized patients with OAUDs. Hospitals have extensive experience using care managers to improve in-hospital and follow-up care for several patient populations at high risk of readmission,[46,47] including acute medical patients,[48] and many have a consultation-liaison service to support the medical team with patients in need of behavioral health care. However, to our knowledge, there are no experimental studies of care management strategies in general or collaborative care models to improve outcomes for inpatients with OAUDs. Further, leveraging the existing consultation-liaison service is an innovative and generalizable approach to managing the large number of hospital inpatients with untreated OAUDs without burdening inpatient physicians and unit case managers who may not have the expertise or time to prescribe medications or resolve barriers to OAUD-focused discharge and follow-up. The consultation-liaison service-based START is a novel, comprehensive program for facilitating MAT initiation in the hospital and linking patients to follow-up care for two of the most common SUDs among inpatients.
- This study will provide several types of new knowledge:

  (1) Whether a START compared with usual care improves care for hospitalized patients with an OAUD. That is, whether START leads to improved initiation of medication and linkage to follow-up care for patients who are admitted to the hospital, either for a problem related to their OAUD or for another medical issue.

  (2) Whether a START compared with usual care reduces substance use.

  (3) Whether a START is feasible and acceptable with in the inpatient medical setting. These knowledge gains will provide invaluable, preliminary information on how to improve the quality of care for hospitalized patients with OAUD and on how to address an unmet need that has severe individual and societal consequences. The knowledge obtained in the study (and even more so in the larger, subsequent RCT) not only will benefit individual patients who participate in the study but also hospitals looking for a pragmatic and feasible way to improve OAUD care. On a societal level, providing a new way to identify and initiate treatment for patients with OAUD could fill a previous unmet need and bring down healthcare costs related to untreated OAUD. We believe that the long-term gains of the study, in terms of knowledge and substantive gains to the community, far exceed any risks for participants.

Table 2: Flowchart of Procedures

Research Procedures	Baseline visit	During course of hospital stay	1-month post-discharge
Eligibility	R		
Informed Consent	R		
Randomization	R		
Sociodemographic Data	R		
Mental health symptoms (PHQ-9, GAD 7); pain (PEG); substance use (WHO ASSIST, NSDUH) consequences of use (SIP-AD), service utilization (NSDUH, GAIN), stigma (SASS)	R		R
Satisfaction with START intervention[a]			R
Medication for alcohol or opioid use disorder [b]		S	
Therapy for alcohol or opioid use disorder [b]		S	
START Addiction Medicine Specialist (AMS) coordinates team-based care[c]		R	R
START Care Manager (CM)[c] coordinates team-based care		R	R

LEGEND
R = Research item/procedure done only for research purposes and covered by the study
S = Standard of care item/procedure that is part of regular care and billed to the patient/insurance

Footnotes:

a. Only for patients randomized to the START intervention arm of the study.
b. For both groups: Usual Care and Start intervention. Includes Brief Negotiated Interview and addiction focused discharge planning and follow-up.
c. The START intervention utilizes established standard-of-care services and procedures (care manager, addiction medicine specialist, medication treatment, therapy, etc.) and helps integrate them into the patient's care in a systematic way. It is this planned coordination and integration that are the intervention, not the services themselves.

- A list of written materials that will be part of the research is included in Appendices - section 8.0 below.

Behavioral Intervention
The START Manual with a full description of the behavioral intervention is provided in a separate document.

Surveys
- Survey methodology – Patient baseline surveys will be conducted in person or remotely by the approved study staff and responses entered directly into the REDCap database using a mobile device or computer. Patient follow-up surveys will be conducted by the approved study staff via telephone.
- Survey selection – validated surveys that are most relevant to the primary and secondary study outcomes and covariates.
- Surveys are available only in English – only subjects fluent in English will be enrolled.
- Surveys used are validated as listed in Table 2: Flowchart of Procedures.

5.0 DATA COLLECTION AND MANAGEMENT

5.1 DATA PROCUREMENT

- Recruitment information will be procured through physician referral, or through review of an existing daily EPIC workbench report* of opioid and alcohol misuse.
- Administrative outcomes will be procured through a monthly EPIC report.**
- Patient Baseline Survey Measures will be procured through patient interviews and will be recorded on a tablet or computer into a web-based survey system (REDCap).
- Some demographic and all diagnosis variables will be procured from eligibility screener conducted in REDCap. (Eligibility screener variables from all patients that screen will be used to assess study feasibility. Data from patients not enrolled in the study will be anonymous, i.e., they will not be linked to an MRN or any identifying information.)
- Patient Follow-up Survey Measures will be procured through a telephone interview by 1-month after the patient is discharged from the hospital. During collection of contact information at the baseline visit, patients may opt-in to receive text message reminders about this interview. These reminders will be sent via Twilio SMS through REDCap and will not contain any identifying information regarding the patient or the specific study.
- Provider Survey Measures will be procured through provider interviews and will be recorded and transcribed.

5.2 TIME PERIOD OF DATA UNDER REVIEW

- Data will be collected prospectively at the following timepoints: Baseline interview (patient); 1-month follow-up interview (patient); Follow-up interview (providers) to be collected post-intervention, in the 3-4 months after the last patient has completed the study.

- Consent forms will be retained at CSMC for seven years after completion of the study. Linking files and identifiable information will be destroyed within a year after study completion. A limited data set will be retained for five years after study completion to allow ample time for analysis and publication.

5.3 VARIABLES COLLECTED

- The following data points/variables will be collected:

Baseline Measures:

Variable	Source Document
Demographics • Age • Sex (Biological at Birth) • Gender (Identity) • Race/ethnicity • Housing status • Marital status • Income • Education	Demographics Form
Mental Health Symptoms • Depression • Anxiety	 PHQ-9 survey[51,52] GAD 7 survey[53-55]
Pain intensity and frequency	PEG[56]
Alcohol/Opioid Diagnosis	WHO ASSIST[57]
30-day Alcohol/Opioid Use: National Survey on Drug Use and Health 30-day use questions	Patient Survey (Adapted from NSDUH[58])
SUD Treatment Utilization	Patient Survey (Adapted from NSDUH[58])
Healthcare Utilization Related to SUD	Patient survey (Adapted from GAIN[59])
Employment	Patient Survey
Negative Consequences	Short Inventory of Problems Alcohol and Drugs (SIP-AD)[60]
Patient Experience of Stigma	Adapted from Grosso et al. 2019.[61] Questions to assess stigma experience.
Self- Stigma	Substance Abuse Stigma Scale (SASS)[62]
Receipt of START Intervention Components (Patient)	
START Intervention Received (Assessment, Engagement, Treatment/Discharge Planning); Length of Intervention (hours)	START Patient Registry
START Intervention Follow Up Received (Number of follow up calls made)	START Patient Registry

Follow-up Survey Measures (Patient)	
Mental Health Symptoms • Anxiety • Depression	PHQ-9 Survey[51,52] GAD 7 Survey[53-55]
30-day Alcohol/Opioid Use: National Survey on Drug Use and Health 30-day use questions	Patient Survey (Adapted from NSDUH[58])
SUD Treatment Utilization	Patient Survey (Adapted from NSDUH[58])
Healthcare Utilization Related to SUD	Patient survey (Adapted from GAIN[59])
Negative Consequences	Short Inventory of Problems Alcohol and Drugs (SIP-AD)[60]
Employment	Patient Survey
Patient Experience of Chronic Illness Care	PACIC[63]
Satisfaction with START intervention	Patient Survey
Provider Interviews (Provider)	
Acceptability/feasibility of START Intervention (Provider Interview Guide)	Provider Interview Guide

Outcome Measures:

Outcome	Measure, Assessment (Type of Variable)	Data Source
Primary Outcomes		
In-hospital MAT initiation	Received an OAUD MAT between admission and discharge (Binary)	CSMC admin data
Linkage to follow-up care	Received at least one visit post-discharge for MAT and/or psychosocial care for OAUD (Binary)	Appointment dates 1-month interview
Past 30-day frequency of heavy drinking days and/or all days of any opioid use	Days of use in the past 30 – Adapted National Survey of Drug Use and Health (NSDUH)[58] (Continuous)	Baseline interview 1-month interview
Secondary Exploratory Outcome		
90-day readmission to CSMC	Readmitted to CSMC up to 90-days after discharge during study period	CSMC admin data
Covariates		
Sociodemographics	Gender, sex, age, race/ethnicity, income, education, occupational status, marital status, zip code, homelessness in past six months.	Eligibility screener; Baseline interview
OAUD diagnosis	Moderate or Severe, ASSIST[45]	Eligibility screener
Pain Level	Pain level between 1-10; Pain interference level between 1-10, PEG[56] (Continuous)	Baseline interview 1-month interview
Primary and secondary diagnosis (inpatient stay)	Medical or mental health conditions as determined by the inpatient physician (Categorical)	CSMC admin data
Length of hospital stay	Number of days of hospital stay (Continuous)	CSMC admin data
Intervention “dose”; exposure	Amount time spent with patient (Continuous)	START Registry
Insurance	Payer name	CSMC admin data

***Daily EPIC Report Elements:**

- Demographics: Patient name; MRN; CSN; Sex; DOB
- Hospital encounter data: Hospital admission date and time; Inpatient admission date and location; Reason for admission; Admission diagnosis; Admitting physician; Attending provider
- Interpreter needed – exclusion criterion
- Patient PCP
- Homeless status
- DRGs (Diagnosis Related Group): ICD10 F10 (Alcohol Use Disorders); F11 (Opioid Use Disorders); F19 (Other psychoactive substance use); Overdose
- CIWA (Clinical Institute Withdrawal Assessment)
- Flowsheet Data: RN Alcohol and Drug Screening Questions
    - CIWA Assessment
    - CIWA Score
    - Current alcohol usage information
    - Current drug usage information
    - Withdrawal risks
- Blood alcohol test
- Urine toxicology screen
- Past Medication orders: Buprenorphine; Naloxone; Naltrexone; Disulfiram; Acamprosate; Topiramate
- Social History: Alcohol usage; Drug usage

****Monthly EPIC Report Elements**

- Demographics: MRN; Age; Age at encounter; Date of Birth; Sex; Race; Ethnicity; City; Zip Code
- Hospital encounter data: Type; Dates; Disposition; Attending provider; PCP; Psychiatry consult;
- Diagnoses during encounter: ICD 10s: F10-F19; Problem list items
- CIWA Protocol and measure information
- Inpatient and discharge medication information: Suboxone; Buprenorphine; Subutex; Methadone; Naltrexone; Naloxone; Disulfiram; Acamprosate; Topiramate; Gabapentin; Narcan; Naloxone.
- Lab results: AST; ALT; GGT; Urine Toxicology Screen; Blood Alcohol Level
- Flowsheet Data: RN Alcohol Screening Questions
- Social History: Tobacco usage; Alcohol usage; Drug usage
- Family history of substance use disorder
- Notes: Physician, Nursing and Allied health Professional documentation
- Hospital Utilization Metrics: Length of Stay; Inpatient admissions in prior 12 months; ED admissions in prior 12 months; Number of 30-day readmissions

5.4 SOURCE DOCUMENTS

- Paper source documents include the patient informed consent form, if collected on paper. All other patient information and data will be entered directly into the REDCap database via computer or mobile device.
- Provider information will be collected via in-person or telephone interview which will be recorded and transcribed. There will be a NDA in place with the transcriber. The

transcriber will not be a part of the study team. With guidance from the Office of Research Administration, all appropriate agreements will be in place prior to the transcriber having any access to research materials. The interviews will take place only after the last patient has completed the study.

5.5 DATA COLLECTION AND STORAGE

- Patient data will be collected in hard copy and electronically, as previously described. All provider interviews will be recorded using a digitally-encrypted recorder and transcribed. There will be a Non-Disclosure Agreement in place with the transcriber.
- Paper consent forms will be stored inside a locked cabinet or locked office. Electronic data will be stored in a secure REDCap database. Recorded interviews will be stored on a digitally-encrypted recorder. Transcribed interviews will be uploaded to a secure file transfer protocol (SFTP) program such as Kiteworks.
- Only members of the study team will have access to study data. A limited date set will be transferred to RAND (collaborating institution) using SFTP programs and may include hospital and study visit dates, patient age, and patient zip codes.
- Linking files and identifiable information will be destroyed within a year after study completion. A limited data set will be retained for five years after study completion to allow ample time for analysis and publication.

5.6 CONFIDENTIALITY AND SECURITY OF DATA

As with any study that involves substance use, an additional risk of the proposed study is breach of confidentiality. Although this would be very serious if it were to occur, breach of confidentiality is unlikely. The hospital already has ample protections in place to protect patient privacy and we will protect interview and administrative data by using password-protected computers and encrypted files.

Verbal permission to discuss a subject's study participation in front of family members will be obtained. Written permission to discuss a subject's condition with family will be obtained as part of the consent form prior to any dissemination of a subject's information.One or more investigators with access to identifiable data are not at Cedars-Sinai, and the study team will work with the Office of Research Administration to execute an appropriate Data Use Agreement before sharing the limited data set.

6.0 DATA AND SAFETY MONITORING

6.1DATA AND SAFETY MONITORING PLAN

I. Responsibility for Data Safeguarding

PI's Ober and Danovitch have joint responsibility for overseeing data safeguarding. They will train the designated CSMC approved study staff and project manager in data safeguarding techniques and will be responsible for the secure transmission of data from CSMC to secure research computers at RAND.

Additional oversight will be provided by our Data and Safety Monitoring Committee, consisting of Dr. Scott Irwin and Dr. Karl Wittnebel of CSMC. Drs. Ober and Danovitch will consult the committee as needed (e.g., to assess randomization issues, patterns of SAEs, etc.) during the course of the 6- 7- month data collection period. This committee is in lieu of a full DSMB due to the short data collection period and small patient size (N=80) of this

pilot study.

II. Risks associated with study participation

The collaborative care START intervention, called substance use treatment and recovery team (START) itself is inherently low-risk and therefore adverse events (AEs) experienced by study subjects are likely to be due to participants' underlying opioid and alcohol use disorders (OAUD) and other illnesses. Based on our prior research with this population, we expect depression and anxiety, medical illness and injury associated with OAUD, and, in some cases, unstable living conditions. Thus, adverse events may be related more to these underlying issues than to the START itself.

III. Handling of adverse events and serious adverse events and safety reporting

AEs and SAEs will be handled the same way in which hospital emergencies are handled. The hospital has several standard procedures in place for emotional or physical distress. If a client presents as suicidal, a social worker meets with him/her and then consults with a licensed mental health clinician (e.g., the CSMC PI Danovitch). The hospital will intervene as necessary, assess the client's state, and develop an appropriate plan. Clients with medical emergencies will be treated with usual hospital services. AEs occurring while the patient is hospitalized will be reported to PI Danovitch. AEs/SAEs occurring after discharge will be assess by the START psychiatrist or care manager and reported to PI Danovitch. Incident reports will be written within one business day. All adverse and serious adverse events will be reported to the IRB and NIH according to CSMC IRB and NIH policies and procedures guidelines.

IV. Availability of trained personnel and referral resources

Prior to data collection Dr. Ober (or designee) will conduct training for the designated CSMC approved study staff and CSMC project manager. The training will address good clinical research practices, including data safeguarding and confidentiality. The approved study staff will be trained to promote standardized and objective collection and recording of participant information. All research staff will complete a human subjects protection course.

V. Procedures for data quality assurance and protecting confidentiality of participant data

A. Types of data needing safeguarding

a. Patient contact information – name, telephone number, address, alternate contact information, entered on a tablet into an electronic record management system.
b. Consent forms. Patients will provide written consent to participate in the study.
c. Patient interview data – baseline and follow-up data from computer-assisted interview, entered on a tablet. (Appendix A).
d. CSMC patient administrative data. Patient data obtained from the hospital electronic medical record (EPIC). (Appendix A).

B. Data sensitivity. This study will collect participant names, phone numbers, addresses, and alternate contact information. These personal identifiers are necessary to obtain informed consent, to notify and contact participants about the follow-up interview and to conduct follow-up monitoring for patients in the START experimental arm of the study. A study ID connecting identifiable information with confidential data will be assigned to each participant. Signed consent forms and contact information will not be

stored in the same database forms as interview or administrative data.

C. Data safeguarding procedures

1. Patient contact information. CSMC will create a secure, encrypted and password-protected record management system using a secure, web-based system called Research Electronic Data Capture (REDCap) (see Appendix B). REDCap will allow the CSMC approved study staff to assign participant IDs to interviews, to maintain a link file between study ID and medical record number through a tablet that is securely linked to the web. REDCap is a secure, web-based tool used by CSMC researchers to build and manage surveys and databases. REDCap was developed at Vanderbilt University in Nashville, Tenn., and is available at no charge. It has become the primary standard for most Clinical and Translational Science Institutes (CTSIs), a national consortium of medical research institutions. The UCLA CTSI, to which Cedars-Sinai belongs, has helped support access to REDCap. There are two production websites — one that handles data that can be linked to an individual (known as protected health information, or PHI, under the federal HIPAA Privacy Rule) and another for non-patient-identified data. Research may build their own database after completing REDCap training or have the REDCap database developed at no charge. The link file will have read and write access restricted to approved study staff and the CSMC project manager.

2. Patient consent forms. If collected on paper, signed consent forms will be stored in a locked file cabinet at CSMC, separate from all study data.

3. Patient interview data.

a. Baseline. CSMC will also use REDCap to house the electronic computer-assisted patient interview. REDCap will allow the CSMC approved study staff to collect baseline data through a tablet that is securely linked to the web. The CSMC project manager will transmit baseline data (identifiable only by study ID) to RAND via secure file transfer protocol (SFTP) site. A program, such as PGP, that provides RSA-level security will be used to encrypt files. These data will not be shared with individuals who are not part of the project team, and no data shared with any members of the project study team will contain participant names.

b. 1-month follow-up. 1- month follow-up interview data will be collected by telephone, encrypted on a password-protected tablet that is connected to the survey through REDCap, only identified by study ID. Data will be collected by the CSMC approved study staff and entered directly into the secure tablet. The CSMC project manager will transmit baseline data (identifiable only by study ID) to RAND via secure file transfer protocol (SFTP) site. A program, such as PGP, that provides RSA-level security will be used to encrypt files. These data will not be shared with individuals who are not part of the project team, and no data shared with any members of the project study team will contain participant names.

4. CSMC administrative data. CSMC administrative data will be pulled from the electronic medical record system, EPIC, via a request submitted to the Research Informatics and Scientific Computing Core (RISCC). The CSMC project manager will replace all medical record numbers with study IDs. The CSMC project manager will then transmit the administrative data to RAND via the SSH File Transfer Protocol (SFTP) which is a network protocol that provides file access, file transfer, and file management functionalities over secure connection. It was designed by the Internet Engineering Task Force (IETF) as an extension of the Secure Shell protocol (SSH)

version 2.0 to provide secure file transfer capability.

D. Disclosure Risks

If private information about substance use is disclosed, possible psychological and social harm could result. However, the risk of such disclosure is rated as minimal given the safeguarding plan, and the magnitude of the harm were a breach of confidentiality to occur is likely to be little harm. We plan to minimize the possibility of a breach of confidentiality by instituting data safeguarding procedures as described above and maintaining identifiable data for only a limited period. We have several mechanisms in place to ensure data integrity and confidentiality. All data will be stored in a password-protected database. Paper files (i.e., consent forms) will be stored in locked file cabinets at CSMC, and electronic files will be stored in encrypted and password-protected files. Furthermore, electronic files transmitted to the RAND research team will be identified only by participant ID numbers. Identifying information linking patients to their study ID number will be retained in an encrypted and password protected record management system at CSMC. Confidentiality policies and procedures will be reviewed with all new staff.

E. Destruction of Data

Consent forms will be retained at CSMC for three years after completion of the study. Linking files and identifiable information will be destroyed within a year after study completion. A limited date set will be retained for five years after study completion to allow ample time for analysis and publication.

VI. Stopping rules for clinical trial

We will employ the following stopping rule for the clinical trial: if there is clear evidence of harm. Although we do not expect any physical harms or serious psychological harms beyond minimal distress, we have several procedures for monitoring harm from the intervention, including asking participants to contact us if they experience any adverse events, offering additional resources to those with very high levels of mental health symptoms and problem drinking or drug use, and providing resources after baseline and at follow-up. We do not expect there to be overwhelming evidence of the benefit of START during this pilot study due to the small sample size, but we will monitor this and stop the trial if this is indicated. We also do not expect that there will be no likelihood of demonstrated treatment benefit (futility) for the intervention as compared to control.

6.2 QUALITY CONTROL AND QUALITY ASSURANCE

- PI Ober and the quantitative analysis team will be responsible for evaluating data for adherence with the protocol and for accuracy in relation to source documents.
- PI Ober and the quantitative analysis team at RAND will be responsible for evaluating data quality. Reports generated from the database will provide a basis for ongoing monitoring of subject accrual and retention, as well as completeness of data. These will be used to identify and resolve problems that may arise. EPIC data will be exported and checked monthly during the study and survey data will be transmitted and checked monthly. Under the direction of a statistician, a quantitative analyst will check the data for completeness.

- Fidelity to intervention methods may be monitored and assessed by anonymous audio recording of up to 5% of intervention sessions of subjects randomized to the intervention arm. Patient confidentiality will be maintained by 1) uploading recordings to a secure Box folder; 2) allowing access to the Box folder by only one RAND study co-investigator (Karen Osilla, PhD); 3) ensuring recordings will be listened to in Box and not downloaded or saved; 4) ensuring recordings are deleted after listening. Verbal permission to record the session will be obtained from subjects prior to the start of recording.

7.0 STATISTICAL CONSIDERATIONS

7.1 STUDY OUTCOME MEASURES

Although we do not anticipate that this pilot study will be sufficiently powered to detect treatment effects, we will estimate models with the primary goals of learning the variance of the treatment effect estimator, which will be used in power calculations for future study design, and detecting areas of potential concern. This model would look for differences in outcomes between intervention (START) and control (UC) conditions, controlling for baseline measure of the outcome, where appropriate, using a generalized linear modeling-based framework. For dichotomous outcomes, we will employ a logistic regression model of the form Pr ($yyii$ = 1) =1/(1 + exp (−($\beta\beta$0 + $\beta\beta$1$xxii$ + $\beta\beta$2$zzii$))). Here i indexes individuals, $\beta\beta$0 represents the overall intercept, $xxii$ represents the treatment status of individual i, 0 for control, and 1 for intervention, and $\beta\beta$1 is the effect of the intervention. The variable $zzii$ represents the baseline measure and $\beta\beta$2 associated coefficient. Continuous outcomes will be modeled using linear regression. We will also perform exploratory analyses to investigate whether there are subgroups that may be responding better or worse to the intervention by interacting the covariates in Table 2 with the treatment indicator. Because there will be nearly as many potential covariates as observations, we will employ the "horseshoe prior" in Bayesian analyses of the outcome. [64] Qualitatively, this model starts from the assumption that most (if not all) of the covariates are unimportant for predicting the outcome, and attempts to learn which covariates are important. The intention is not so much to detect significant differences, but rather to highlight areas of potential concern. For example, if individuals with high pain levels respond less well to START recipients, this exploratory approach could draw attention to potential issues that could be optimized ahead of a future trial.

7.2 SAMPLE SIZE CONSIDERATIONS

- Due to the short 1-month duration of participation, subject withdrawal from the study is not anticipated to be significant.
- The proposed sample size (40/condition) is consistent with those recommended for small intervention tests in staged intervention development. [65] Based on administrative data for 54,466 hospitalizations in 2014, 1,037 hospitalizations involved implementation of CIWA protocols (indicating moderate to severe alcohol use) and 719 involved a diagnosis of an opioid use disorder. We expect that the majority (at least 1400) of these are unique patients, suggesting that about 117 patients per month will be identified through EPIC, with more referred directly by physicians and social workers. Although, we believe our enrollment rate of 16 per month over 5 months is realistic, if not conservative, this pilot provides the opportunity to confirm feasibility of this enrollment rate.

- It is not feasible to blind the staff to study condition because the study condition requires specific care by the START. While it is likely (and expected) that medical teams will treat patients in both the experimental and usual care (UC) conditions, patients in the START will have an enhanced experience because they (unlike patients in the UC condition) will be receiving START components designed to increase their readiness to take the medication and link to follow-up care. Moreover, the support provided by the START to medical teams for each START patient is the component that we hypothesize will take the burden off of the medical team and increase the likelihood of the patient receiving medication. Even as medical teams become more aware of medication for OAUD and perhaps increase prescribing, we hypothesize that patients whose medical teams receive support for their START patients will still be more likely to receive medication, even if medical teams are aware they can prescribe these medications. Thus, over time, while we might see increased medication initiation for patients in both study conditions, we still hypothesize statistically and clinically significant differences for patients in the CCT group. Nevertheless, we still plan to safeguard against any biases and effects of UC patients receiving the START. The research team will review electronic health record data to determine whether the START AMS or CM accidentally treated UC patients. Further, as part of this developmental study and pilot test, we are carefully assessing whether (and why) contamination occurs and, if it does, we will take additional steps to further safeguard the experimental condition in the future RCT.

8.0 APPENDICES (MAY BE FOUND AS SEPARATE DOCUMENTS AS LISTED BELOW)

8.1 RECRUITMENT AND ENROLLMENT

- ELIGIBILITY SCREENER
- ELIGIBILITY CHECKLIST
- STUDY PHYSICIAN FLYER
- PHYSICIAN SCREENING CARD
- PHYSICIAN RECRUITMENT LETTER
- PHYSICIAN TO PATIENT LETTER
- PATIENT & FAMILY EDUCATION MATERIALS

8.2 EVALUATION

- BASELINE SURVEY
- FOLLOW-UP SURVEY
- PROVIDER INTERVIEW INFORMATION SHEET
- PROVIDER INTERVIEW GUIDE

8.3 INTERVENTION

- START MANUAL & APPENDICES
  - APPENDIX A: START ROLES AND RESPONSIBILITIES TABLE
  - APPENDIX B: START ASSESSMENT FORM
  - APPENDIX C: REGISTRY INSTRUCTIONS
  - APPENDIX D: CARE MANAGER HANDOUTS
  - APPENDIX E: START REFERRAL RESOURCE GUIDE
  - APPENDIX F: MEDICATION ASSISTED TREATMENT START CARDS – ALCOHOL USE DISORDER
  - APPENDIX G: MEDICATION ASSISTED TREATMENT START CARDS – OPIOID USE DISORDER

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