Statistical Analysis Plan

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1 Abbreviations and Definitions

Table 1. Abbreviations and Definitions

AE	Adverse events
AMS	Addiction medicine specialist
ASSIST	Alcohol, Smoking, and Substance Involvement Screening test
BH	Baystate Health
BMC	Boston Medical Center
CC	Collaborative care
CCT	Collaborative care team
CL	Consultation liaison
CM	Care manager
CSMC	Cedars-Sinai Medical Center
ED	Emergency Department
EMR	Electronic medical record
FDA	United States Federal Drug Administration
GAIN	Global Appraisal of Individual Needs
GAD-7	Generalized anxiety disorder-7
IPW-MI	Inverse probability weighting and multiple imputation
MOUD	Medication(s) for opioid use disorder
NSDUH	National Survey on Drug Use and Health
OAMAT	Opinions about MAT
OUD	Opioid use disorder
PACIC	Patient assessment of chronic illness care
PCP	Primary care provider
PEG	Pain, Enjoyment of Life, and General Activity scale
PHQ-9	Patient Health Questionnaire-9
PROMIS	Patient-Reported Outcomes Measurement Information System
PTSD	Post-traumatic stress disorder
RCT	Randomized controlled trial
REDCap	Research Electronic Data Capture system
SAE	Severe adverse event
SAP	Statistical Analysis Plan
SAS	Statistical analysis system
SDCC	(UNM) Statistics and Data Coordinating Center
SRG	Survey Research Group
START	Substance Use Treatment and Recovery Team
UC	Usual Care
UNM	University of New Mexico

2 Introduction

The purpose of this study is to evaluate whether an intervention by an interdisciplinary collaborative care team (Substance Use Treatment and Recovery Team (START) intervention) compared with usual care for hospitalized patients with opioid use disorder (OUD) can increase initiation of medication for opioid use disorder (MOUD) and improve linkage to OUD-focused follow-up care. If the aims of the research are achieved, we hope to improve MOUD initiation and linkage to follow-up care as well as clinical outcomes, and, ultimately, create a generalizable, sustainable model of care to increase OUD treatment delivery and decrease the downstream effects of untreated OUD. If effective, this translational model also can be used to increase uptake of evidence-based practices for other substance use and associated behavioral health disorders.

3 Study Objectives and Endpoints

3.1 Study Objectives

3.1.1 Primary Objectives

3.1.1.1 Primary Objective 1: To test the effectiveness of the START intervention on MOUD initiation relative to usual care.

3.1.1.2 Primary Objective 2: To test the effectiveness of the START intervention on linkage with post-discharge OUD treatment relative to usual care.

3.1.2 Secondary Objectives

3.1.2.1 Secondary Objective 1: To test the effectiveness of the START intervention on addiction-focused discharge planning.

3.1.2.2 Secondary Objective 2: To test the effectiveness of the START intervention on MOUD engagement relative to usual care.

3.1.2.3 Secondary Objective 3: To test the effectiveness of the START intervention on linkage to medical care relative to usual care.

3.1.2.4 Secondary Objective 4: To test the effectiveness of the START intervention on self-reported days of opioid use relative to usual care.

3.1.3 Exploratory Objectives

3.2 Endpoints

The objectives described above will be measured with the following endpoints. Intervention arms are described in Section 4.2.

3.2.1 Primary Endpoints

Primary Endpoint 1: Proportion of patients in each arm who initiate MOUD prior to discharge, defined as use of any FDA-approved pharmacotherapy for OUD, including buprenorphine, naltrexone and methadone.

3.2.2 **Primary Endpoint 2:** Proportion of patients in each arm who attend at least one OUD-related care visit within 30 days of hospital discharge.

3.2.3 Secondary Endpoints

3.2.4 **Secondary Endpoint 1:** Proportion of patients in each arm with an after-hospital care plan that specifies a date and time for a post-discharge addiction care appointment.

3.2.5 **Secondary Endpoint 2:** Proportion of patients in each arm who initiate MOUD or continue

MOUD treatment within 30 days following hospital discharge.

3.2.6 **Secondary Endpoint 3:** Proportion of patients in each arm who complete at least one visit to an outpatient medical provider within 30 days of hospital discharge.

3.2.7 **Secondary Endpoint 4:** Days of opioid use in the past 30 days.

3.2.8 **Exploratory Endpoints**

4 Study Methods

4.1 General Study Design and Plan

This is a multisite, pragmatic randomized controlled trial (RCT) assessing the effectiveness of the START intervention (an interdisciplinary collaborative care team) for hospitalized patients with OUD as compared to usual care. Participants are inpatients at three medical hospitals in California, Massachusetts, and New Mexico. They must be 18 years or older, are admitted for any reason, and screen positive for moderate to severe OUD using the ASSIST. They are identified through provider referral and through a daily report produced from electronic medical records (EMR) at each site, pre-screened for potential eligibility, and then approached for screening by research coordinators. If eligible and interested, the participant is consented, completes the baseline interview, and is randomized to either the START intervention or usual care. Between 30- and 60-days following discharge, the participant is contacted by phone to complete a follow-up interview. See Figure 1 for the study CONSORT diagram. Primary and secondary outcomes measures are obtained from the EMR and from follow-up interviews.

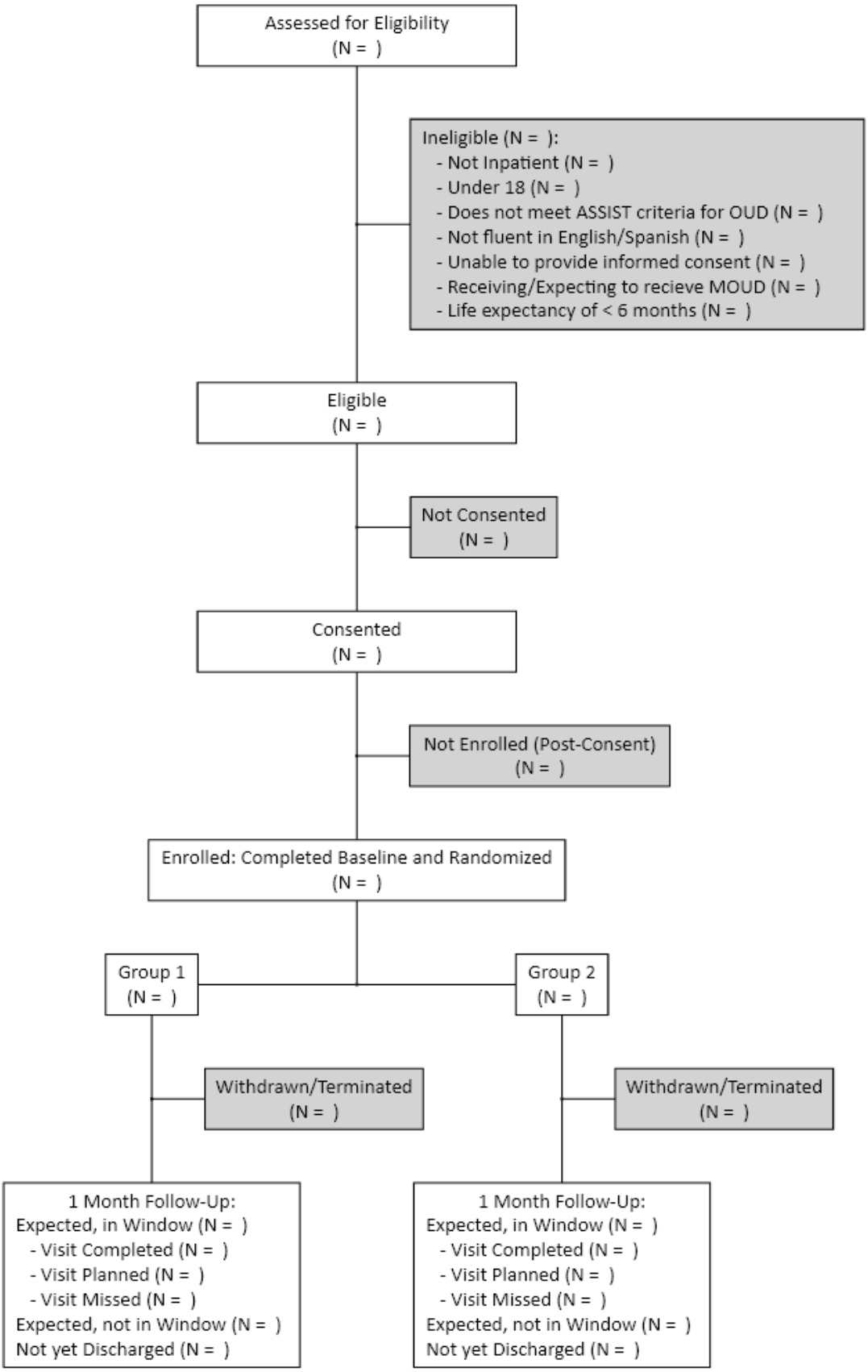
Each site has research coordinators who screen participants for eligibility, perform the consent and baseline interview, and randomize them to one of the two intervention arms. The RAND Survey Research Group (SRG) performs the 1-month phone follow-up interviews. All eligibility, baseline, and 1-month follow-up interview data are entered by the described site staff into the UNM instance of REDCap. The UNM Statistics and Data Coordinating Center (SDCC) is responsible for developing the REDCap databases, providing technical support to staff, and managing the data to ensure the quality of the data, and creating analytical data sets. Each site is responsible for obtaining EMR-based outcomes data from their EMR and sending it via approved, secure methods to the UNM SDCC. Enrollment was originally expected to last approximately 11 months, but has been extended to approximately 32 months due to the impact of the COVID-19 global pandemic and slower than expected enrollment.

4.2 Intervention Arms

4.2.1 **The START intervention arm** consists of an addiction medicine specialist (AMS) and a care manager (CM) who use evidence-based tools such as motivational interviewing and addiction-focused discharge planning to decrease barriers to MOUD and engage patients with post-discharge OUD care.

4.2.2 **UC** consists of each hospital's current practices for managing patients identified with OUD along with each patient enrolled in the study receiving MOUD education and referral information. We use UC as the comparator because there are no other evidence-based interventions for achieving our proposed outcomes. At CSMC, patients randomized to the UC study condition may receive a referral to the existing consultation liaison (CL) psychiatry service if the patient's medical team determines the need for a consult, or they will be treated and provided discharge planning directly by the medical team. At UNM and BMC hospitals, patients randomized to the UC study condition can be treated directly with MOUD and provided discharge planning by the medical team. At BMC Hospital, the referring physician has the option of contacting the standard psychiatric CL or addiction consult service for patients in the UC study condition, which will not include an AMS or CM. If the START AMS or CM at any hospital is approached by a member of the medical team for consultation on an OUD patient, they will refer them to the California Bridge

Figure 1. START CONSORT Diagram



Program Tools and Resources website None of the hospitals in this study currently employs a collaborative care team that consists of an AMS – CM team that uses a set of principles based on collaborative care along with evidence-based tools to support the medical team in intervening with patients with OUD and delivering for OUD treatment in the hospital and after discharge.

4.3 Study Population

4.3.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Admitted to an inpatient bed at Cedars-Sinai Medical Center (CSMC), University of New Mexico Hospital (UNM), or Baystate Health (BH)
- Age 18 and older
- Have a probable OUD diagnosis, defined by scores of >3 on the opioid section of the Alcohol, Smoking, and Substance Involvement Screening test (ASSIST)
- Speaks English or Spanish as primary language
- Able to provide informed consent

4.3.2 Exclusion Criteria

An individual who meets any of the following criteria is excluded from participation in this study:

- Currently receiving FDA-approved medication treatment for an opioid use disorder*
- <6 months life expectancy

*"Currently receiving medication" is defined as medications received by patient while in the hospital, as indicated by the EMR, medical team, or by patient self-report on the eligibility screener of taking the medication since their admission.

4.4 Randomization and Blinding

4.4.1 Randomization

Participants are randomized to either the START intervention or usual care. A stratified, block randomization design is used to stratify by site and prior MOUD exposure (yes/no), with randomly permuted block sizes of 2, 4, and 8. The intervention arm allocation was programmed in R 4.1 using the package blockrand[1] and outputted as a .CSV file for upload into REDCap's randomization module. Two allocation schedules have been generated: one for testing and a separate one for production. Research staff access their site-specific randomization module and enter which MOUD stratum the patient is in and the intervention arm assignment is displayed. Enrollment will be continuous with the goal of reaching the target sample size. Some sites may enroll more or less than the target for each arm. Prior MOUD exposure is defined as ever taken medications to treat an opioid use problem (specific medications are buprenorphine, buprenorphine/naloxone, methadone, naltrexone).

4.4.2 Blinding

The baseline interview occurs prior to randomization so research staff conducting baseline interviews are blind to study condition. Follow-up interviews are performed by RAND SRG research staff who initially will be blinded to study condition at the beginning of the interview, although blinding is broken during the course of the follow-up interview due to branching questions for START participants only.

4.5 Study Assessments

4.5.1 Schedule of Study Assessments

Table 2 displays the scheduled study assessments.

4.5.2 Visit Windows

Participants are randomized, and hence considered enrolled, following completion of consent

and the baseline interview. The 1-month follow-up assessment occurs within a 60-day window starting at 30 days post-discharge from hospital (i.e., between Day 30 to Day 90, with Baseline being Day 0).

Study staff will not attempt to contact a participant after their visit window has closed. If the 1-month follow-up visit is not completed by Day 90, they will be considered lost to follow-up.

Table 2. RCT Schedule of Assessments

Instrument/Questionnaire	Screening	Consent and Baseline visit	1-month post-discharge
ASSIST	X		
Current MOUD Utilization	X		
Informed Consent	X		
Sociodemographic Data	X	X	
Pain Intensity and Frequency (PEG)		X	X
Depression (PHQ-9)		X	X
Anxiety (GAD-7)		X	X
30-Day Opioid (and other substance) Use (adapted from NSDUH)		X	X
SUD Treatment Utilization (adapted from NSDUH)		X	X
SUD Healthcare and Mental Health Utilization (adapted from GAIN)		X	X
Severity of Substance Use (PROMIS)		X	X
Overdoses		X	X
Experience of Stigma		X	
Social Support (MSPSS)		X	
Opinions about MAT(MOUD)		X	
Significant Other with OUD		X	
Criminal Justice Involvement		X	
MOUD Utilization			X
Patient Experience of Chronic Illness Care (PACIC)			X
Therapeutic Alliance (CAHPS) [a]			X
Satisfaction with START [a]			X

[a] Only for participants randomized to the START intervention arm of the study

4.6 Description of Variables

4.6.1 Description of Outcome Variables

Table 3 describes the outcome variables and data sources.

Table 3. Outcome variables and sources

Outcome	Endpoint	Data Source
Primary Outcomes		
In-hospital initiation of MOUD therapy	Proportion of patients in each arm who initiate MOUD prior to discharge, defined as use* of any FDA-approved pharmacotherapy for OUD, including buprenorphine, naltrexone and methadone. *Use means the MOUD was noted as ordered or administered in the EMR.	EMR (See Appendices A and B)

Linkage to follow-up OUD care	Proportion of patients in each arm who attend at least one OUD-related care visit within 30 days of hospital discharge	1-month interview
Secondary Outcomes		
OUD-specific discharge plan	Proportion of patients in each arm with an after-hospital care plan that specifies a date and time for a post-discharge addiction care appointment	EMR chart review for non-START patients and the registry for START patients (See Appendices A and B)
Any post-discharge MOUD utilization	Proportion of patients in each arm who initiate MOUD or continue MOUD treatment within 30 days following hospital discharge	1-month interview
Post-discharge outpatient medical care	Proportion of patients in each arm who complete at least one visit to an outpatient medical provider within 30 days of hospital discharge. Visit must be specifically related to opioid use and may include an emergency department visit.	1-month interview
Past 30-day number of days with any opioid use (each substance separately and substance days (sum of substances)	Mean (or median, depending on distribution) days of use in the past 30 days after hospital discharge– Adapted National Survey of Drug Use and Health (NSDUH).[2] "Use-days" range from 0 to 120 days with up to 30 days of use reportable for each of four opioid categories: pain medications excluding fentanyl, fentanyl, heroin/opium alone, heroin/opium mixed with another drug	Baseline interview 1-month interview

The following EMR data elements will be obtained to derive the outcome variables and/or to describe the sample:

- Hospital encounter data: Type; Dates; Disposition; Attending provider; PCP; Psychiatry consult;
- Reason for admission
- Diagnoses
- Inpatient medication (listed by generic names): Buprenorphine; Buprenorphine/Naloxone; Methadone; Naltrexone; Naloxone.
- Hospital utilization metrics: Length of stay; Inpatient admissions in prior 12 months; ED admissions in prior 12 months; Number of 30-day readmissions
- Insurance type
- Presence of an OUD-specific discharge plan in the record

4.6.2 Description of Other Measures

4.6.2.1 Table 4 lists other outcomes, covariates, potential mediators and moderators.

Table 4. Description of other outcomes, covariates, potential mediators and moderators

Variable	Measure	Data Source	Response Values/Scales
Sociodemographics	***(Covariate; Potential Moderator)***		
• Age		Eligibility Screener	Continuous
• Sex (Assigned at Birth)		Eligibility Screener	Binary
• Gender Identity		Eligibility Screener	Categorical (1-4)
• Hispanic		Eligibility Screener	Binary
• Race		Eligibility Screener	Categorical (1-5)

Table 4. Description of other outcomes, covariates, potential mediators and moderators

Variable	Measure	Data Source	Response Values/Scales
• Current homeless status		Eligibility Screener	Binary
• Marital status		Baseline Interview	Categorical (1-6)
• Income		Baseline Interview	Continuous
• Education		Baseline Interview	Categorical (1-20)
• Insurance type	Payer name	EMR	Text (code to numeric)
Mental Health Symptoms	***(Covariate; Potential Moderator/ Mediator)***		
• Depression (9 items)	PHQ-9[3,4]	Baseline Interview 1-month Follow-up	Likert-type (1-4)
• Anxiety (7 items)	GAD-7[5-7]	Baseline Interview 1-month Follow-up	Likert-type (1-4)
Social Support Scale	***(Covariate; Potential Moderator)***		
• Social support: Family, Friends, Significant Other (6 items; 2 each scale)	Modified Multidimensional Scale of Perceived Social Support[8]	Baseline Interview 1-month Follow-up	Likert-type (1-7)
Medical Symptoms/Treatment	***(Covariates; potential mediator/moderator)***		
• Overdoses (lifetime, past 3 mos)	N/A	Baseline Interview 1-month Follow-up	Continuous
• Primary and secondary diagnosis (inpatient stay)	Medical or mental health conditions as determined by the inpatient physician	EMR	Text (ICD codes)
• Pain intensity and duration	PEG[9]	Baseline Interview 1-month Follow-up	0-10 scale
• Length of hospital stay	Days in hospital	EMR	Continuous
Substance Use Treatment History	***(Covariates; potential moderator)***		
• Ever used an MOUD • Times started an MOUD	N/A	Eligibility Screener	• Binary • Continuous
• Type of MOUD medication	N/A	Eligibility Screener	Categorical (1-4)
• Treatment other than MOUD • Times had treatment other than MOUD	N/A	Eligibility Screener	• Binary • Continuous

Table 4. Description of other outcomes, covariates, potential mediators and moderators

Variable	Measure	Data Source	Response Values/Scales
Recent Substance Use Treatment Utilization; Opinions; Consequences Stigma	***(Outcomes*; Covariates)***		
SUD Treatment Utilization* (5 items) • Past 90 days baseline • Past 30 days from discharge follow-up* ***Linkage outcome***	Adapted from National Survey on Drug Use and Health (NSDUH)[2]	Baseline Interview 1-month Follow-up	Binary
Healthcare Utilization (ER, Inpatient, Outpatient) Related to SUD (5 items) • Past 90 days baseline • Past 30 days follow-up	Adapted from Global Appraisal of Individual Needs (GAIN)[10]	Baseline Interview 1-month Follow-up	Continuous
• Familiar with MOUD • Opinions about MOUD (3 items)	Opinions about MAT (OAMAT)[11]	Baseline Interview	Likert-type (1-5)
Severity of Substance Use (7-items)	PROMIS	Baseline Interview 1-month follow-up	Likert-type (1-5)
Patient Experience of Stigma (5 items)	Adapted from Grosso et al. 2019.[12]	Baseline Interview	Binary
Patient Experience of Chronic Illness Care (11 items)	Patient Assessment of Chronic Illness Care (PACIC)[13]	1-month Follow-up	Binary
Criminal Justice Involvement • Ever arrested • Times arrested past 90 days	Locally developed	Baseline Interview	• Binary • Continuous

5 Sample Size

5.1 Original Sample Size Determination

In-patient MOUD initiation: A sample size of n=432 (allowing for 20% attrition) and adjusted type I error rate of 2.5% provides 84% power to detect an OR=2.3 comparing the in-patient MOUD initiation rates in the CCT and UC arms, stratified on prior MOUD use. Based on literature, 14% of UC patients who are MOUD-naïve initiate MOUD in hospital.[14] Assuming the average of MOUD-naïve and MOUD-experienced in-patient MOUD initiation rates is 20%, we have an adequate sample size and power to detect this increase of in-patient MOUD initiation in the CCT arm (37%) compared to UC.[14-16]

Linkage to OUD Care: We base the sample size estimate on the linkage to care measure since the probabilities of successful linkage are lower than for in-patient MOUD initiation. Linkage to care rates reported in the literature range between 10%-17% in usual care settings. To err on the side of caution, we estimate linkage to care in UC for MOUD-naïve and MOUD-experienced to be 5% and 10%,[14-17] respectively, yielding an average of 7.5%. We hypothesize that at least 20% of patients randomized to the START arm will link to OUD care (attend at least one OUD-related visit) within 30 days following discharge. Assuming a Bonferroni-corrected, two-sided type I error rate of 2.5% to adjust for two primary endpoints, we will enroll a minimum of 432 patients (216 in each intervention arm) to have 80% power to detect this difference. This estimate includes an adjustment for up to 20% attrition. This effect size corresponds to a clinically meaningful odds ratio of 3.0. Prior studies in different settings have found larger effects,[16-18] supporting our ability to conduct this test.

Sample size calculations for the primary endpoints were performed in PASS 14 using stratified Mantel-Haenszel tests for two proportions between two groups,[19] with strata defined as 50% MOUD-naïve and 50% MOUD-experienced.[16-18,20,21] Due to the short 1-month duration of participation, subject withdrawal from the study is not anticipated to be significant.

5.2 Revised Sample Size Determination

Our original sample size estimates were based on an assumption for the stratification variable, prior MOUD exposure, that equal proportions would be observed (50% with prior MOUD exposure and 50% without). As of February 2023, we are presently observing 76% with prior MOUD exposure and 24% without. Based on this new information about our randomization strata, we recalculated the sample size needed to analyze our primary outcomes MOUD, linkage to OUD treatment). We determined that the sample sizes needed to analyze both primary outcome effect sizes originally proposed with 80% power and type I error = 2.5% (Bonferroni-corrected for two primary outcomes) are:

- MOUD initiation: n = 288. Given that this outcome is observed on every enrolled participant, there is no need to inflate the target sample size for attrition.
- Linkage to care: n = 299. With an observed attrition of 30%, we require enrolling 426 participants, still requiring enrollment through the end of the study period.

6 General Analysis Considerations

6.1 Timing of Analyses

The study databases will be locked to data entry 90 days following the last enrolled participant's discharge from hospital. This allows for one month following study completion of the last participant for completion of standard quality control queries. Any additional queries identified following the data lock will be addressed and any final query resolutions to the data will be hard-coded into the data management programs and documented in the code.

Analyses described in this SAP will commence once the locked data set is created and will be completed during the final year of the study.

6.2 Analysis Populations

6.2.1 Intention to Treat (ITT) Population

All subjects who consented, enrolled, and were randomized into either arm. Participants who complete the informed consent or part of the baseline interview but are not randomized will be excluded from analysis.

6.2.2 Per Protocol (PP) Population

All subjects who consented, enrolled, and were randomized into either arm and who completed the 1-month follow-up interview.

6.3 Covariates and Subgroups

6.3.1 Covariates

Potential covariates are listed in Table 4.

6.3.1 Subgroups

We will conduct exploratory analyses to see if patient sex or gender, or race/ethnicity has an effect on primary outcomes or retention. Adjusted odds ratios and their 95% confidence intervals will be calculated from interaction effects between treatment group and sex or gender from the specified linear models for the primary and secondary outcome measures.

6.3.2 Multi-Center Studies

This is a multisite study consisting of three sites. The data will be pooled across sites to assess the primary

and secondary outcomes. Randomization is stratified by site and thus site will be included in all analyses as an influential covariate and interaction effects between site and treatment arm will be assessed.

6.4 Missing Data

Study endpoints are cross-sectional in time. Every effort will be made to obtain all necessary outcome and covariate data. We will use inverse probability weighting and multiple imputation (IPW-MI) to adjust for missing covariate data.[22] Specifically, we will examine whether observable baseline characteristics differ by attrition status, and if so we will adjust our comparisons using weights. MI will be used to impute intermittently missing data for study completers. We will not impute outcomes, but only covariates.

6.5 Summary of Study Data

Data will be summarized with descriptive statistics including frequencies, means, standard deviation, medians, quartiles, minima, and maxima for continuous data, as appropriate. Frequencies and percentages will be used to summarize categorical data. Categorization of continuous variables for frequency tables will be predetermined by logical cutoffs, e.g., 5-year age groups, or tertiles and quartiles.

6.6 Subject Disposition

Study status of subjects will be summarized with descriptive statistics, as described above, throughout the study. For the one-month follow-up visit, we will summarize the number and proportion of subjects whose interview occurred, how many dropped out, were terminated from the study and for what reasons, and how many were lost-to-follow-up. Early termination reasons include:

1. Found to be ineligible after randomization
2. Participant withdrew consent
3. Participant death
4. Other

6.7 Protocol Deviations

Reported protocol deviations are missed visits and visits that occurred beyond the defined window period (+ 60 days from target date). We will report the total number of deviations and the frequency and percentage of each reason. Individual listings will also be produced.

The following reasons are being collected:

1. Incomplete visit
2. Missed visit
3. Visit out of window
4. Informed consent deviation
5. Missing or incorrect documentation
6. Eligibility deviation
7. HIPAA violation
8. Single subject protocol exception
9. Other (describe)

6.8 Demographic and Baseline Variables

Intervention arms will be compared on baseline characteristics (e.g., demographics, mental health characteristics) using descriptive statistics. Planned comparisons are below.

- Site
- Age
- Sex at birth
- Gender identity
- Ethnicity (Hispanic/Latino)
- Race
    - American Indian/Alaska Native

    - Asian/Pacific Islander
    - Black/African American
      White
    - Multiple Races
    - Other Race
- Insurance Status
- Income
- Housing Status
- Depression (PHQ-9)
- Anxiety (GAD-7)
- Severity of Substance Use (PROMIS)
- Sever to moderate substance use of other substances (ASSIST)
- Substance use treatment prior to hospitalization (eligibility screener)
- Pain severity (PEG) and duration (survey question)

6.9 Outcome Analyses

Analyses comparing demographic and clinical characteristics of the treatment arms will be assessed as follows:

Continuous variables:

- ANOVA or Mann Whitney tests will be used to compare across 3 or more groups
- *t* tests or Wilcoxon rank sum tests for comparing 2 groups

Categorical variables:

- Tests of proportions for comparing 2 groups
- $\chi 2$ tests, or Fisher exact tests, as appropriate for the data type for 2 or more categories
- Logistic regression for interaction effects between group and given variable.

Such analyses will be used to assess baseline homogeneity of the treatment groups as well as to help us identify potential covariates to be included in linear models for assessment of outcome measures; however, clinically relevant covariates will also be included regardless of the outcomes of these analyses. All analyses will be performed in SAS 9.4[23] or higher, R 4.2[24] or higher, and/or Stata 17[25] or higher.

6.10 Baseline Descriptive Analyses

Intervention arms will be compared on baseline characteristics (e.g., demographics, mental health characteristics) using descriptive statistics. Planned comparisons are for the variables described in section 6.8.

6.11 Primary Outcome Analysis

6.11.1 Primary Hypotheses

6.11.1.1 Primary Hypothesis 1

We hypothesize that, compared to patients who receive usual care, patients in the START condition will be more likely to initiate MOUD while hospitalized. Alternatively, our null hypothesis is that there will be no difference in likelihood of in-hospital MOUD initiation between patients in the START and UC conditions.

6.11.1.2 Primary Hypothesis 2

We hypothesize that, compared to patients who receive usual care, patients in the START condition will be more likely to receive linkage to post-discharge MOUD care (i.e., attend at least one OUD-related care visit within 30 days of hospital discharge). Alternatively, our null hypothesis is that there will be no difference in linkage to post-discharge MOUD care for patients in the START condition compared to those in UC condition.

6.11.2 Primary Analysis

6.11.2.1 Original Primary Analytical Plan

Unadjusted point estimates and confidence intervals for proportions and means will be reported by arm and

by prior MOUD use for endpoints. Primary endpoints will be compared between arms by fitting a multivariable logistic regression model to each that includes as independent variables: intervention arm, prior MOUD exposure and site, as well as relevant baseline characteristics as covariates, including age, income or insurance status (as a marker for income), race, and ethnicity. Additional covariates that may be included are substance use severity, homelessness and length of index hospitalization, as well as any other variables also thought to be associated with outcomes that demonstrated imbalance between treatment arms.[18] Site will be included as a fixed effect to reflect the study design and to control for potential variability in CCT implementation. Odds ratios and their Bonferroni-adjusted 97.5% Wald confidence intervals will be reported for the two primary outcomes.

6.11.2.2 **Revised Primary Analytical Plan**

Upon initial descriptive analyses of the primary outcomes, we discovered that the proportion of patients in each treatment arms who initiated MOUD in the hospital and who linked to care post-discharge was much higher than hypothesized. Odds ratios (ORs) are frequently used to report effect sizes for dichotomous outcomes; however, when the outcome rates are not rare, ORs tend to overestimate the effect size which could lead to overinterpretation of the results. We determined that risk ratios (RRs) are a better estimate of the true effect and are less likely to lead to overinterpretation of effects. Therefore, multivariable Poisson regression models were fitted to each of the primary endpoints to compare treatment arms. These models will include the covariates described for the original analysis plan (age, insurance status, race, and ethnicity) and the independent variables previously stated (intervention arm, prior MOUD exposure, and site). Additional covariates as described previously may be considered. RRs and their 97.5% Wald confidence intervals will be reported for the two primary outcomes.

6.12 Secondary Outcome Analyses

6.12.1 **Secondary Hypotheses**

6.12.1.1 **Secondary Hypothesis 1**

We hypothesize that, compared to patients who receive usual care, patients in the START condition will be more likely to receive addiction-focused discharge planning. Alternatively, our null hypothesis is that there will be no difference in likelihood of receiving addiction-focused discharge planning between patients in the START and UC conditions.

6.12.1.2 **Secondary Hypothesis 2**

We hypothesize that, compared to patients who receive usual care, patients in the START condition will be more likely to receive MOUD treatment after discharge (i.e., initiate MOUD or continue MOUD treatment within 30 days following hospital discharge). Alternatively, our null hypothesis is that there will be no difference in likelihood of receiving MOUD treatment between patients in the START and UC conditions.

6.12.1.3 **Secondary Hypothesis 3**

We hypothesize that, compared to patients who receive usual care, patients in the START condition will be more likely to receive linkage to post-discharge medical care (i.e., complete at least one visit to an outpatient medical provider within 30 days of hospital discharge). Alternatively, our null hypothesis is that there will be no difference in linkage to post-discharge medical care for patients in the START condition compared to those in UC condition.

6.12.1.4 **Secondary Hypothesis 4**

We hypothesize that, compared to patients who receive usual care, patients in the START condition will be more likely to significantly reduce opioid use after discharge (i.e., days of opioid use in the 30 days between discharge and follow-up). Alternatively, our null hypothesis is that there will be no difference in likelihood of reducing opioid use between patients in the START and UC conditions.

6.12.2 **Secondary Analyses**

6.12.2.1 **Original Secondary Analytical Plan**

Similar analyses as described for the primary endpoints will be performed for these secondary proportions

outcomes, but instead reporting 95% confidence intervals. For Secondary Endpoint 4, a general linearized model to number of days of opioid use will be fitted along with the covariates described for the logistic regression models. An appropriate link function will be identified and used based on the distribution of the outcome data.

6.12.2.2 **Revised Secondary Analytical Plan**

For the same reasons described in Section 6.11.2.2, we determined that multivariable Poisson regression models were more appropriate for the data than logistic regression models and, therefore, were applied to Secondary Endpoints 1-3 with independent variables as previously described. For these, we will report RRs and their 95% CIs. For Secondary Endpoint 4, we fit a multivariable negative binomial regression model with log link function to opioid use-days with the covariates previously described with the addition of baseline opioid use-days. Contrasts will be calculated to estimate the incident rate ratio (IRR) to compare treatment arms, along with its 95% CI.

6.13 Exploratory Outcome Analyses

To explore possible mechanisms of how START works, we may conduct the following exploratory analyses: (1) Assess the mediating effect of inpatient MOUD initiation on use of MOUD and linkage with OUD treatment post-discharge; (2) Assess the mediating effect of completion of an OUD-specific discharge plan on linkage with OUD treatment 30-days post-discharge; (3) Assess the moderating effects of patient characteristics (e.g., gender, race, ethnicity, insurance status) on post-discharge linkage. Analysis plans for these exploratory assessments will be written separately.

6.14 Interim Analyses

Given the additional information about the reduced sample size (from our original, pre-study calculations) needed for the medication initiation outcome, and the desire to minimize participant burden, an interim analysis will be conducted on the second primary outcome (linkage) when we reach n = 288 enrolled (the sample size required to estimate our primary outcome measure of MOUD initiation). This will provide approximately n = 288×0.70 = 202 participants for this analysis, or ~68% (202/299) of our final analytic sample size for this outcome. We will utilize an alpha-spending method[26,27] to ensure that, should we continue the study until full enrollment, we control the family-wise type I error rate to be 2.5% for each outcome. Using a two-sided test, this approach will allow us to assess superiority of the intervention over the control or the control over the intervention. If we reject the null hypothesis at the interim analysis, we will discontinue the study. Should we fail to reject the null hypothesis at the interim analysis, we will continue to full enrollment for final analysis. The interim analysis two-sided type I error level was calculated in the R package “rpact”, yielding a comparison of this outcome’s p-value to α=0.0062.

6.15 Sub-Group Analyses

We will conduct exploratory analyses to see if patient sex or gender, or race/ethnicity has an effect on primary outcomes or retention. Adjusted odds ratios and their 95% confidence intervals will be calculated from interaction effects between treatment group and sex or gender from the specified linear models for the primary and secondary outcome measures.

6.16 Post-Hoc Analyses

The START leadership team (Ober, Danovitch, Page, Friedmann, and Murray-Krezan) will encourage collaboration across all sites and provide guidance to promote and support scientific research dissemination. Research “ideas” for abstracts, manuscripts and presentation will be generated on “Concept Sheets” and submitted for review to the START Leadership group. Concept sheets will each have detailed analysis plans for the proposed study question/s. All papers will include a biostatistician in the collaborative/authorship group. In general, we expect both descriptive and comparative analyses will be conducted on cross-sectional and longitudinal data collected in the START cohort study.

6.17 Safety Analyses

All adverse events (AEs) will be categorized and graded for severity as described above. (S)AEs will be

summarized via the same methods described in section 8.0, by site and overall. SAEs will be individually listed for DSMB review and will also be categorized and summarized similarly to AEs. We report AEs and SAEs by number of events (# AEs may be > N), as well as by the subject's most severe AE and its severity (#AEs ≤ N). These analyses will be performed on the ITT defined in Section 6.2.1.

6.17.1 Adverse Events

The START protocol defines an adverse event (AE) as any unfavorable and unintended symptom or disease that an investigator or study staff learns about which occurs during a patient's enrollment in the study, if it is considered by the site study team to be possibly related to a study treatment or procedure ("possibly related" means there is a reasonable possibility that AE may have been caused by research procedures).

6.17.2 Serious Adverse Events

6.17.2.1 Definition of SAE

The START protocol defines a serious adverse event (SAE) as an AE that an investigator or study staff learns about that is fatal, life-threatening, prolongs initial hospitalization, requires inpatient rehospitalization, or is medically significant and which the investigators and/or clinicians regard as serious based on appropriate medical judgment. With the exception of fatalities, other SAEs documented this study are considered those is possibly related to the study; other events occurring during the normal of the hospital stay will be numerous and thus not documented unless possibly related to the study.

6.17.3 Relationship to Study Intervention and Severity of (S)AEs

All (S)AEs will be rated as Mild, Moderate, or Severe and will be used as a factor in determining expectedness of an event. All (serious) adverse events will have their relationships to the study intervention assessed and rated as either Definitely Related, Probably Related, Unlikely to be Related, or Not related.

6.17.4 Pregnancies

Pregnant people are not excluded from participation in this study. We do not follow pregnancy outcomes given the short duration of the study period. Nevertheless, any adverse events for pregnant participants will be documented in accordance with our AE/SAE reporting protocol.

7 Reporting Conventions

The following reporting conventions will be applied to all reports:

- P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "p<0.001".
- The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.
- Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant figures.

8 Summary of Changes to the SAP

- The SAP was updated in April 2023 to revise the sample sizes needed for the primary outcomes given observed rates of the prior exposure to MOUD stratification variable. Additionally, we added a proposed an interim analysis to determine whether would be adequately powered to detect hypothesized primary effects with a smaller sample size given updated information about prior MOUD exposure and the attrition rate.

- The SAP was updated in March 2024 to describe the revised regression modeling for the Primary and Secondary Endpoints.

- The SAP was updated in December 2024 to clarify definitions of Secondary Endpoints 3 and 4.

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APPENDIX A: Electronic Health Record Outcome Variables

Description	Expected data type	Time Frame	Notes
Visit type	Inpatient or Observation	Visit FIN provided	
Visit admit date	Date	Visit FIN provided	
Visit discharge date	Date	Visit FIN provided	
Disposition	Categorical	Visit FIN provided	
Reason for admission	Free response	Visit FIN provided	
In-hospital ordering of MOUD therapy medications (listed on Medications tab).	List of medications *ordered* (Date/time)	Visit FIN provided	First order of MOUD med within hospital visit is sufficient
Date/time of medication administered	Date/time	Visit FIN provided	First administration of MOUD med within hospital visit is sufficient
Insurance type (Primary and Secondary)	Payer name	Visit FIN provided	
Primary and secondary diagnoses (problem list for that visit)	ICD codes	Visit FIN provided	Problem list translated to comorbidity score - ICD10 codes vs text?
Length of stay	Number	Visit FIN provided	
Inpatient admissions in prior 12 months	Number	12 months prior to visit	
30-day readmissions	Indicator	30 days since visit FIN provided	
Reason for admission	Free response	30 days since visit FIN provided	
Readmission admit date	Date	30 days since visit FIN provided	
Readmission FIN	ID	30 days since visit FIN provided	

APPENDIX B: Medications Prescribed for Treatment Initiation from Electronic Health Record

Prescribed MOUD
Belbuca
Bunavail
Buprenex
buprenorphine
Butrans
Naltrexone*
Probuphine
Suboxone
Subutex
Sublocade
Vivitrol*
Zubsolv
buprenorphine-naloxone (could be written differently depending on the EHR, e.g., buprenorphine/ naloxone; use whatever convention applies for your EHR)
Methadone
*must be associated w/OUD dx