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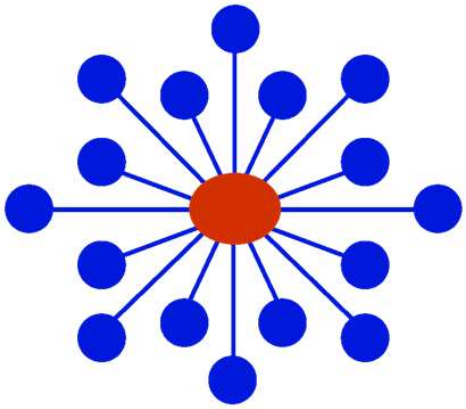

Statistical Analysis Plan for NIDA Protocol CTN-0101

Subthreshold Opioid Use Disorder Prevention (STOP) Trial

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Version 2.0

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BPI	Brief Pain Inventory
CBT	Cognitive Behavioral Therapy
CCC	Clinical Coordinating Center
CCM	Chronic Care Model
CCTN	Center for Clinical Trials Network
CFR	Code of Federal Regulations
CIDI	Composite International Diagnostic Interview
CoC	Certificate of Confidentiality
Co-I	Co-Investigator
Co-LI	Co-Lead Investigator
COMM	Current Opioid Misuse Measure
COT	Chronic Opioid Therapy
CRF	Case Report Form
CTN	Clinical Trials Network
DM	Data Management
DSC	Data and Statistics Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture system
HER	Electronic Health Record
EUC	Enhanced Usual Care
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HSP	Human Subjects Protection
ICF	Informed Consent Form
IRB	Institutional Review Board
LI	Lead Investigator
LN	Lead Node
LT	Lead Team
MAR	Missing at Random
MCAR	Missing Completely at Random
MCMC	Markov Chain Monte Carlo
MME	Morphine Milligram Equivalents
MI	Multiple imputation
MNAR	Missing Not at Random

Abbreviation	Definition
MOP	Manual of Procedures
MOUD	Medication for Opioid Use Disorder
NCM	Nurse Care Manager
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OEND	Overdose Education and Naloxone Distribution
OHRP	Office for Human Research Protection
OUD	Opioid Use Disorder
PCP	Primary Care Provider
PD	Protocol Deviation
PDSQ	Psychiatric Diagnostic Screening Questionnaire
PEG Tool	Pain, Enjoyment of life and General Activity Tool
PhenX Toolkit	Phenotypes and Exposures Toolkit
PHQ-8	Patient Health Questionnaire
PI	Principal Investigator
PRB	Protocol Review Board
PROMIS	Patient-Reported Outcomes Measurement Information System
PSS	Patient Safety Screener
QA	Quality Assurance
QUIT	Quit Using Drugs Intervention Trial
RA	Research Assistant
RC	Research Coordinator
RCT	Randomized Control Trial
SA	Self-Administered
SAE	Serious Adverse Event
SBI	Screening and Brief Intervention
SBIRT	Screening, Brief Intervention, and Referral to Treatment
SCOPE	Safer/Competent Opioid Prescribing Education
SF-12	12 Item Short Form Health Survey
SPMZINB	Shared Parameter Marginal Zero-inflated Negative Binomial
SOC	Standard of Care
SOP	Standard Operating Procedure
STOP	Subthreshold Opioid Use Disorder Prevention
SUD	Substance Use Disorder
TA	Technical Assistance
TAPS Tool	Tobacco, Alcohol, Prescription medicine, and other Substance use Tool
TEACH	Targeting Effective Analgesia in Clinics for HIV
THC	Telephone Health Coach
TLFB	Timeline Follow-Back
TOPCARE	Transforming Opioid Prescribing in Primary Care
UDS	Urine Drug Screen
ZINB	Zero-inflated Negative Binomial

1.0 INTRODUCTION

The Statistical Analysis Plan (SAP) for CTN-0101 Subthreshold Opioid Use Disorder Prevention (STOP) Trial was developed by the Clinical Trials Network's (CTN) Data and Statistics Center (DSC) and the Lead Node (LN) according to version 8.0 of the protocol and describes all planned analyses for the primary, key secondary, and safety outcome measures for final analyses occurring after data lock.

The Clinical Trial Network (CTN)'s Data and Statistics Center (DSC) will conduct the analyses for the Final Study Report (FSR) as listed in Table 1 below and the Lead Node (LN) will conduct the analyses as noted.

Table 1: Analysis Responsibilities

Content	Section Number	Responsible for Analysis
Participant Enrollment, Disposition, and Follow-up	4.0	DSC
Participant Baseline Characteristics	5.0	DSC
Intervention Exposure	6.0	DSC
Analyses of Primary Outcome	7.2	DSC
Analyses of the Key Secondary Outcome Measures (H2.1-H2.5, and UDS)	7.7	DSC
Analyses of the Other Secondary Outcome Measures (H2.6-H2.15, H3.1-H3.4)	7.7	LN
Analyses of the Exploratory Outcome Measures	7.9	LN
Safety Outcomes	8.0	DSC
Data Quality	12.0	DSC

2.0 SUMMARY OF STUDY DESIGN AND PROCEDURES

2.1 Study Design

This randomized clinical trial aims to examine the efficacy of a primary care Subthreshold Opioid Use Disorder Prevention (STOP) intervention to reduce opioid use and overdose risk, and to prevent progression of opioid use disorder (OUD) in adult patients with risky opioid use. Specifically, STOP is a behavioral early intervention strategy targeting individuals with subthreshold OUD, with a goal of reducing risky opioid use, to prevent the development of moderate-severe OUD.

This cluster-randomized trial, randomized at the level of the PCP, aims to test the efficacy of STOP versus enhanced usual care (EUC). The trial will be conducted in 5 primary care sites, and across all sites will enroll approximately 100 PCPs and 300 adult primary care patients. Patient participants with providers assigned to the intervention condition can receive the full STOP intervention, in addition to primary care treatment as usual. Those with providers assigned to EUC will receive primary care treatment as usual plus printed educational materials addressing opioid-related overdose prevention.

This cluster-randomized trial will compare the STOP intervention to enhanced usual care (EUC) for 12 months from the date of initial intervention. Eligible PCPs and their eligible patients will be consented and enrolled in the study. PCP participants will be randomized 1:1 to the STOP or EUC condition. Patient participants will receive STOP or EUC, according to the assignment of their PCP. The study will be conducted at five sites, each having one or more participating primary care clinics. Patients will be informed that their PCP is participating in a "healthy living study" and will be blinded to the study condition of their PCP. Patients who do not enroll in the study will receive primary care as usual (i.e., standard of care primary care treatment).

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective (Aim 1) of the STOP trial is to determine the efficacy of the STOP collaborative care intervention, in comparison to enhanced usual care (EUC), for reducing risky opioid use in adult primary care patients, over 12 months of follow-up. Risky opioid use is defined for the primary outcome measure as nonmedical use of prescribed opioids (taking a higher dose or taking an opioid more frequently than prescribed; taking pharmaceutical opioids that were not prescribed to the individual taking them), or any use of illicit opioids. Our primary hypothesis (H1.1) is that patient participants with primary care providers assigned to the STOP intervention will have fewer days of risky opioid use, measured at 6 months from baseline (primary outcome), and at 3, 9, and 12 months from baseline (secondary outcome (H1.2)), in comparison to patient participants with primary care providers assigned to EUC. Because the most intensive intervention period is during the initial 3-4 months, the primary outcome is measured at 6 months in order to capture the main intervention effect. The 3-month secondary outcome measure will assess early intervention effects, while the 9- and 12-month secondary outcome measures will assess the durability of intervention effects (which may be maintained, increased, or decreased) over time.

2.2.2 Secondary Objectives

The trial has two secondary objectives, which capture patient participant-level and provider-level impacts of the STOP intervention.

The patient-level secondary objective (Aim 2) is to examine the impact of STOP on important patient-level outcomes of substance use that increases opioid-related overdose risk (binge alcohol use, benzodiazepine and stimulant use), other drug use, OUD and other drug and alcohol use disorders, overdose risk behaviors and nonfatal overdose events, pain symptoms and related functioning, mental health symptoms (depression, anxiety, suicidality), sleep, health-related quality of life, and acute health care utilization. We hypothesize that patient participants in the STOP condition, in comparison to participants in the EUC condition, will have:

- H2.1 Fewer days of binge alcohol use.
- H2.2 Fewer days of benzodiazepine use.
- H2.3 Fewer days of stimulant use (cocaine and amphetamine-type stimulants).
- H2.4 Fewer days of marijuana use.
- H2.5 Fewer days of other drug use (not including opioids, benzodiazepines, stimulants, and marijuana).
- H2.6 Lower proportion of individuals having increased days of illicit or nonmedical opioid use.
- H2.7 Reduced prescription opioid misuse behaviors, among patients receiving prescribed opioids.
- H2.8 Lower incidence of moderate-severe OUD.
- H2.9 Lower rates of non-opioid drug use disorder or alcohol use disorder.

H2.10 Lower rates of self-reported overdose risk behavior and nonfatal opioid-related overdose events.

H2.11 No worsening of pain symptoms and pain-related functioning.

H2.12 Fewer symptoms of depression (including suicidality) and anxiety.

H2.13 Better sleep quality.

H2.14 Better health-related quality of life.

H2.15 Lower rates of acute health care utilization (ED and hospital visits).

The provider-level secondary objective (Aim 3) is to characterize the impact of STOP on primary care provider behaviors, including medications prescribed, lab tests, diagnosis of OUD, and frequency of medical visits. Our hypothesis is that providers assigned to the STOP condition, in comparison to providers in EUC, will have, over 12 months of follow-up…

H3.1 Lower rates of prescribing of high-dose opioids (defined as prescriptions totaling >90 morphine milligram equivalents (MME)) to patients with risky opioid use.

H3.2 Fewer patients with risky opioid use who are prescribed benzodiazepines.

H3.3 Higher proportion of patients with risky opioid use receiving at least one prescription for a naloxone kit.

H3.4 Increased monitoring of patients with risky opioid use, defined as urine drug screen, diagnosis of OUD, and higher visit frequency.

2.2.3 Exploratory Objectives

Exploratory Objective 1 is to assess the impact of STOP on patient participants' engagement in primary care. There is potential for the intervention to disrupt the patient-PCP relationship, particularly if it leads to a dose reduction or cessation of opioid prescribing by the PCP. In the Transforming Opioid Prescribing in Primary Care (TOPCARE) study [1], a post-hoc analysis indicated that patients in the intervention arm whose opioids were discontinued were less likely to follow up with their PCP. We believe that the multicomponent STOP intervention, which also includes telephone health coaches and PCP brief advice to support patient participants in reducing their opioid use, will not lead to decreased primary care engagement. However, this could be an important unintended consequence of the intervention. We will assess primary care engagement by measuring the frequency of kept appointments and missed appointments in each arm.

Exploratory Objective 2 is to examine the time to development of moderate-severe OUD or opioid-related overdose for patient participants in both treatment conditions. We anticipate a low rate of these events in our 12-month trial. However, given the lack of knowledge regarding opioid use trajectories among individuals with subthreshold OUD, our study may contribute valuable descriptive data to inform future interventions.

Exploratory Objective 3 is to measure the rate of fatal opioid-related overdose deaths. We anticipate very low rates, and potentially no overdose deaths, during the 12-month trial. However, given the importance of this outcome, it will be measured for participants in both treatment conditions. Where information about cause of death is available, we will seek to identify opioid-related overdose deaths, other substance overdose deaths, and other causes of death.

Exploratory Objective 4 is to examine the receipt of addiction treatment (including MOUD) and harm reduction services. Individuals with subthreshold OUD (as opposed to those with moderate-severe OUD) are expected to have little or no involvement with addiction services, but some participants (particularly those who develop moderate-severe OUD during the course of the study or have a co-occurring non-opioid substance use disorder) may utilize such services. Through the involvement of telephone health coaches and a NCM that can recommend and facilitate

treatment and harm reduction referrals, the STOP intervention could result in higher engagement in addiction services in the intervention group. We will use self-reported and EHR data to track addiction service utilization in both groups.

Exploratory Objective 5 is to measure days of substance use as captured by 90-day timeline follow-back (TLFB). Like the monthly assessments, the TLFB will assess days of risky opioid use, binge alcohol use, and other drug use (benzodiazepines, cocaine, stimulants, marijuana, and other drugs). The TLFB results may be examined alongside the days of substance use reported in the monthly assessments, in order to describe the consistency of results with these two measurement approaches for the purpose of informing future research.

Exploratory Objective 6 is to measure the rate of PCP counseling on risks of opioid use (including overdose, addiction, impact on health conditions). For patient participants who have a PCP encounter integrated with the baseline research visit, counseling is measured with the baseline exit survey. For all patient participants, information on any discussion or counseling provided during follow-up PCP encounters will be assessed with a quarterly patient experience questionnaire.

2.3 Study Procedures

2.3.1 Study Assessments

2.3.1.1 PCP Assessments

After study launch at each site, PCPs will be recruited and enrolled prior to the enrollment of patients. PCP participants will complete questionnaires on demographic and clinic characteristics. Those who are eligible will be provided with an IRB-approved informed consent form on paper and/or electronically and will be asked to sign this document. Provider practices, including prescribing and monitoring for patient participants with subthreshold OUD, are assessed from the electronic health record (EHR).

PCP participants in both arms will self-administer questionnaires at baseline and the end of the intervention period (approximately 6-10 months after the last patient is enrolled unless PCP withdraws early). Provider counseling will be assessed from medical chart review and from patient exit interviews conducted at quarterly assessments. Research staff will conduct a structured chart review to collect data from the EHR for patient participants who are enrolled in the study. To provide data on the baseline provider behavior as well as any changes during the course of the study, the chart review will span the 12 months prior to study participation and the 12 months following enrollment.

PCP participants follow up will occur until the last patient participant from the site completes 12 months of follow-up. If a PCP participant withdraws from the study early, the PCP will be asked to complete the end of study survey prior to their departure.

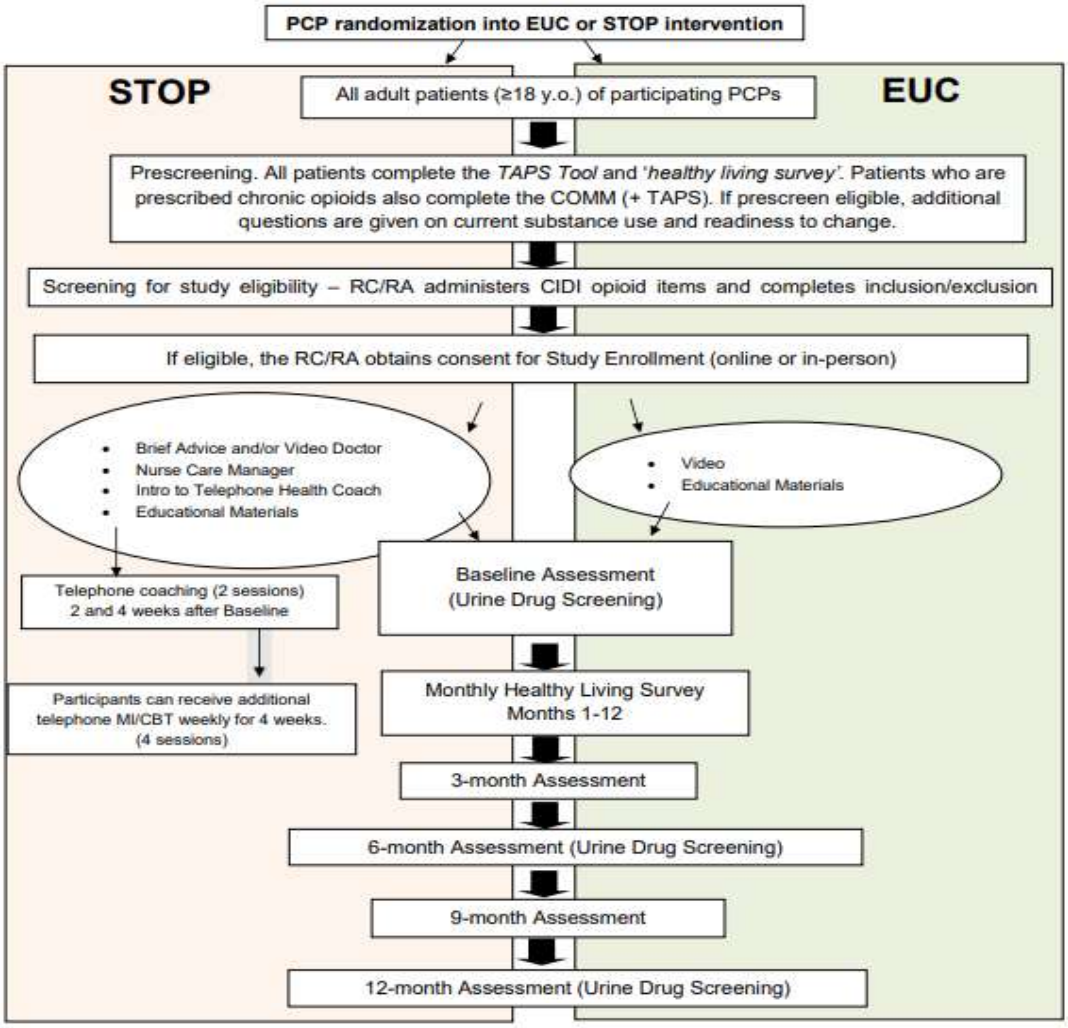
2.3.1.2 Patient Participant Assessments

Patients aged 18 or older of participating PCPs will be asked to complete prescreening questionnaires. Patients with prescreening results indicating that they may be eligible for the study will be guided to complete the Healthy Living Monthly (HLM) and Readiness to Change assessments. Patients who are eligible after these initial surveys will be contacted by the RC/RA for further screening (CIDI, and eligibility review) and consent. Patients with subthreshold OUD as determined by meeting study inclusion/exclusion criteria will be enrolled after signing written or electronic informed consent. Patient participants will complete assessments with research staff electronically at baseline and for the following 12 months using structured questionnaires. An assessment of days of substance use, diet, exercise, and smoking in the past 30 days will be completed by text message or online, at baseline and monthly. Other assessments will be

administered at baseline and quarterly, or less frequently, and are completed online and by telephone. Urine Drug Screens (performed at baseline and twice during the follow-up period) will be used to verify self-reported information.

The general information of study design and assessment is shown in Figure 1.

Figure 1. Study Design and Assessments



The details of assessments schedule, assessments administered to PCP participants, patient participants respectively, protocol specific assessments, as well as the measures of the primary outcome and the secondary outcomes can be referred to Section 11.0 STUDY ASSESSMENT in the protocol.

2.3.2 Study Intervention Treatments

STOP is a collaborative care model consisting of (1) a practice-embedded nurse care manager (NCM) who provides patient participant education and supports the primary care provider (PCP) in engaging and monitoring patient participants who have risky opioid use; (2) brief advice delivered to patient participants by their PCP; and (3) telephonic health coaching of patient participants to motivate and support behavior change. Patient participants who fail to improve

after the telephone health coaching sessions can be stepped up to receive additional health coaching sessions that incorporate motivational interviewing and cognitive behavioral therapy.

In the EUC arm, PCPs conduct primary care as usual, without support of the nurse care manager. Patient participants receive an educational pamphlet about overdose prevention and watch a brief video on “healthy living” that is not specific to substance use.

The details of treatments in STOP intervention arm and EUC control arm are referred to Section 10.6 Study Treatments in the protocol.

2.3.3 Treatment Randomization

This is a cluster-randomized trial in which PCPs are the clusters. In study sites where PCPs practice in teams, randomization will be at the team level (for example, if PCPs practice in teams of two, the two PCPs will be treated as one cluster in the randomization). PCPs will be randomized, stratified by site, in a 1:1 fashion to the STOP or EUC condition.

Patient participants enrolled in the study will receive STOP or EUC according to the assignment of their PCP.

2.3.4 Blinding

Randomization is at the level of the PCP, and PCPs will be aware of their assignment to the STOP vs. EUC condition. NCMs and telephone health coaches will only interact with patient participants in the intervention condition and will not be informed about patient participants who are enrolled in the EUC condition or who are not participating in the study. Patient participants are blinded to the treatment condition of their PCP and will be informed that their PCP is participating in a “healthy living study”.

2.4 Eligibility Criteria for Selection of Study Populations

Participants include both PCPs and their patients. Individuals must meet all the group-specific (PCP or patient participant) inclusion criteria at screening in order to be eligible to participate. Individuals meeting any of the exclusion criteria at screening will be excluded from study participation. Participant characteristics are anticipated to reflect the characteristics of PCPs and their adult patients in the participating sites. Patient participants will include a diversity of racial and ethnic groups, males and females and all will be at least 18 years of age.

2.4.1 PCP Participant

2.4.1.1 Inclusion Criteria

1. Licensed medical professional (MD, DO, PA, NP).
2. Currently providing care to approximately 4 or more adult patients (18 years or older) who are receiving chronic opioid treatment and/or have risky opioid use. Chronic opioid treatment is defined as having at least three opioid prescriptions, at least 21 days apart, in the past six months, with EHR documentation of active opioid prescription within the 60 days prior to screening. For PCPs who practice in a team, the care of patients receiving chronic opioid treatment may be shared with other team members who also meet criteria for participation in the study.
3. Total patient volume is approximately 40 or more adult patients (18 years or older) per week on a typical week (excluding vacation and inpatient rounding weeks).
4. Willing to be randomized to either of the two study conditions.

2.4.1.2 Exclusion Criteria

1. Planning to resign from the clinic in the next 24 months, per PCP self-report.
2. Planning to change their schedule in the next 24 months such that they would no longer meet the inclusion criteria for patient volume, per PCP self-report.

2.4.2 Patient Participant

2.4.2.1 Inclusion Criteria

1. PCP is enrolled in the study.
2. Age 18 years or older at time of prescreening.
3. Proficient in spoken and written English, as determined by patient self-report and research staff evaluation.
4. Risky opioid use in the past 90 days from date of prescreening, as determined by a TAPS score >1 for heroin and/or prescription opioids, and/or a positive response (>Never) to any of the three COMM items indicating taking more opioid medication than prescribed.

   COMM items used for determining eligibility:

   - Item 9: In the PAST 30 DAYS, how often have you needed to take pain medications belonging to someone else?
   - Item 14: In the PAST 30 DAYS, how often have you had to take more of your medication than prescribed?
   - Item 15: In the PAST 30 DAYS, how often have you borrowed pain medication from someone else?
5. Access to phone that can receive text messages, and access to internet (via smartphone, tablet, or computer), per patient self-report.
6. Able to provide sufficient contact information (minimum of 1 reliable locator).
7. Able to provide informed consent.

2.4.2.2 Exclusion Criteria

1. Patients with moderate-severe OUD, defined as meeting 4 or more DSM-5 criteria for OUD at screening, as assessed by research staff using the modified-CIDI opioid items.
2. Receiving MOUD or engaged in an opioid treatment program in the past 30 days from screening date, per patient self-report.
3. Receiving opioids for end-of-life care, per patient self-report.
4. Pregnancy (females aged 18-50), as determined by patient self-report at the time of screening.
5. Are currently in jail, prison, or other overnight facility as required by court of law or have pending legal action that could prevent participation in study activities.
6. Plan to leave the area or the clinical practice within the next 12 months, per patient self-report.
7. Other factors that may cause harm or increased risk to the participant or close contacts or preclude the patient's full adherence with or completion of the study.

3.0 GENERAL ANALYSIS POPULATIONS, DEFINITIONS, AND CONVENTIONS

3.1 PCP Participant Analysis Populations

3.1.1 Screened Population

The screened population consists of all PCP participants who completed the self-reported eligibility screening survey.

3.1.2 Randomized Population

The randomized population consists of all randomized PCP participants. Since randomization is conducted at the level of the PCP cluster, both counts of individual PCPs and PCP clusters will be reported.

3.1.3 PCP Participant Clusters with at Least One Patient Enrolled

Because some randomized PCP participants had no patients participating in the study (because none of their patients met the eligibility criteria), a population of interest is PCP participants clusters with at least one patient enrolled.

3.1.4 Study Completer Population

The PCP study completer population consists of the randomized PCPs who do not indicate early withdrawal on the Provider Eligibility Review (PCP) form.

3.2 Patient Participant Analysis Populations

3.2.1 Prescreened Population

The prescreened population consists of all patient participants who took the anonymous prescreening survey (Healthy Living Study (HLS) Survey).

3.2.2 Screened Population

The screened population consists of all patient participants who provided verbal consent at the initiation of the screening process.

3.2.3 Intent-to-Treat Population

The Intent-to-Treat (ITT) population consists of all enrolled patient participants whose PCP / PCP cluster is randomized to STOP or EUC. The ITT population will be analyzed according to the randomization assignment of their PCP regardless of potential exposure to the opposite assignment. The ITT population is used for the primary outcome analysis.

3.2.4 Complete Case Population

The complete case population is a subgroup of the ITT population which includes the patient participants who have no missing data for the variables of interest for the primary outcome analysis. The variables of interest include the primary outcome data collected in Months 1-6 and the baseline value of risky opioid use.

3.2.5 Per Protocol Population

The Per Protocol (PP) population is a subgroup of the ITT population with the following patient participants excluded:

- Had visits with PCPs in the opposite treatment arm as collected on the Chart Abstraction Visits (EMV) form. If the patient participant does not have the EMV form (e.g. the site did not do chart abstraction because the patient participant withdrew consent), they will be excluded from the PP population.

- Deviated from the protocol in terms of intervention exposure, including the participants who were shown the video doctor for the opposite treatment arm.

3.2.6 Primary Outcome Available Population

The primary outcome available population is a subset of the ITT population and consists of the patient participants who have each of the first 6 months of the Healthy Living Monthly Survey (HLM) collected to calculate the primary outcome of days of risky opioid in the past 180 days. The algorithm of calculating the number of days of risky opioid use measured in HLM is described in Section 7.2.1.

3.2.7 Primary Outcome Not Available Population

The primary outcome not available population is a subset of the ITT population and consists of the patient participants who missed one or more of the variable(s) used to calculate the primary outcome in the first 6 months of the Healthy Living Monthly Survey (HLM) due to dropout or intermittent missingness. The primary outcome not available population is the complementary set to the primary outcome available population.

3.2.8 Study Completer Population

The patient participant study completer population consists of the patient participants who finish the 12-month follow-up visit as indicated in the Study Completion Form (STC).

3.2.9 Safety Population

The safety population includes all patient participants who are enrolled in the study. This population should be summarized according to the randomization assignment of their PCPs since the study is designed as a minimal risk study and the intervention components are not anticipated to cause related adverse events or serious adverse events.

3.3 General Definitions

3.3.1 Risky Opioid Use

Risky opioid use is defined as nonmedical use of prescribed opioids (taking a higher dose or taking an opioid more frequently than prescribed), any use of illicit opioids, or taking pharmaceutical opioids that were not prescribed to the individual taking them.

3.3.2 Study Day

Study Day 1 is defined as the day of patient participant enrollment.

3.3.3 Study Month

The Healthy Living Monthly (HLM) Survey is collected monthly for 12 months following patient participant enrollment. Study Months are defined as 30 days. Participants are asked to specify the number of days of substance use in the past 30 days (range is 0-30 days). Study Months 1-12 are defined as follows: day 30, day 60, day 90, day 120, day 150, day 180, day 210, day 240, day 270, day 300, day 330, and day 360.

3.3.4 Baseline Value

The baseline values for HLM, TAPS Tool, Current Opioid Misuse Measure (COMM), and Readiness to Change assessments are collected in the prescreening survey and all other baseline values are collected at the screening and baseline visits.

3.3.5 Safety Event

Safety reporting will be limited to reporting the following Safety Events: non-fatal alcohol or drug overdose events, suicidal ideation, hospitalizations, emergency department (ED) visits, and deaths.

Because this is a minimal risk study with no pharmacological intervention, causally related Adverse and Serious Adverse events are not anticipated for this study. Collection and reporting of Adverse Events and Serious Adverse Events is not required in the data system.

3.4 Scoring Conventions

For patient participant assessments that require scoring and that will be summarized in the baseline demographic summary (Section 5.2) and/or used as potential covariates (Section 7.4), the following scoring algorithms will be used:

Assessment (eCRF)	Name of Score	Number of Items	Score Range	Scoring Algorithm
Current Opioid Misuse Measure (HLS (baseline), CMM (other timepoints))	COMM Score	17	0-68	Sum of the seventeen 0-4 rated items
Psychiatric Diagnostic Screening Questionnaire (PDQ)	Alcohol Use Disorder Score	6	0-6	Sum of the yes (1)/no(0) alcohol items
Psychiatric Diagnostic Screening Questionnaire (PDQ)	Drug Use Disorder Score	6	0-6	Sum of the yes (1)/no(0) drug items
Overdose Risk Behavior (ORB)	Overdose Risk Behavior Score	9	0-34	Sum of the eight 0-4 rated items and one 0-2 rated item
Brief Pain Inventory Short Form (BPI)	Pain Severity Score	4	0-10	Average of the four 0-10 rated severity items
Brief Pain Inventory Short Form (BPI)	Pain Functioning or Interference Score	7	0-10	Average of the seven 0-10 rated interference items
PROMIS Anxiety Short Form (PMA)	Anxiety Score	8	0-32	Sum of the eight 0-4 rated items
Patient Health Questionnaire-8 (PHQ)	Depression Score	8	0-24	Sum of the eight 0-3 rated items
PROMIS Sleep Disturbance Short Form (PMS)	Sleep Disturbance Score	4	4-20	Sum of the four 1-5 rated items with last two items reversed scored
Short Form 12 (SFM)	Health related Quality of Life (QoL): Overall Score		0-100	Scored using QualityMetric proprietary software
Short Form 12 (SFM)	Health Related QoL: Mental Health Component Score		0-50	Scored using QualityMetric proprietary software
Short Form 12 (SFM)	Health Related QoL: Physical Health Component Score		0-50	Scored using QualityMetric proprietary software

When participants are missing one or more of the items that comprise the score, prorated scores by averaging the available items will be used to compute the score. The prorated score is calculated using the following equation:

$$T_P = \left(\frac{T_R}{N_R}\right) \times N_T$$

where
T_P = Prorated total score
T_R = Total raw score based on those items with a response
N_R = Number of items with a response
N_T = The total number of items which comprise the score.

A prorated score is computed when less than 20% of the items are missing. Otherwise, the score is set to missing.

The Overdose Risk Behavior Questionnaire consists of 9 items (eight 0-4 rated items and one 0-2 rated item). Using the above rule, the prorated score will be calculated when no more than 1 item is missing. If the missing item is one of the items on the 0-4 rating scale, the prorated score is derived by averaging the 7 remaining items on the 0-4 scale and multiplying by the number of items with a response and then adding the raw score of the item on the 0-2 scale using the following equation:

$$T_{ORB} = \left(\frac{T_{0-4}}{N_{R(0-4)}}\right) \times N_{T(0-4)} + T_{0-2}$$

where
T_{ORB} = Prorated total overdose risk behavior score
T_{0-4} = Total raw score based on those items on the 0-4 rating scale which have a response
$N_{R(0-4)}$ = Number of items on the 0-4 rating scale which have a response
$N_{T(0-4)}$ = Total number of items on the 0-4 rating scale; it should be 8
T_{0-2} = Raw score of the item on the 0-2 rating scale.

If the one missing item is the item on the 0-2 rating scale, the missing item score is imputed by averaging the 8 available items on the 0-4 rating scale and multiplying by ½. The prorated score is then derived by adding the total score from the 8 items on the 0-4 scale and the imputed score of the item on the 0-2 rating scale using the following equation:

$$T_{ORB} = T_{0-4} + \left(\frac{T_{0-4}}{N_{T(0-4)}}\right) \times {}^{1}/_{2}$$

where
T_{ORB} = Prorated total overdose risk behavior score
T_{0-4} = Total raw score based on those items with 0-4 rating scale
$N_{T(0-4)}$ = Total number of items with 0-4 rating scale; it should be 8.

The scores for Short Form 12 (SFM) will use the missing data estimation method (Maximum Data Recovery) provided within the Quality Metric proprietary software.

3.5 Table, Figures and Listings Conventions

Analyses of PCP participants described in this document are for the screened, randomized and study completer populations. They include the following:

- Summary of the screened PCPs by site and overall

- Summary of the randomized PCPs by site, intervention treatment arm and overall
- Summary of the study completers by intervention treatment arm and overall

Tables will include a total column or row. The descriptive text in the SAP, and the name of the table, listing, or figure, will indicate whether it is by treatment arm or site.

Analyses of patient participants include the population sets for the prescreened, screened, Intent-to-Treat, per protocol, complete case, primary outcome available, primary outcome not available, and study completer populations. They include the following:

- Summary of prescreened population by site and overall
- Summary of screened population by site and overall
- Summary of Intent-to-Treat population by intervention treatment arm, by site and overall
- Summary of per protocol population by intervention treatment arm, by site and overall
- Summary of completer case population by intervention treatment arm, by site and overall
- Summary of primary outcome available population by intervention treatment arm and overall
- Summary of primary outcome not available population by intervention treatment arm and overall
- Summary of study completer population by intervention treatment arm and overall.

Similarly, tables will include a total column or row. The descriptive text in the SAP, and the name of the table, listing, or figure, will indicate whether it is by treatment arm or site.

Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, percentiles (median, 25th and 75th percentiles, maximum and minimum). Categorical variables will be summarized in terms of frequencies and percentages in terms of non-missing counts.

4.0 PARTICIPANT ENROLLMENT, DISPOSITION, AND VISIT ATTENDANCE

4.1 PCP Participant

4.1.1 Participant Enrollment

The number of PCP participants screened, and the corresponding reasons for ineligibility on screening, will be summarized by site.

The distribution of individual PCP participant level and PCP cluster level treatment assignments by site will be presented.

The number of patient participants enrolled per PCP cluster will be presented by site and treatment arm both numerically and categorically.

4.1.2 Participant Disposition

PCP participants are considered early study terminations if the Provider Eligibility Review (PCP) form indicates the PCP withdrew from the study early and are defined as study completers if the withdrawal section is not complete on the form. PCP participant disposition will be summarized by site and treatment arm for the number of PCP participants completing the study, the number of PCP participants terminating early from the study, and the reasons for early study termination.

The CONSORT flow diagram will be generated for PCP participants [2].

4.2 Patient Participant

4.2.1 Participant Enrollment

The number of patient participants prescreened and screened, and the corresponding reasons for ineligibility on prescreening and screening, will be summarized by site. Note that patient participants may prescreen multiple times. Patient participants that prescreened multiple times will be considered for all attempts. The summary of prescreening will present both number of attempts and number of unique patients that prescreened eligible. Note that patient participants may be screened more than once. Patient participants who were screened more than once will only be considered for the last completed screening.

The trajectory of actual enrollments versus the expected number of enrollments (according to the date of site open for enrollment and under the assumption that eight patient participants are expected to be enrolled per month per site until November 2021 for the 5 initial sites, and 4.5 patient participants per site per month for the remaining 4 open sites until the date the proposed target of 300 is reached or the end of enrollment whichever occurs first) along with the proposed number of enrollments (300) will be graphed by site and overall. Proposed versus actual enrollments will be summarized by site in a tabular fashion.

The distribution of treatment assignments by site will be presented.

4.2.2 Participant Disposition

Patient participants are defined as study completers if the Month 12 Study Visit is completed as indicated on the Study Completion (STC) form and they are considered early study terminations if this visit is not completed. Patient participant disposition will be summarized by site and treatment arm for the number of patient participants completing the study, the number of patient participants terminating early from the study, and the reasons for early study termination.

The CONSORT flow diagram will be generated for patient participants [2].

4.2.3 Healthy Living Monthly Survey Completion

The primary outcome and several secondary outcomes are measured using the Healthy Living Monthly Survey (HLM). The self-reported HLM Survey assesses for risky opioid use and for specific classes of non-opioid substance use in the past 30 days for 12 months (12 surveys). The number of days of risky (illicit or nonmedical) opioid use is assessed in the monthly self-administered surveys that specify the number of days of illicit opioid use and of nonmedical opioid use in the past 30 days (range is 0-30 days). Also, days of non-opioid substance use are measured using the same approach as the days of opioid use for the following categories: binge drinking (4+ drinks/day for women; 5+ drink/day for men), benzodiazepines, illicit stimulants (cocaine and methamphetamine), prescription stimulants (amphetamines), marijuana, and other drugs, in the past 30 days. The number and percentage of patient participants submitting the survey and the number and percentage of patient participants completing the risky opioid use questions in each of the monthly surveys will be summarized by site and treatment arm.

4.2.4 Visit Attendance

The number and percentage of patient participants attending the five study visits will be summarized at baseline and at 3, 6, 9, and 12-months post-baseline by treatment arm. Information on missed visits during the study will be presented by treatment arm, including the number of missed visits, the number of patient participants with at least one missed visit, and the reasons for the missed visits. The expected number of study visits is calculated based on the general rule that five total visits are expected per patient participant. The average number of missed visits per patient participant will be calculated by dividing the number of missed visits by

the number of patient participants. For early study terminations, visits are only considered missed during active study participation if they occur before the study termination date.

5.0 ANALYSIS OF PARTICIPANT BASELINE CHARACTERISTICS

5.1 PCP Participant

Baseline demographics and characteristics including gender, age, ethnicity, race, and medical profession will be summarized by site and treatment arm for all randomized PCP participants. Age will be summarized as a continuous and categorial variable. A summary of baseline demographics and characteristics will also be presented for study completers by treatment arm. Because randomization is expected to produce balance at baseline between the treatment arms of the trial, comparisons of treatment arms with respect to baseline characteristics will be descriptive. If meaningful differences between treatment arms are suspected, statistical testing may be performed.

5.2 Patient Participant

Baseline demographics and characteristics including sex, age, ethnicity, race, education level, marital status, employment status, insurance status, time spent in jail or prison, number of risky opioid, binge alcohol, benzodiazepine, stimulant, marijuana, and other drug use days at prescreening, prescription for opioids in past 6 months at prescreening (y/n), COMM score, overdose risk behavior score, pain scores, anxiety, depression, sleep quality, health related quality of life, and addiction treatment and harm reduction program utilization will be summarized by site and treatment arm for all enrolled patient participants. Age will be summarized as a continuous and categorial variable. A summary of baseline demographics and characteristics will also be presented for study completers by treatment arm. Additionally, a summary of baseline demographics and characteristics by treatment arm will also be presented for the patient participants with the 6-month primary outcome available vs without the 6-month primary outcome available. It is expected that the balance of baseline characteristics at the patient participant level might not be ideal since randomization is conducted at the PCP cluster level. Comparisons of treatment arms with respect to baseline characteristics will be descriptive. If meaningful differences between treatment arms are suspected, statistical testing may be performed.

6.0 INTERVENTION EXPOSURE

6.1 STOP Exposure

The STOP intervention is comprised of several components delivered by the PCP, the nurse care manager (NCM), and the telephone health coach (THC). This information is captured on intervention checklists completed by the research staff, PCPs, the NCMs, and the THCs.

The number and percentage of patient participants in the STOP arm who received the PCP brief advice within and outside of the 10-day window, who received the Health Living Study Report Card and opioid overdose pamphlet, and who received the video doctor, and average number of minutes spent with PCP discussing opioid use will be presented by site.

The number and percentage of patient participants in the STOP arm who were educated on overdose prevention by the NCM, who received the workbook, who received information on how to access naloxone, and the distribution of contacts with the NCM over the 12 months of study participation will be presented by site. Receiving information to access naloxone is defined as any of the following: received a prescription, was given information to access it, was handed Narcan kit, or already has it, as reported on the NCM Intervention Checklist (NIC) form.

The number and percentage of patient participants in the STOP arm who completed 0, 1, 2, …, 6 coaching sessions, and the distribution of coaching sessions completed per participant will be presented by site.

6.2 EUC Exposure

Information on the exposure of patient participants in the EUC arm (receipt of educational materials and video viewing) is not collected in the data system and will not be presented.

7.0 EFFICACY ANALYSIS

7.1 Definition of the Primary Outcome Measure

The primary outcome (H1.1) measure is self-reported number of days of risky (illicit or nonmedical) opioid use in the past 180 days, assessed at 6 months after the baseline visit using single items based on questions used in the Addiction Severity Index (ASI) [3,4], and Current Opioid Misuse Measure (COMM) [5,6]. Participants are asked to specify the number of days of illicit opioid use and of nonmedical opioid use in the past 30 days (range is 0-30 days). Illicit opioid use includes use of heroin or synthetic opioids. Nonmedical opioid use includes using prescribed opioids more than prescribed (e.g., taking 2 tablets when the prescription indicates a dose of 1 tablet) or taking pharmaceutical opioids that were not prescribed to the individual taking them. Prescription opioids may be prescribed by the participating PCP or by another medical provider. The measure is calculated as the sum of all days of use reported on the assessments of past 30-day drug use for the first 6 months (i.e., the sum of days of use from the measures collected on day 30, day 60, day 90, day 120, day 150, and day 180).

7.2 Analysis of the Primary Outcome Measure

7.2.1 Calculation of the Number of Days of Risky Opioid Use for the Primary Outcome

Days of risky opioid use as measured in the Healthy Living Monthly Survey (HLM) will be used for the primary outcome analysis. No other data source, including Timeline Followback (T01), will be incorporated into the primary outcome analysis. The decision rule for generating the number of days of risky opioid use (illicit opioid use and nonmedical opioid use) during the past 30 days is to add up the days of different kinds of risky opioid use (e.g., use own prescription opioid medications more than prescribed, use opioid medications belonging to someone else, etc.), and then subtract the days when the risky opioid use was counted multiple times due to overlap (e.g., using heroin or fentanyl on the same day as using prescription opioids more than prescribed should only count as one day). The days of different kinds of risky opioid use are collected in the following questions:

For patient participants that report they currently have a prescription for an opioid pain medication (HMOPIRX=1):

a) (HMPNKOTH) During these 30 DAYS, on how many days did you need to take pain medications **belonging to someone else**? *(Enter "0" for never);*
b) (HMRXMORE) During these 30 DAYS, on how many days did you have to **take more of your medication than prescribed**? *(Enter "0" for never);*

For patient participants that do not report currently having a prescription for an opioid pain medication (HMOPIRX=0):

c) (HMOPINP) During these 30 DAYS, on how many days did you use **prescription opioid medications** that were not prescribed to you? *(Enter "0" for never)*

For all patient participants:

d) (HMHERFYL) During these 30 DAYS, on how many days did you use **heroin or fentanyl**? *(Enter "0" for never)*

The days of overlap are collected in the following questions:

For patient participants that report currently having a prescription for an opioid pain medication (HMOPIRX=1) and reported > 0 days for both HMPKOTH and HMRXMORE:

e) (HMPOSDNY) During these 30 DAYS, did you ever use your own prescription opioid medications more than prescribed **on the same day** that you used opioid medications that belonged to someone else? (y/n);

f) If the answer to HMPOSDNY is Yes: (HMPOSDDY) During these 30 DAYS, on how many days did you use your own prescription opioid medications more than prescribed **on the same day** that you used opioid medications that belonged to someone else? *(Enter "0" for never)*

For all patient participants that reported > 0 days for HMHERFYL **and** > 0 days for (HMPKOTH **or** HMRXMORE **or** HMOPINP):

g) (HMHEROPI) During these 30 DAYS, did you ever use heroin or fentanyl **on the same day** you used prescription opioid medications more than prescribed or that were not prescribed to you (including medications that belonged to someone else)? (y/n)

h) If the answer to HMHEROPI is Yes: (HMHEROSP) During these 30 DAYS, on how many days did you use heroin or fentanyl **on the same day** you used prescription opioid medications more than prescribed, or that were not prescribed to you (including medications that belonged to someone else)? *(Enter "0" for never)*

Therefore, the algorithm of generating the days of risky opioid use in the past 30 days to adjust for the days of overlap when different types of risky opioid use occurred on the same day is to:

For patient participants with HMOPIRX=1:

1. Add the items (a) and (b) and subtract (e/f)
2. Add the result from #1 to (d) and subtract (g/h)

For patient participants with HMOPIRX=0:

1. Add the items (c) and (d) and subtract (g/h)

If the calculated days of risky opioid use in the past 30 days is greater than 30 based on the algorithm (e.g., due to the patient participant incorrectly completing the overlap questions), the calculated days of risky opioid use in the past 30 days will be set to 30.

When there are multiple submissions collected for HLM from the same patient participant in the same month, the data from the first submission will be used to calculate the primary outcome. If the data from the first submission is missing, the data in the second submission will be used to calculate the primary outcome. In general, the primary outcome will be calculated from the first collected non-missing data.

The number and percent of patient participants with the primary outcome data collected in the 6 monthly surveys will be summarized by intervention treatment arm. The primary outcome is considered available for a patient participant if all the questions for risky opioid use (illicit and non-medical) are completed on all six of the monthly surveys. Multiple imputation will be used to impute missing primary outcome data so that there are no missing outcome data in the primary outcome analysis.

7.2.2 Statistical Analysis Methods for Primary Outcome

Because the most intensive intervention period is during the initial 3-4 months, the primary outcome is measured at 180 days (6 months) to capture the main intervention effect. Given the primary outcome is the number of days of risky opioid use within the first 180 days following the baseline assessment collected with HLM, a mixed effects negative binomial model with a log link will be fit to estimate the difference in means between treatment and control groups. Fixed effects include treatment effect, site effect, and the baseline value of the response variable (days of use within 30 days prior to the baseline assessment timepoint), which may improve precision. Random PCP intercepts are to account for within-PCP correlation of participant response values. Since randomization was at PCP team level where PCPs practiced in teams and shared patients regularly, PCP cluster was specified as PCP/PCP team which was the unit of randomization, that is, if two or more PCPs are randomized as a single cluster, they will be analyzed as a single cluster. Letting Y_{jk} denote the response variable of a participant in site j with PCP k, treatment denotes a binary treatment indicator variable, site denotes a multi-level categorical variable representing study sites, and baseline denote the baseline value, the formula for the log-transformed expectation of Y_{jk} is given:

$$\log[E(Y_{jk})] = \beta_0 + \beta_1 \cdot \text{treatment} + \beta_2 \cdot \text{baseline} + \beta_3 \cdot \text{site} + \gamma_k,$$

where γ_k is normally distributed with mean zero and standard deviation σ_γ representing random effect by within-PCP correlation of participant responses. The negative binomial model allows for potential overdispersion of the response variable, so is more flexible than a Poisson distribution which would require the mean to be equal to the variance.

The primary hypothesis will be evaluated by testing whether the treatment effect, β_1, is different from zero. This is equivalent to testing whether the control mean is different from the intervention mean.

The template SAS code for the primary analysis is:

```
PROC GLIMMIX DATA=dat METHOD=quad;
        CLASS PCP treat site;
        MODEL daysin180 = treat site baseline / solution DIST=negbin LINK=log ddfm=bw;
        RANDOM intercept / SUBJECT= PCP;
RUN;
```

Where:

"dat" is the name of the dataset with one row per patient participant,

"daysin180" is the name of the primary outcome, a continuous variable indicating the number of days of risky opioid use within the first 180 days following the baseline assessment,

"treat" is a binary indicator variable coded as "1" for intervention arm STOP and "0" for control arm EUC,

"baseline" is a continuous variable indicating the number of days of risky opioid use during past 30 days prior to baseline assessment,

"site" is a categorical variable for 5 participating sites, and

"PCP" is a character variable representing PCP clusters.

The option method = quad indicates that the likelihood will be evaluated using the Gaussian quadrature method. Assessment of model fit will be reported based on standard goodness-of-fit metrics (e.g., deviance) and inspection of Pearson residuals.

The treatment effect of STOP from this model will be given as a rate ratio, the exponentiated estimate of the treatment effect, along with a 95% confidence interval. This can be interpreted as a ratio of the mean total number of days of risky opioid use for those enrolled to STOP versus EUC within the first 180 days post-randomization, when all other variables in the model are held constant. A risk ratio less than 1 would indicate fewer days of risky opioid use for those assigned to STOP compared to those assigned to EUC.

The primary outcome analysis will be performed on the Intent-to-Treat (ITT) Population, analyzing patient participants according to their PCP's randomization assignment regardless of potential exposure to the opposite assignment. The primary analysis will use multiple imputation to account for missingness of the primary outcome variable with details provided in Section 7.2.3.

7.2.3 Multiple Imputation for Missingness of the Primary Outcome

The primary outcome, number of days of risky opioid use within the first 180 days since baseline, is measured by repeated monthly assessments. For each monthly assessment, participants will record the number of days of risky use within the previous 30 days. We consider two types of missing data for this outcome:

- *Missingness due to dropout:* patient participants may withdraw early from the study and miss all subsequent monthly measurements.
- *Intermittent missingness:* patient participants may miss one or more monthly surveys, or fail to complete the opioid items on the survey, while remaining enrolled in the study.

It was anticipated during the study design stage that up to 20% of participants may be missing data for the primary endpoint due to dropout and/or nonresponse. Exclusion of those participants with missing values could lead to underestimation of variance and biased estimated parameters. Multiple imputation (MI) will be performed for the primary analysis to account for missingness of the primary outcome variable. For the sake of best practice, if a patient participant misses the response values at baseline and in each of the monthly surveys for the risky opioid use questions for all 12 post-baseline collections, the patient participant will be excluded from multiple imputation since the analysis has little or no information to inform what those actual values might have been.

Multiple imputation consists of three steps:

1. Imputation step. An 'imputation' generally represents one set of plausible values for missing data – multiple imputation represents multiple sets of plausible values. When using multiple imputation, missing values are filled in to generate multiple completed datasets.
2. Completed-data analysis (estimation) step. The desired analysis is performed separately for each dataset that is generated during the imputation step.
3. Pooling step. The results obtained from each completed data analysis are combined into a single multiple imputation result.

Data for the primary outcome analysis is collected from the HLM survey. The analysis dataset includes monthly risky opioid use in Month 1, Month 2, Month 3, …, Month 6 for the first 6 months post-enrollment, along with baseline risky opioid use, site, treatment, and PCP cluster.

Missing patterns of the information in monthly survey for risky opioid use for the first 6 months in terms of the number and proportion will be examined and reported. The following SAS statements are used to examine the missing patterns of the data:

```
PROC MI DATA=datmiss NIMPUTE=0;
        VAR daysinmon1-daysinmon6;
        ODS OUTPUT missPattern=pattern;
RUN;
```

where

"datmiss" is the name of the dataset including variables of each monthly risky opioid use for the first 6 months with one row per patient participant,

"daysinmon1-daysinmon6" are the six continuous variables indicating the number of days of risky opioid use from month1 to month6 post-baseline.

Table 2 displays an example of the dataset having 200 patient participant records outputted from the above SAS code; it is a summary of the missing data patterns for the number of days of risky opioid use for month1 to month6.

Table 2: Missing Data Patterns

Group	Daysinmon1	Daysinmon2	Daysinmon3	Daysinmon4	Daysinmon5	Daysinmon6	Freq	Percent	Group Means		
									Daysinmon1	Daysinmon2	……
1	X	X	X	X	X	X	160	80.0	24	21	…
2	X	X	X	X	X						
3	X	X	X	X							
4	X	X		X	X						
5		X		X	X	X					
6	……										
7	……										
8	……										

In the primary outcome analysis dataset, there are two types of missing data patterns: monotone missingness and non-monotone missingness.

- The monotone missingness pattern indicates if an outcome is not observed at a particular month for a patient participant, the outcome will not be observed in all subsequent months for that patient participant. Patient participants who drop-out of the study never to return to complete any of the monthly assessments are considered to have a monotone missingness pattern.
- If the pattern is not monotone, it is called non-monotone, and indicates a structure where there is no particular pattern in the missing data structure. Intermittent missingness in which patient participants miss a monthly survey but return to complete one or more other monthly surveys is considered to be non-monotone missing.

In the example in Table 2, Group 1 consists of 160 patient participants who completed the risky opioid use questions in all 6 months, which covers 80% of the total 200 observations (160/200) with a mean of 24 days of risky opioid use in month 1 and a mean of 21 days of risky opioid use in month 2. Groups 2 and 3 present two monotonic missingness data patterns in which patient participants drop out after the Month 5 and Month 4 surveys, respectively. Groups 4 and 5 present two non-monotonic missing data patterns showing intermittent missingness.

The impact of missing data depends on the missingness mechanism, of which there are three: Missing Completely at Random (MCAR), Missing at Random (MAR) and Missing Not at Random

(MNAR). In MCAR, missingness is unrelated to any measured or unmeasured characteristic, and the missing observations are a random subset of all observations. In this study, MCAR is unlikely and is not considered further. In MAR, there may be systematic differences between the missing and observed values, but they can be explained by other observed variables and with MNAR, the missingness can only be explained by unobserved data.

Five missing data patterns for risky opioid use (no missing data, intermittent missing, missing due to dropout, both intermittent missing and missing due to dropout, and all missing) will be summarized by treatment arm in the ITT population. The number and percentage of patient participants with each individual pattern and a summary of number of patient participants per pattern will be presented by treatment arm.

For CTN-0101, the following assumptions will be made:

1. For the patient participants with intermittent missingness, assume MAR.
    - While the missingness are from intermittent missingness, in which an unobserved outcome can be followed by observed outcomes since the patient participants remain in the assigned intervention group, therefore the observed outcomes can effectively predict the propensity of the missing values and the missing mechanism is missing at random (MAR).
2. For the patient participants who dropout, assume MNAR.
    - It is assumed that patient participants who drop out will have higher use after their dropout date than those who remain in the study, that is, that days of use after the withdrawal timepoint for dropouts in the treatment arm may more closely resemble that of controls than that of other treated patient participants. The values of missingness due to dropout might not retain the trend of prior observations since they are not exposed in the study environment due to various reasons, therefore the mechanism of missingness is assumed missing not at random (MNAR).

For the imputation of the primary outcome, two separate imputation procedures will be used to complete the imputation process for intermittent missingness and dropout. In the first step, the MI procedure statement uses the Markov Chain Monte Carlo (MCMC) method to impute the values of missing outcomes from intermittent missingness under the missing assumption of MAR. The variables specified in the mixed-effect regression model in Section 7.2.2, are included for imputation of primary outcome. The SAS code for imputing missing data from intermittent missingness is given below.

```
/* imputing the intermittent missingness with MAR assumption */
PROC MI DATA=datamiss nimpute=30 OUT=outimp1 SEED = 100623
  min=. . 0 0 0 0 0 0 0
  max=. . 30 30 30 30 30 30 30;
  by treat;
  mcmc impute=monotone;
  VAR treat site baseline daysinmon1-daysinmon6;
RUN;
```

In this step, this MI procedure produces 30 imputed datasets by filling in the missing values from intermittent missingness with statement “impute=monotone”, and then produces the datasets as monotone missingness. The missing values due to intermittent missingness are imputed assuming that the intervention effect is still carried out while they remain enrolled in the study.

Next, MI procedure is to impute missing values from the dropouts under assumption of missing not at random (MNAR), which is a control-based pattern imputation assuming that after dropout, the unobserved values in the intervention group follow the path of observed values in control group. Based on this assumption, only the observed values in EUC group are used to derive the posterior distribution of the parameters from which the missing values in both EUC and STOP group are imputed. This approach is conservative as it tends to reduce the difference between STOP group and EUC group. The SAS code for imputing missing data from dropout is given below.

```
/* imputing the dropouts with MNAR assumption */
PROC MI DATA=outimp1 nimpute=1 OUT=outimp2 SEED = 100623
  min=. . 0 0 0 0 0 0 0
  max=. . 30 30 30 30 30 30 30;
  CLASS treat site;
  VAR treat site baseline daysinmon1-daysinmon6;
  monotone REG;
  MNAR model(daysinmon1-daysinmon6/ modelobs=(treat="0"));
RUN;
```

As the 30 completed datasets are generated, analyses of the 30 imputed datasets using the standard procedure for the mixed effects negative binomial model are performed separately for each imputed dataset using "by _imputation" statement.

```
/* analysis model */
PROC GLIMMIX DATA = outmi NOCLPRINT;
  BY _imputation_;
      CLASS PCP treat site;
      MODEL daysin180 = treat site baseline / DIST=negbin LINK=log;
      RANDOM intercept / SUBJECT = PCP;
      LSMEANS treat / pdiff ILINK;
      ODS OUTPUT PARAMETERESTIMATES=GPARMS;
RUN;
```

To draw statistical inference based on the results from the 30 imputations, the combination rules are applied in MIANALYZE procedure [7, 8]. Proc MIANALYZE is set to estimate the pooled variance from two components: within-imputation variance and between-imputation variance. Within-imputation variance is the average of the mean of the within variance estimate in each imputed dataset. Between-imputation variance reflects the extra variance due to the missing data, which is estimated by taking the variance of parameter of interest estimated over imputed datasets. Simulations indicate that the 30 imputations will produce enough efficiency to avoid diminishing power for detection of the treatment effect [9].

```
  /* pooling the individual estimates from each imputed datasets into one set of estimates*/
PROC MIANALYZE PARMS=mixparms;
  CLASS visno;
  MODELEFFECTS intercept treat site baseline;
 RUN;
```

Statistical inferences of the treatment effect will be presented as the rate ratio along with its 95% confidence interval adjusting for site effect and the values of risky opioid use within 30 days prior to the baseline assessment based on the combination of the 30 imputed datasets.

7.3 Sensitivity Analyses of the Primary Outcome Measure

Mechanisms of missingness cannot be determined from observed data alone, therefore sensitivity analyses will be done to compare different assumptions of missingness in order to assess the robustness of the conclusions from the primary outcome analysis with multiple imputation. The following sensitivity analyses of the primary outcome will be conducted:

1. Conducting a complete-case analysis. Here the complete case population (a subset of the ITT population) will be fit with the same model as specified in Section 7.2.2. The complete case population is the set of the patient participants with no missing values for the primary outcome in Months 1-6 and baseline level of days of risky opioid use. Note that the variables of treatment, site, and PCP cluster will have no missing values.
2. Conducting multiple imputation by assuming the missing data mechanism is MAR for both the intermittent missingness pattern and the dropout scenario under the assumption that the values of missingness remain the trend of the observed values regardless of the exposure in the study environment.

7.4 Supplemental Analyses of the Primary Outcome Measure

Adjusting for demographic and baseline characteristics in the analysis of randomized clinical trials is advised by both the European Medicines Agency [10] and the US Food and Drug Administration [11] in order to increase the precision of the estimator for the treatment effect, that is to increase statistical efficiency and avoid conditional bias from covariate imbalance. A mixed effects regression model using the ITT population will include more individual-level covariates which may be associated with the response. Those individual-level covariates pre-specified in the protocol were expected to have an influence on the primary outcome, including demographic variables, baseline measures of risk behaviors, substance use at baseline, presence of alcohol or drug use disorder, pain ratings, mental health symptoms or conditions, and health-related quality of life. Table 3 lists the covariates that will be used to explore the relationship of the treatment effect on the primary outcome adjusting for potential covariates.

Table 3: Potential individual-level covariate variables

Covariate	*Source variable names*[1]	*Coding in analysis*	*Description of covariate*
Site	COREVARS.SITE	categorical	5 sites
Sex	COREVARS.SEX_CAT	categorical	Male/Female
Age	COREVARS.AGE	continuous	Age at enrollment
Ethnicity	COREVARS.ETHNIC	categorical	Hispanic/Non-Hispanic
Race	COREVARS.RACE_CAT	categorical	Black/White/Other
Education	DEM.DEEDUCTN	categorical	Less than Bachelor's degree/Bachelor's degree and above
Marital Status	DEM.DEMARTL	categorical	Married + Living with partner/Other
Job	DEM.DEJOB	categorical	Working now/Retired/Other
Baseline Risky Opioid use	COREVARS.OPI30 (HLS)	continuous	Number of days of risky opioid use during past 30 days prior to baseline assessment

Table 3: Potential individual-level covariate variables			
Covariate	***Source variable names[1]***	***Coding in analysis***	***Description of covariate***
Prescription Opioid Misuse Behaviors (COMM) at Baseline	COREVARS.CMMSCR (HLS)	continuous	Score to measure opioid misuse behaviors at baseline
Alcohol Use Disorder at Baseline	COREVARS.AUDSCR (PDQ)	continuous	Score to measure alcohol use disorder at baseline
Drug Use Disorder at Baseline	COREVARS.DUDSCR (PDQ)	continuous	Score to measure drug use disorder at baseline
Overdose risk behavior at Baseline	COREVARS.ORBSCR (ORB)	continuous	Score to measure overdose risk behavior at baseline
Pain severity at Baseline	COREVARS.BPISCR_SEV (BPI)	continuous	Score to measure pain severity at baseline
Pain interference at Baseline	COREVARS.BPISCR_INT (BPI)	continuous	Score to measure pain interference or functioning at baseline
Anxiety symptom at Baseline	COREVARS.PMASCR (PMA)	continuous	Score to measure anxiety symptoms at baseline
Depression Symptoms at Baseline	COREVARS.PHQSCR (PHQ)	continuous	Score to measure depression symptoms at baseline
Sleep quality at baseline	COREVARS.PMSSCR (PMS)	continuous	Score to measure sleep disturbance at baseline
Health-related Quality of Life at Baseline	COREVARS.SFMSCR (SFM)	continuous	Score to measure overall health-related quality of life at baseline

[1] Covariates that are calculated or scores are in the COREVARS analysis dataset and are derived from the data from the form name listed in paratheses.

The aim of covariate adjustment is not to determine the true relationship between covariates and the primary outcome variable but to provide an unbiased estimate of the true treatment effect. The regression model is based on a linear relationship between the covariates and the primary outcome when the covariate is continuous. However, increasing the number of covariates can decrease the power of the study and cause collinearity, so the following steps will be taken to identify the covariates to be included in the regression model:

1. Include the two covariates of site (stratification factor) and baseline value of response as identified in the primary outcome analysis model in Section 7.2.2.
2. Include all covariates from Table 3 that will result in 70% or more of the ITT population being included in the analysis. Since the mixed effect model will remove the entire patient record from the analysis if it is missing any covariate value, covariates with a significant amount of missing data will be removed.

3. Run correlation analyses among the covariates, and select the covariate set with low or moderate correlation to avoid collinearity and provide efficiency gains.
4. To gain analytical power, a general rule of thumb is that 10-20 observations should be used for estimating a parameter [12]. If the number of covariates after steps 2 and 3 is more than 10, the distributions of the remaining covariates will be compared by intervention group to select the potential confounders associated with baseline imbalances.

Multiple imputation will not be performed in the individual-level covariate adjusted regression model. The estimates of treatment effect will be compared between the regression models with and without the individual-level covariate adjustment to assess the robustness of the conclusion drawn from the primary analysis.

Subgroup analyses for sex (Male, Female), age (18 – 54 years, 55 years or greater), race (Black, White, Other) and ethnicity (Hispanic or Latinx, Not Hispanic or Latinx) will be performed as required by the NIH [13]. Responses of “Unknown,” “Don’t know” and “Refused to answer” will not be analyzed. These subgroup analyses will utilize the same mixed-effect model as for the primary outcome analysis, but with the inclusion of an interaction term between treatment arm and the demographic subgroup. Contrasts will be used to test for statistically significant differences in the primary outcome hypothesis by subgroup.

An analysis using the Per Protocol (PP) population will be performed using the same methods as described in Section 7.2.2. This population will exclude participants who had appointments with PCPs in the opposite treatment arm or had deviation from the protocol in terms of intervention exposure including the participants who were shown the wrong video doctor. No multiple imputation will be conducted for the PP population.

7.5 Definition of Other Outcome Measures Related to Primary Objective

Related to the primary objective, the hypothesis (H1.2) is that patient participants with primary care providers assigned to the STOP intervention will have fewer days of risky opioid use, measured at 3, 9, and 12 months from baseline, in comparison to patient participants with primary care providers assigned to EUC. The 3-month secondary outcome measure will assess early intervention effects, while the 9- and 12-month secondary outcome measures will assess the durability of intervention effects (which may be maintained, increased, or decreased) over time.

Therefore, the other outcomes related to the primary objective include days of risky opioid use at specified time points:

i. In the past 30 days, measured at baseline and monthly for 12 months.
ii. In the past 90 days, assessed at 3, 6, 9, and 12 months.
iii. In the past 180 days, assessed at 12 months.

7.6 Supportive Analysis of Other Outcome Measures Related to Primary Objective

Data for the supportive analysis of other outcomes related to the primary objective will be from the HLM survey, and no imputation of missing outcome data will be conducted for those outcomes. The ITT Population will be used for the analyses.

Visualization presentation using box plots and descriptive summary statistics including mean, standard deviation, median and range will be provided for days of risky opioid use in the past 30 days measured at baseline and monthly for 12 months, in the past 90 days measured at 3, 6, 9, and 12 months, and in the past 180 days measured at 6 and 12 months by intervention treatment arm.

Treatment effect, time variability, and temporal trends will be evaluated for risky opioid use during the past 30 days based on a longitudinal data framework treating monthly risky opioid use as a count outcome. A mixed effects negative binomial model will be fit including treatment, time, and the interaction of treatment × time to explore time trends and time variability between the two treatment arms through the 12 months of the study period. Time trend analysis will be repeated for monthly observations of the 30-day sum of risky opioid use days in order to further understand and describe temporal patterns. The piecewise linear function will be used to accommodate varying trends of change in opioid use during different period segments. This function will allow accurate description and easy interpretation of the non-linear trend over time associated with change of opioid use throughout the 12 months of intervention and follow-up duration. A piecewise linear mixed-effects model allows different linear functions of time (varying time slopes) corresponding to breaking points (knots) during the whole study period. To investigate the time trend and time variability in change of risky opioid use, different breaking points will be assessed in conjunction with graphical presentation, e.g., a spaghetti plot, to depict the growth trajectory patterns. The final breaking points to fit the piecewise linear function of time will be determined by the data structure and statistical criteria of good of fit, e.g., AIC or likelihood ratio test.

Fixed effects include treatment, piecewise linear function of time, interaction of treatment × piecewise linear function of time, baseline risky opioid use and site. A random effect term for patient participants will be included to account for the correlation of repeated measures within the same patient participant and within-PCP correlation of participant responses. The autoregressive covariance structure will be used to take into account the correlation of the repeated measures of monthly risky opioid use. This structure specifies that observations that are more proximate to one another are more correlated than those that are more distant.

The following is an example of a model with piecewise linear functions at the breaking point of month 6 to allow the slopes that represent the change in the outcome over time to vary between Months 1-6 and Months 7-12.

The SAS code to create a linear spline variable to specify time spline “timespl” equal to “0” when time is from Months 1 to Month 6, or equal to “time – 6” when the time is greater than Month 6 is as follows.

```
DATA datmonthly;
        SET datmonthly;
        Chgpoint=6;
        If time <= Chgpoint then timespl=0;
         else if time >Chgpoint then timespl = time - 6;
RUN;
```

The model investigates whether there is treatment effect on change of monthly risky opioid use over 12 months. The estimates of time and piecewise linear time spline will provide information on the change of risky opioid use before and after Month 6. The interaction terms of treatment with time and time spline assess the difference in change of opioid use associated with the treatment effect during the two time segments. The “Estimate” statement is used to derive the following estimates and corresponding p-values:

1. Difference of time slopes in change of risky opioid use during Months 1-6 between the two treatment groups
2. Difference of time slopes in change of risky opioid use during Months 7-12 between the two treatment groups.

```
PROC GLIMMIX DATA=datmonthly METHOD=quad;
    CLASS PATID PCP time treat site;
    MODEL daysmonthly = treat time timespl treat*time treat*timespl site baseline / solution
    DIST=negbin LINK=log ddfm=bw;
    RANDOM intercept / SUBJECT= PCP;
    REPEATED / SUBJECT=PATID TYPE=AR(1);
    Estimate “Difference of change Months 1-6”
    time 0 timespl 0 treat*time 1 -1 treat*timespl 0 0/ CL ilink;
    Estimate “Difference of change Months 7-12”
    time 0 timespl 0 treat*time 1 -1 treat*timespl 1 -1/ CL ilink;
RUN;
```

where

“datmonthly” is the name of the dataset with one row for each month of risky opioid use for each patient participant in a long format,

“daysmonthly” is the name of the outcome, a continuous variable indicating monthly use of risky opioid use (days),

“treat” is a binary indicator variable coded as “1” for intervention arm STOP and “0” for control arm EUC,

“time” is a continuous variable indicating the number of the month when the opioid use is collected,

“timespl” is a continuous variable equal to 0 when time is in Months 1-6, or equal to time – 6 when the time is months 7-12;

“baseline” is a continuous variable indicating the number of days of risky opioid use during past 30 days prior to baseline assessment,

“site” is a categorical variable for the 5 participating sites,

“month” is a categorical variable for month during the study,

“PATID” is a character variable representing patient participant ID, and

“PCP” is a character variable representing PCP clusters.

Comparison of the time trend measured by time slopes in change of risky opioid use in treatment arm STOP compared to EUC during Months 1-6 and Months 7-12 separately will be reported as the estimated risk ratio along with a 95% confidence interval given the linear combination of estimated parameters shown in the Estimate statement.

Another supportive analyses will explore temporal patterns of number of days of risky opioid use during the past 3 months. The 3-month (days of use in the first 90 days post-baseline) and 6-month (days of use in days 91-180 post-baseline) outcome measures will assess early intervention effects. The measures at 9 and 12 months (days of use in days 181-270 post-baseline and in days 271-360 post-baseline, respectively) will assess the durability of intervention effects (which may be maintained, increased, or decreased) over time. These data analyses will utilize a longitudinal mixed effect negative binomial regression model treating quarterly risky opioid use during months 1-3, months 4-6, months 7-9 and months 10-12 as the dependent count variables. Fixed effects include treatment, time indicator in terms of duration of past 3 months, site and an interaction between treatment and time indicator. Time indicator will enter the model as a categorical variable (1 for months 1-3; 2 for months 4-6; 3 for months 7-9 and 4 for months 10-12) to allow greater flexibility. A random effect term for patient participants will be included to account for correlation of repeated measures on the same patient participant and within-PCP

correlation of participant responses. The template SAS code to fit the model in estimating treatment effect of STOP during Months 1-3 is given below.

```
PROC GLIMMIX DATA=datquar METHOD=quad;
    CLASS PATID PCP time treat site;
    MODEL daysquar = treat|time site baseline / solution DIST=negbin LINK=log ddfm=bw;
    RANDOM intercept / SUBJECT= PCP;
    REPEATED intercept/ SUBJECT=PATID TYPE=AR(1);
    Estimate “Treatment effect during Months 1-3” treat 1 -1 treat*time 1 0 0 0 -1 0 0 0/ CL
    ilnik;
    Contrast “Treatment effect during Months 1-3” treat 1 -1 treat*time 1 0 0 0 -1 0 0 0/ CL
    ilnik;
RUN;
```

where

“datquar” is the name of the dataset with one row for each quarterly risky opioid use for each patient participant,

“daysquar” is the name of the outcome, a continuous variable indicating quarterly use of risky opioid use (days),

“treat” is a binary indicator variable coded as “1” for intervention arm STOP and “0” for control arm EUC,

“time” is a categorical variable to indicate the time of past 3 months,

“baseline” is a continuous variable indicating the number of days of risky opioid use during past 30 days prior to baseline assessment,

“site” is a categorical variable for 5 participating sites,

“PATID” is a character variable representing patient participant ID, and

“PCP” is a character variable representing PCP clusters.

The treatment effect of STOP from this model will be presented as a rate ratio given the treatment effect and interaction of treatment x time along with a 95% confidence interval. The STOP intervention’s ability to reduce risky opioid use during months 1-3 compared to EUC is assessed by the treatment effect and interaction of treatment × time of the duration of months 1-3. The rate ratio, 95% confidence interval, and p-value will be reported for the treatment effect during months 1-3. Similarly, treatment effects of durations of months 4-6, months 7-9 and month 10-12 are obtained from the same mixed effect model.

To assess the number of days of risky opioid use during the past 180 days measured at 12 months, the data will be analyzed with a longitudinal mixed effect negative binomial regression model treating days of risky opioid use during months 1-6 and months 7-12 as the dependent count variable. The model for past 180 days is similar to the one for past 90 days specifying time indicator as a categorical variable (1 for months 1-6, and 2 for months 7-12). The STOP intervention’s ability to reduce risky opioid use during months 7-12 compared to EUC is assessed by the treatment effect and interaction of treatment × time of the duration of months 7-12.

7.7 Definition of Secondary Outcome Measures

Measures of Patient-Level Outcomes

1. Days of substance use: Self-reported days of substance use are collected at baseline and once every 30 days. Patient participants are asked to specify the number of days of use in the past 30 days (range is 0-30 days, value=0 for substances that were not used). For

binge alcohol use, the measure defines the cutoff as 5+ drinks (for men under age 65), and 4+ drinks (for women and men age 65 and over). Measures of substance use are calculated as the sum of consecutive assessments of days of use in the past 30 days. For example, days of use in the past 90 days is calculated as the sum of three consecutive assessments of days of use in the past 30 days.

a. H2.1. Days of binge alcohol use:
    i. In the past 30 days, measured at baseline and monthly for 12 months.
    ii. In the past 90 days, assessed at 3, 6, 9, and 12 months.
    iii. In the past 180 days, assessed at 6 and 12 months.

b. H2.2. Days of benzodiazepine use:
    i. In the past 30 days, measured at baseline and monthly for 12 months.
    ii. In the past 90 days, assessed at 3, 6, 9, and 12 months.
    iii. In the past 180 days, assessed at 6 and 12 months.

c. H2.3. Days of stimulant drug use (cocaine and amphetamine-type stimulants):
    i. In the past 30 days, measured at baseline and monthly for 12 months.
    ii. In the past 90 days, assessed at 3, 6, 9, and 12 months.
    iii. In the past 180 days, assessed at 6 and 12 months.

d. H2.4. Days of marijuana use.
    i. In the past 30 days, measured at baseline and monthly for 12 months.
    ii. In the past 90 days, assessed at 3, 6, 9, and 12 months.
    iii. In the past 180 days, assessed at 6 and 12 months.

e. H2.5. Days of other drug use (not including opioids, benzodiazepines, stimulants and marijuana).
    i. In the past 30 days, measured at 3, 6, 9, and 12 months.

f. H2.6. Increase in number of days of risky opioid use from baseline to follow-up at 6 and 12 months:
    i. Days of opioid use in the past 30 days, measured at baseline and monthly for 12 months.
    ii. Days of opioid use in the past 180 days, assessed at 6 and 12 months.

g. H2.7. Prescription opioid misuse behaviors, among participants receiving prescribed opioids:
    i. Days of taking prescribed opioids for symptoms other than for pain, using prescribed opioids more than prescribed, or taking pain medication belonging to someone else, measured at baseline and monthly for 12 months.
    ii. COMM score, assessed at screening and at 6 and 12 months.

h. Urine Drug Screens are used to verify self-reported drug use. Urine drug screens are conducted at baseline and at 6 and 12 months.

i. For participants receiving prescribed opioids, the COMM provides an additional measure of prescription opioid misuse, collected at baseline and at 6 and 12 months.

2. Substance use disorder: Opioid use disorder is assessed at baseline and at 6 and 12 months using the modified World Mental Health Composite International Diagnostic Interview (CIDI). Drug (other than opioid) and alcohol use disorder measures are collected using the PDSQ at baseline and at 6 and 12 months. The PDSQ is used rather than the CIDI for these measures because it is brief and self-administered, which makes it more feasible for these follow-up assessments.
    a. H2.8. Moderate-severe opioid use disorder (CIDI opioid items)
    b. H2.9. Drug use disorder (PDSQ drug items)
    c. H2.9. Alcohol use disorder (PDSQ alcohol items)
3. Overdose risk behaviors and events
    a. H2.10. Overdose risk behavior and behavioral intention to reduce risk is measured at baseline and at 6 and 12 months (Overdose Risk Behavior Questionnaire)
    b. H2.10. Episodes of non-fatal overdose are measured at baseline and at 6 and 12 months (Non-Fatal Overdose Questionnaire)
4. Pain symptoms and pain-related functioning
    a. H2.11. Pain symptoms (severity, impact on functioning) are measured at baseline and at 3, 6, 9, and 12 months using the BPI short form (items #3-6 for pain symptoms and items #9A-9G for functioning).
5. Mental health
    a. H2.12. Anxiety symptoms are measured at baseline and 6 and 12 months (PROMIS short form)
    b. H2.12. Depression symptoms and suicidality are measured at baseline and at 6 and 12 months (PHQ-8 and PSS)
    c. H2.13. Sleep quality is measured at baseline and at 6 and 12 months (PROMIS Sleep 4a)
6. Health-related quality of life and acute health care utilization
    a. H2.14. Health-related quality of life is measured at baseline and at 6 and 12 months (SF-12)
    b. H2.15. ED and hospital utilization is measured using participant self-report of acute care events (ED visits, hospitalizations for medical reasons, hospitalizations for detoxification), collected at baseline and at 6 and 12 months.

Measures of provider-level outcomes

Measures of provider treatment practices are collected from the EHR at baseline and 12 months, for patient participants. The data extracted for each patient participant will be for the period beginning 12 months prior to study participation, through 12 months following enrollment.

1. H3.1. Prescriptions for opioids: number of patient participants receiving prescriptions for high-dose opioids (>90 MME); moderate-dose opioids (50-90 MME); and any opioids: number of prescriptions; daily prescribed dose; and total number of days prescribed.
2. H3.2. Prescriptions for benzodiazepines: number of patient participants receiving benzodiazepine prescriptions and number receiving both chronic opioid and benzodiazepine prescriptions: number of prescriptions; daily prescribed dose, and total number of days prescribed.

3. H3.3. Prescriptions for naloxone: number of patient participants receiving at least 1 prescription.
4. H3.4. Urine Drug Screens: number ordered and completed for each patient participant.
5. H3.4. Diagnosis of OUD: number of patient participants receiving a new diagnosis of OUD during the study period.
6. H3.4. Primary care visits: number of scheduled visits per patient participant.

7.8 Analyses of Secondary Outcome Measures

The DSC will analyze the following secondary outcomes: H2.1, H2.2, H2.3, H2.4, H2.5 and descriptive analysis for urine drug screens. The LN will analyze the rest of the secondary outcomes.

A secondary aim is to evaluate the impact of the STOP intervention on days of alcohol and drug use that increases risk of opioid related overdose. For this aim, those variables will be analyzed separately for:

1. number of days of binge alcohol use (H2.1),
2. number of days of benzodiazepine use (H2.2),
3. number of days of stimulant use (H2.3),
4. number of days of marijuana use (H2.4),
5. number of days of other drug use (H2.5).

The analyses without exploring time effects will be executed in the same way described for the analyses of days of risky opioid use in Section 7.2.2. Time trend analyses will be executed as described above in Section 7.6. If the number of days of use is very few, only descriptive analyses will be reported. No multiple imputation will be performed for secondary outcome analyses.

Similar to the days of risky opioid use, descriptive summary statistics of mean, standard deviation, median and range are reported for each of the secondary outcomes of non-opioid substance use above in the past 30 days measured at baseline and monthly for 12 months, in the past 90 days measured at 3, 6, 9, and 12 months, and in the past 180 days measured at 6 and 12 months. Note that there will not be descriptive summary statistics reported monthly for 12 months for other drug use (HLM.HMDRGSP) in the past 30 days since these data are only collected every 3 months. Thus, these will be reported for the past 30 days at 3 months, 6 months, 9 months and 12 months.

Urine Drug Screens at baseline and at 6 and 12 months will be reported by treatment arm in terms of the number of opioid positive UDS results, number of opioid + MOUD positive UDS results, and number of any substance positive UDS results. The number of positive results by individual substance will also be presented. A UDS is considered opioid positive if positive for any of the following substances: opiates (300 ng), oxycodone (100 ng), and fentanyl (20 ng). A UDS is considered opioid + MOUD positive if positive for any of the following substances: opiates (300 ng), oxycodone (100 ng), methadone (300 ng), buprenorphine (10 ng), and fentanyl (20 ng). Urine drug screens will not be used for the primary outcome analysis.

This table will be repeated by visit and prescription for opioids in the past 6 months (yes/no) as reported on the COMM. The table will present the number and percentage of participants at that visit that reported having an opioid prescription in the past 6 months. If a patient participant does not complete the COMM assessment at that visit, the previous COMM response will be used to determine if the patient participant has an opioid prescription. For example, if the patient participant does not do the 12-month COMM assessment but has a 12-month UDS, the COMM response from the 6-month visit will be used to categorize the participant at the 12-month visit. If

the patient participant does not have any COMM responses from the baseline, 6 or 12-month visits but has UDS collected for those visits, it will be assumed the patient participant does not have an opioid prescription for any of the visits.

The following analysis will be done by the LN:

The proportions of individuals whose average number of days (within 30 days) of illicit or nonmedical opioid use during 180 days of follow-up increased relative to their baseline measure (days of use in the 30 days before the baseline assessment, H2.6) will be compared between groups at 6 months and 12 months using chi-square test respectively.

Descriptive summary statistics for COMM score assessed at screening and at 6 and 12 months (H2.7 h), Comparisons of the secondary outcomes between the two treatment arms will be conducted using t-tests or Mann-Whitney tests for continuous measures, chi-square tests for categorical measures.

Generalized estimating equations (GEE) to account for correlation of responses within PCP cluster will be fit for the incidence of moderate to severe OUD (defined as a score of at least 4 on the CIDI, H2.8) and drug use disorder (PDSQ drug items, H2.9) and alcohol use disorder (PDSQ alcohol items, H2.9) assessed at 6 and 12 months separately. Treatment effect is estimated adjusting for baseline level of each measurement. Time trend is evaluated using a time variable.

Self-reported overdose risk behavior will be measured by the overdose risk behavior questionnaire (which gives a numeric score) at baseline, 6, and 12 months. Mean scores will be compared between groups at 6 and 12 months in a random-effect regression model. Also, the total number of non-fatal opioid-related overdose events in the past 3 months will be measured at baseline, 6, and 12 months. Mean numbers of opioid-related overdose events will be compared between groups in a random-effect regression model (H 2.10).

Changes in pain-related symptoms and functioning from baseline as measured by the BPI (which calculates a numeric score) will be compared between treatment arms using Mann-Whitney tests. As the scientific goal is to demonstrate no worsening of pain, a noninferiority test will compare changes in BPI score between treatment and control groups with a minimal clinically important difference of 1 based on the IMMPACT recommendations. A secondary analysis will distinguish the effect of STOP on the change in pain-related symptoms for participants with opioid prescriptions at baseline, and the effect for those who were enrolled solely due to illicit use.

Symptoms of depression, suicidality, anxiety (H2.12), and poor sleep (H2.13) in the past two weeks will be measured at baseline and quarterly (PHQ-8) and at baseline, 6, and 12 months (PROMIS anxiety and sleep measures and PSS). Mean values will be compared between treatment arms in random-effect regression models.

Health-related quality of life (H2.14), and ED and hospital utilization (H2.15) in the past two weeks will be measured at baseline and at 6 and 12 months. Mean values will be compared between treatment arms in random-effect regression models.

Similar models will be fit for the Aim 3 objectives, but these will use provider rather than patient as the unit of observation, so will not need a PCP effect to adjust for within-PCP correlation. Regression models will be used to compare number of prescriptions of high-dose opioids within 12 months of follow-up between treatment arms as well as number of days prescribed during 12 months follow-up. Similar analyses will be done for number of prescriptions for any opioids or benzodiazepines, numbers of naloxone kits prescribed, numbers of urine toxicology tests ordered and completed, and number of patient participants receiving a new diagnosis of OUD.

7.9 Definition of the Exploratory Outcome Measures

The following additional measures will be collected to assess exploratory outcomes, characterize domains from conceptual models, and may be used to adjust models of the primary and secondary outcomes. These measures are collected at the baseline study visit and at the study visits specified in Tables 5 and 6 (schedule of assessments) in the protocol.

1. Patient engagement in primary care (Exploratory Objective 1): Number and frequency of kept appointments and missed appointments for primary care visits.
2. Time to development if moderate-severe OUD or opioid related overdose for participants in both treatment conditions (Exploratory Objective 2).
3. Overdose death is expected to be a rare event in this population (Exploratory Objective 3) and will be assessed from the EHR and from other administrative data kept by the health system or government entities, for participants who cannot be reached at the time of the 12-month study visit.
4. Addiction treatment and harm reduction program utilization (Exploratory Objective 4): Self-reported number of weeks of addiction treatment or harm reduction program services, and self-reported number of weeks receiving MOUD is assessed at baseline and at 6 and 12 months. Prescriptions for MOUD received in the primary care clinic are additionally assessed from the EHR from at 12 months.
5. TLFB measure of substance use in the past 90 days (Exploratory Objective 5): A 90-day TLFB administered at the 3- and 6-month quarterly assessments, will capture days of risky opioid use, binge alcohol use, and other drug use including benzodiazepines, cocaine, stimulants, marijuana, and other drugs. For any prescription opioids, benzodiazepines, and amphetamine-type stimulants, the TLFB will measure non-medical use.
6. Frequency of PCP counseling on opioid use (Exploratory Objective 6): For patient participants who have a PCP encounter integrated with the baseline research visit, counseling is measured with the baseline exit survey. For all patient participants, information on any discussion or counseling provided during follow-up PCP encounters will be assessed with a quarterly patient experience questionnaire.

   Other exploratory outcomes listed in the protocol included:
7. Patient participants' self-assessments of readiness to change risky opioid use and other substance use will be measured using two items that query self-reported readiness and confidence to change, rated on a 10-point scale.
8. Social support will be assessed using the PROMIS instrumental and emotional health short forms.
9. PCP knowledge and attitudes regarding substance use, subthreshold OUD, and opioid management, assessed at baseline and at the end of the intervention period.

7.10 Analyses of the Exploratory Outcome Measures

The LN will analyze all exploratory outcomes. For the exploratory objectives, regression models with PCP as the unit of observation will compare the mean number of primary care visits attended and number of scheduled visits missed between treatment arms over the 12-month follow-up period. Time-to-event analysis will be used to compare time to development of moderate to severe OUD between treatment arms. Proportions of fatal overdose deaths will be presented by treatment arm with 95% confidence intervals. TLFB results will be described and examined alongside the days of substance use reported in the monthly assessments, in order to describe the consistency of results with these two measurement approaches. Proportions of PCP visits with counseling on risks of opioid use will be compared between groups. For PCP knowledge and

attitudes, analyses will describe and compare responses at baseline and end of intervention, for PCPs assigned to the intervention versus control condition.

8.0 SAFETY OUTCOMES AND ANALYSIS

Because this is a minimal risk study with no pharmacological intervention, causally related Adverse Events and Serious Adverse events are not anticipated for this study. Collection and reporting of Adverse Events and Serious Adverse Events is not required in the data system.

Safety reporting will be limited to reporting the following Safety Events: non-fatal alcohol or drug overdose events, suicidal ideation, hospitalizations, emergency department (ED) visits, and deaths.

The safety population will be used for reporting Safety Events.

8.1 Non-fatal Drug or Alcohol Overdoses

The number of patient participant self-reported non-fatal drug or alcohol overdoses in the past 6 months is collected at baseline, 6-months, and 12-months. A non-fatal drug or alcohol overdose is defined as taking too many drugs and/or medications/pills, or drinking too much alcohol, which causes ‘poisoning’, ‘passing out’, ‘nodding out’, ‘blacking out’, or an ‘overdose’ or ‘OD’.

A summary table of the total number of self-reported non-fatal overdoses, number of patient participants reporting at least one non-fatal overdose as well as the number of non-fatal overdoses reported per patient participant at each visit will be presented by treatment arm. A listing of the number of overdoses reported at each visit for patient participants who have reported at least one overdose at any visit by treatment arm will be provided. The listing will include Site, Participant ID, date of enrollment, visit, date of assessment, number of overdoses, and comments from the Non-Fatal Overdose Questionnaire (NFO).

8.2 Suicide Risk

The questions ‘Over the past 2 weeks, have you had thoughts of killing yourself?’ and ‘Have you ever attempted to kill yourself? If yes, when did this last happen?’ are asked on the Patient Safety Screener (PSS) assessment at baseline, 6-months, and 12-months. A response of ‘yes’ to having suicidal thoughts over the last 2 weeks or ‘yes’ to attempting suicide within the last 24 hours (including today) or within the last month (but not today) indicates potential suicide risk.

A summary table of the number of patient participants endorsing suicidal ideation at baseline, 6-months, and 12-months, as well at the number of patient participant endorsing suicidality at either 6 or 12-months, will be presented by treatment arm. A listing for all visits for patient participants endorsing suicidality at least one visit will be presented by treatment arm. The listing will include Site, Participant ID, date of enrollment, visit, date of assessment, and the questions ‘Over the past 2 weeks, have you had thoughts of killing yourself?’ and ‘Have you ever attempted to kill yourself? If yes, when did this last happen?’ from the PSS assessment.

8.3 Hospitalizations

Post-baseline research assistant (RA) collected hospitalizations will be summarized by treatment arm. The number of hospitalizations, the number of patient participants with hospitalizations, and the number of hospitalizations per patient participant (both numerically and categorically (0, 1, 2, 3, 4, and 5 or more visits)) will be presented. A listing of hospitalizations by treatment arm will be generated. The listing will include Site, Participant ID, date of enrollment, date of hospitalization, discharge date, primary, secondary, and tertiary diagnosis/complaint, severity, and outcome.

8.4 Emergency Department Visits

Post-baseline RA collected ED visits will be summarized by treatment arm. The number of ED visits, the number of patient participants with ED visits, and the number of ED visits per patient participant (both numerically and categorically (0, 1, 2, 3, 4, and 5 or more visits)) will be presented. A listing of ED visits by treatment arm will be generated. The listing will include Site, Participant ID, date of enrollment, date of ED visit, discharge date, primary, secondary, and tertiary diagnosis/complaint, severity, and outcome.

8.5 Death

A listing of deaths by treatment arm will be presented and will include Site, Participant ID, date of enrollment, date of death, source of death report, primary, secondary, and tertiary cause of death, and MedDRA® coded preferred term and system organ class. Narratives of deaths will also be provided.

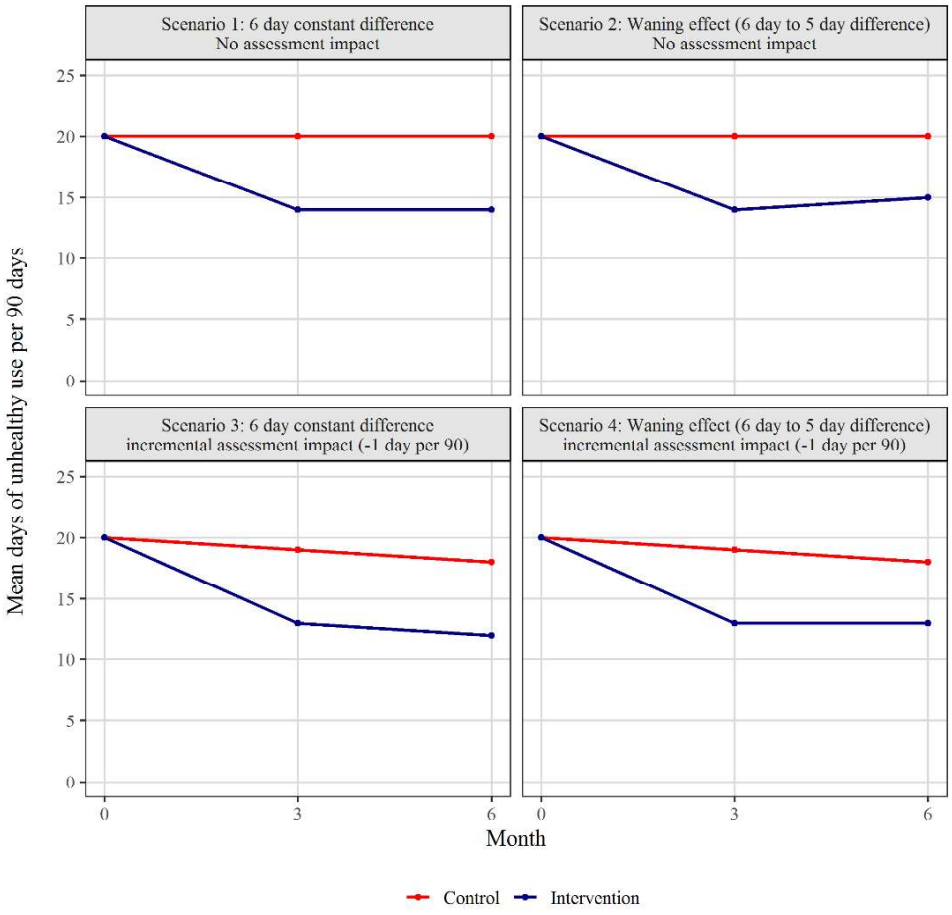
9.0 SIGNIFICANCE TESTING AND MULTIPLICITY

The primary outcome will be evaluated using a two-sided test with a type I error rate of 5%. There are several secondary outcomes; however, adjustments for multiple comparisons will not be performed since these are not part of the study's primary objective. The resulting p values will be interpreted appropriately in the context of the multiple tests being performed. Effect estimates will be presented with confidence intervals, and interpretation of hypothesis tests for multiple secondary outcomes will take into consideration the number of tests that were performed. Reporting of results will be transparent, with null as well as significant findings reported.

10.0 SAMPLE SIZE AND POWER

Power was based on simulations exploring four possible scenarios to consider different time trends of the intervention effect as well as possible assessment impact in the control group. Assessment impact means that the repeated monthly assessments alone could lead to a decrease in the control group in the response variable. The four scenarios are depicted in Figure 5. This figure shows the mean values of unhealthy days (within the past 90 days) assumed in each arm at 0, 3, and 6 months. The mean in the control arm is expected to be between 10 and 20, and 20 was selected for simulations because it is the most conservative (i.e., gives the lowest power), assuming that the additive effect size does not change as the control group mean changes. Scenario 1 has a 6-day constant difference between groups at both time points; in scenario 2 the intervention effect wanes to a 5-day difference during months 4-6. Scenarios 3 and 4 are the same as 1 and 2, but with assessment impact included, decreasing the mean by an additional 1 day per 90 days in each arm.

10.1 Figure 5: Mean Values in Treatment and Control Groups for Four Different Simulation Scenarios



Numbers of days of risky opioid use for each patient participant are drawn from binomial distributions for the two 90-day time intervals. The size parameter of the binomial distribution is 90. The probability parameter is the specified mean number of days divided by 90, but also includes a PCP intercept (randomly drawn from a normal distribution with mean zero and variance 0.15) and an individual intercept (randomly drawn from a normal distribution with mean zero and variance 0.25). The PCP intercepts induce within-PCP correlation of simulated responses. The individual intercepts create overdispersion to more realistically reflect individual variability. The overdispersed distribution may be more appropriately modelled with a negative binomial distribution than a binomial or poisson distribution. The variance parameters were selected to be conservative and to generate data with most values less than 30 and few values over 45 (per 90 days). The PCP variance parameter describes how much the PCP-specific mean values tend to vary from each other (which is a reflection of the Intra Class Correlation (ICC)). With the specified parameters, the middle 50% of the PCP-specific means in the control arm lie between 17 and 25. The true within-PCP correlation is not known for this outcome, but this is expected to be an upper limit on the expected variability of the PCP-specific means so should provide a conservative power estimate. For each simulated data set, a negative binomial model was fit with random PCP intercepts and a fixed treatment effect. One thousand iterations were performed per scenario. Power was estimated as the proportion of simulated data sets with significant ($p \leq 0.05$) treatment effect estimates based on a two-sided test.

The original protocol planned to enroll 60 PCPs with approximately 8 participants per PCP. As of November 2021, recruitment challenges led to our re-evaluating whether a reduced sample size was possible with minimal impact to power. Additional simulations were run to examine various conditions of number of PCPs and patient participants per PCP, with 20% participant dropout assumed for all simulations. The original power estimates are provided for completeness and to show there is minimal loss of power when modifying the assumptions related to number of PCP and patient participants.

Table 6 shows power for the two outcomes in the four simulated scenarios described above, under four conditions (A-D) of number of PCPs and patient participants per PCP.

Condition A shows the power for the original situation of 60 PCPs and 8 participants per PCP, with Conditions B and C illustrating the impact to power when keeping the number of PCPs at 60 but reducing the number of participants per PCP to 4 or 5. As a sensitivity analysis, we also examined the situation in which 50 PCPs had 4 participants each (Condition D), which we believe is a worst case scenario in which less than 60 PCPs are contributing patients and those that do have participants enrolled from their panel have fewer than the expected 5.

Effect of time trends of the intervention effect and possible assessment impact in the control group: The additive treatment effect for the 180-day period is the sum of the 90-day additive effects for the two 3-month time intervals. For example, Scenario 1 indicates 90-day means of 20 and 14 in the two groups at both the 3- and 6-month time points, which translate into 180 day means of 40 and 28 in the two groups, so a treatment effect of -12 days. In scenarios 2 and 4, the waning of the effect causes this outcome to lose power. The scenarios with assessment impact have more power because there is higher power for lower control group mean values due to lower variability of the binomial distribution for a lower probability parameter (and because we are assuming equal assessment impact between the two groups). If the impact were higher in the control group, the treatment effect would be reduced, reducing power.

10.2 Table 6: Power Estimates Based on 1000 Simulations

Condition	No. of PCPs	No. of pts per PCP	Scenario	Group means (3-mo, 6-mo)		Power
				Control	Treatment	
A	60	8	1: Constant effect, no assessment impact	20, 20	14, 14	0.98
			2: Waning effect, no assessment impact	20, 20	14, 15	0.95
			3: Constant effect, assessment impact	19, 18	13, 12	0.99
			4: Waning effect, assessment impact	19, 18	13, 13	0.97
B	60	4	1: Constant effect, no assessment impact	20, 20	14, 14	0.97
			2: Waning effect, no assessment impact	20, 20	14, 15	0.93
			3: Constant effect, assessment impact	19, 18	13, 12	0.97
			4: Waning effect, assessment impact	19, 18	13, 13	0.95
C	60	5	1: Constant effect, no assessment impact	20, 20	14, 14	0.97
			2: Waning effect, no assessment impact	20, 20	14, 15	0.93
			3: Constant effect, assessment impact	19, 18	13, 12	0.99
			4: Waning effect, assessment impact	19, 18	13, 13	0.97
D	50	4	1: Constant effect, no assessment impact	20, 20	14, 14	0.93
			2: Waning effect, no assessment impact	20, 20	14, 15	0.89
			3: Constant effect, assessment impact	19, 18	13, 12	0.94
			4: Waning effect, assessment impact	19, 18	13, 13	0.91

Note: All simulations assume 20% dropout.

Within the anticipated range of mean values (10-20 days per 90), power increases as the control group mean decreases. Therefore, power would be even higher if the control group mean is 10 or 15 instead of 20, as long as the additive decrease remains the same (-6 days per 90). Additionally, power will be higher if the additive decrease is higher than planned.

Effect of Reducing Number of PCPs and patient participants per PCP: All scenarios and conditions presented have power in the range of 89% - 99%, allowing us to conclude that 1) reducing number of patient participants for each of 60 PCPs has minimal impact to power; and 2) even if 50 PCPs enrolled 4 participants each for a total of 200 participants, power is still in the acceptable range across all scenarios of time trends of the intervention effect and assessment impact in the control group.

11.0 INTERIM ANALYSES AND DATA MONITORING

No interim analyses were planned.

12.0 DATA QUALITY

12.1 Data Audits

A summary of data audit results from site interim monitoring visits conducted by Clinical Coordinating Center (CCC) monitors will be presented by site, including total fields audited, total data discrepancies, and error rate.

12.2 Protocol Deviations

Protocol deviations will be summarized by site and will include the number of deviations reported, the number of patient participants each deviation affects, frequencies for the types of protocol deviations, and information on whether the protocol deviation was deemed minor or major. A detailed listing of protocol deviations by deviation category will be provided.

13.0 SOFTWARE TO BE USED FOR ANALYSES

All analyses described in this document to be performed by the DSC will use SAS® Version 9.4 software. R-studio was used for the sample size estimation and sample size re-estimation.

14.0 ADDENDUM

14.1 Zero-Inflated Negative Binomial Model for the Primary Outcome

CTN-0101 is a prevention study, enrolling individuals who have risky opioid use but do not meet DSM-5 diagnostic criteria for a moderate or severe opioid use disorder (OUD). As such, it is anticipated that some participants may avoid all risky opioid use during the primary outcome measurement period. This is expected to result in an excess of zero-use days (i.e., zero-inflation) in the sample. In this case, the treatment effect may be in two forms: 1. Higher likelihood for people to have no risky opioid use; and 2. Lower days of use for people with non-zero days of risky opioid use.

To investigate this, as a post hoc analysis to the primary outcome analysis, a zero-inflated negative binomial (ZINB) model will be fit for the primary outcome data. The ZINB model accounts for excess zeros by assuming that they arise from a mixture of two processes: (1) participants who completely avoided risky opioid use during the treatment period, and (2) participants who did not completely avoid risky opioid use during the treatment period but may still have reported zero days of opioid use during this period. This model provides two estimates of the treatment effect: an odds ratio for “completely avoiding opioid use” and a rate ratio for the number of days of risky opioid use. The treatment effects of STOP from this model will be given as 1) an odds ratio, the

exponentiated estimate of the treatment effect from the logit model, along with a 95% confidence interval, and 2) a rate ratio, the exponentiated estimate of the treatment effect from the negative binomial model, along with a 95% confidence interval. Additionally, the overall treatment effect will be estimated using the shared parameter marginal ZINB (SPMZINB) model [14]. The treatment effect of STOP from this model will be given as a rate ratio, the exponentiated estimate of the treatment effect, along with a 95% confidence interval. Both models will be fit in SAS using Proc GENMOD (ZINB model) and Proc NLMIXED (SPMZINB model) and will use the multiply imputed primary outcome datasets. The results from these models will be used to explore the extent and impact of zero-inflation in the primary outcome for this study.

15.0 UPDATES TO THE STATISTICAL ANALYSIS PLAN

Table 4: SAP Revision History

SAP Version	Date of Approval	Summary of Changes
1.0	02JUL2024	Initial Version
2.0	23MAY2025	Added Section 14 ADDENDUM for zero-inflated negative binomial post hoc analyses of the primary outcome

16.0 REFERENCES

1. Liebschutz JM, et al. Improving Adherence to Long-term Opioid Therapy Guidelines to Reduce OpioiMisuse in Primary Care: A Cluster-Randomized Clinical Trial. *JAMA Intern Med*. 2017. **177**(9): p. 1265-1272. (*Trial Registration ClinicalTrials.gov ID NCT01909076, Protocol ID DA034252, http://www.clinicaltrials.gov)*
2. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. (2010). CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomized trials. *J Clin Epi*. *63*(8), e1-e37. https://doi.org/10.1016/j.jclinepi.2010.03.004
3. Leonhard C, et al. The Addiction Severity Index: a field study of internal consistency and validity. *J Subst Abuse Treat*. 2000. 18(2): p. 129-35.
4. Rosen CS, et al. Consistency of self-administered and interview-based Addiction Severity Index composite scores. *Addiction*. 2000. 95(3): p. 419-25.
5. Butler SF, et al. Cross validation of the current opioid misuse measure to monitor chronic pain patients on opioid therapy. *Clin J Pain*. 2010. 26(9): p. 770-6.
6. Meltzer EC, et al. Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the Current Opioid Misuse Measure (COMM). *Pain*. 2011. 152(2): p. 397-402.
7. Little RJA, Rubin DB. Statistical Analysis with Missing Data. 2nd edition. John Wiley & Sons, Hoboken. 2002.
8. van Buuren S. Multiple Imputation of Discrete and Continuous Data by Fully Conditional Specification. *Statistics Methods in Medical Research*. 2007, 16, 219–242.
9. European Medicines Agency. Guideline on adjustment for baseline covariates in clinical trials. London, UK: European Medicines Agency, EMA/CHMP/295050/2013, 2015.
10. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. *Prev Sci*. 2007 Sep;8(3):206-13. doi: 10.1007/s11121-007-0070-9. Epub 2007 Jun 5. PMID: 17549635.
11. Food and Drug Administration. Adjusting for covariates in randomized clinical trials for drugs and biologics with continuous outcomes. Guidance for industry. Draft. Rockville, MD, 2019.
12. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology*. 1996; 49(12): 1373–1379.
13. NIH. (2016). Guidelines for the Review of Inclusion on the Basis of Sex/Gender, Race, Ethnicity, and Age in Clinical Research. National Institues of Health. Retrieved from https://grants.nih.gov/grants/peer/guidelines_general/Review_Human_subjects_Inclusion.pdf.
14. Preisser JS, Das K, Long DL, Divaris K. Marginalized zero-inflated negative binomial regression with application to dental caries. *Statistics in Medicine*. 2016;35(10):1722-1735. doi:https://doi.org/10.1002/sim.6804.

17.0 LIST OF PROPOSED TABLES, FIGURES, AND LISTINGS

The below listing contains the tables, listings, and figures which will be provided by the DSC.

Section	Title	Population
Participant Enrollment and Disposition: PCP Participants	Summary of Screening by Site	Screened
	Cluster Level Randomizations by Site and Treatment Arm	Randomized
	Individual Level Randomizations by Site and Treatment Arm	Randomized
	Summary of Disposition by Site	Randomized
	Summary of Disposition by Treatment Arm	Randomized
	Summary of Number of Patient Participants Enrolled per PCP Participant Cluster by Site	Randomized
	Summary of Number of Patient Participants Enrolled per PCP Participant Cluster by Treatment Arm	Randomized
	CONSORT Flow Diagram	Screened
Participant Characteristics at Baseline: PCP Participants	Summary of Baseline Characteristics by Site	Randomized
	Summary of Baseline Characteristics by Treatment Arm	Randomized
	Summary of Baseline Characteristics in Study Completers by Treatment Arm	Study Completers
Participant Enrollment and Disposition: Patient Participants	Summary of Prescreens by Site	Prescreened
	Summary of Screens by Site	Screened
	Summary of Prescreens, Screens, and Enrollments by Site	Prescreened
	Enrollments by Site and Treatment Arm	ITT
	Figure of Expected versus Actual Enrollments Overall	ITT
	Figure of Expected versus Actual Enrollments by Site	ITT
	Proposed and Actual Enrollments by Site	ITT
	Summary of Disposition by Site	ITT
	Summary of Disposition by Treatment Arm	ITT
	CONSORT Flow Diagram	Prescreened
Participant Characteristics at Baseline: Patient Participants	Summary of Baseline Characteristics by Site	ITT
	Summary of Baseline Characteristics by Treatment Arm	ITT
	Summary of Baseline Characteristics by Primary Outcome Availability and Treatment Arm	ITT
	Summary of Baseline Characteristics in Study Completers by Treatment Arm	Study Completers
Monthly Survey Completion: Patient Participants	Summary of Healthy Living Monthly Assessment Completion by Site	ITT
	Summary of Healthy Living Monthly Assessment Completion by Treatment Arm	ITT
Visit Attendance: Patient Participants	Summary of Attendance at Study Visits by Treatment Arm	ITT
	Summary of Missed Visits by Treatment Arm	ITT
	Summary of Primary Care Provider Interactions by Site	ITT

Section	Title	Population
STOP Intervention Exposure: Patient Participants	Summary of Nurse Care Manager Interactions by Site	ITT
	Summary of Telephone Heath Coach Interactions by Site	ITT
Primary Outcome	Summary of Primary Outcome Availability by Treatment Arm in ITT Population	ITT
	Summary of Missing Risky Opioid Use Data Patterns by Treatment Arm in ITT Population	ITT
	Summary of Participants by Missing Risky Opioid Use Data Pattern and Treatment Arm in ITT Population	ITT
	Summary of Primary Outcome Analysis by Treatment Arm Using Multiple Imputation in ITT Population	ITT
Sensitivity Analyses of the Primary Outcome	Summary of Primary Outcome Analysis by Treatment Arm in Complete Case Population	Complete Case
	Summary of Primary Outcome Analysis by Treatment Arm Using Multiple Imputation Assuming Missing at Random in ITT Population	ITT
Supplemental Analyses of the Primary Outcome	Summary of Primary Outcome Analysis by Treatment Arm with Individual-level Covariate Adjustment in ITT Population	ITT
	Summary of Primary Outcome Analysis by Sex and Treatment Arm	ITT
	Summary of Primary Outcome Analysis by Age and Treatment Arm	ITT
	Summary of Primary Outcome Analysis by Race and Treatment Arm	ITT
	Summary of Primary Outcome Analysis by Ethnicity and Treatment Arm	ITT
	Summary of Primary Outcome Analysis in Per Protocol Population	Per Protocol
Supportive Analysis of the Primary Outcome	Summary Statistics of Risky Opioid Use by Treatment Arm	ITT
	Summary of Risky Opioid Use in Past 30 Days by Treatment Arm	ITT
	Summary of Risky Opioid Use in Past 90 Days by Treatment Arm	ITT
	Summary of Risky Opioid Use During Months 7-12 by Treatment Arm	ITT
Secondary Outcomes (Patient-level): Binge Alcohol use	Summary Statistics of Binge Alcohol Use by Treatment Arm	ITT
	Summary of Binge Alcohol Use in Past 30 Days by Treatment Arm	ITT
	Summary of Binge Alcohol Use in Past 90 Days by Treatment Arm	ITT
	Summary of Binge Alcohol Use in Past 180 Days by Treatment Arm	ITT
Secondary Outcomes (Patient-	Summary Statistics of Benzodiazepine Use by Treatment Arm	ITT
	Summary of Benzodiazepine Use in Past 30 Days by Treatment Arm	ITT

Section	Title	Population
level): Benzodiazepine use	Summary of Benzodiazepine Use in Past 90 Days by Treatment Arm	ITT
	Summary of Benzodiazepine Use in Past 180 Days by Treatment Arm	ITT
Secondary Outcomes (Patient-level): Stimulant Drug Use	Summary Statistics of Stimulant Drug Use by Treatment Arm	ITT
	Summary of Stimulant Drug Use in Past 30 Days by Treatment Arm	ITT
	Summary of Stimulant Drug Use in Past 90 Days by Treatment Arm	ITT
	Summary of Stimulant Drug Use in Past 180 Days by Treatment Arm	ITT
Secondary Outcomes (Patient-level): Marijuana Use	Summary Statistics of Marijuana Use by Treatment Arm	ITT
	Summary of Marijuana Use in Past 30 Days by Treatment Arm	ITT
	Summary of Marijuana Use in Past 90 Days by Treatment Arm	ITT
	Summary of Marijuana Use in Past 180 Days by Treatment Arm	ITT
Secondary Outcomes (Patient-level): Other Drug use	Summary Statistics of Other Drug Use in Past 30 Days by Treatment Arm	ITT
Secondary Outcomes (Patient-level): Urine Screen Test Results	Summary of Positive UDS Results by Visit and Treatment Arm	ITT
	Summary of Positive UDS Results by Visit, Prescription for Opioids, and Treatment Arm	ITT
Safety: Patient Participants	Summary of Non-fatal Drug or Alcohol Overdoses in the Past 6 Months by Treatment Arm	Safety
	Summary of Suicide Risk by Treatment Arm	Safety
	Summary of Hospitalizations by Treatment Arm	Safety
	Summary of Emergency Department Visits by Treatment Arm	Safety
	Listing of Non-fatal Drug or Alcohol Overdoses by Treatment Arm	Safety
	Listing of Suicide Risk by Treatment Arm	Safety
	Listing of Hospitalizations by Treatment Arm	Safety
	Listing of ED Visits by Treatment Arm	Safety
	Listing of Death by Treatment Arm	Safety
	Death Narratives	Safety
Data Quality	Summary of Data Audits	N/A
Protocol Deviations	Summary of Protocol Deviations by Site	N/A
	Listing of Protocol Deviations	N/A

18.0 APPENDICES

18.1 Proposed Tables, Listings, and Figures

1 Participant Enrollment and Disposition: PCP Participants

Table 1: Summary of Screening by Site

PCP Participants

	Chase-Brexton Health Center	Dartmouth-Hitchcock	Annville Family Medicine	University of Utah	The Ohio State University	Total
Number of potentially eligible provider participants	N					
Number not approached for screening[1]	N (X.X%)					
Criterion resulting in ineligibility for screening[2]						
Not providing care to approximately 4 or more adult patients receiving chronic opioid treatment and/or have risky opioid use	N (X.X%)					
Total patient volume not approximately 40 or more patients per week						
Number approached for screening[1]	N (X.X%)					
Number that did not take screening survey[3]	N (X.X%)					
Number screened[3]	N (X.X%)					
Number of eligible screens[4]	N (X.X%)					
Number of ineligible screens[4]	N (X.X%)					
Criterion resulting in ineligibility[5]						
Not a licensed medical professional (MD, DO, PA, NP)	N (X.X%)					
Not willing to be randomized to either of the study conditions						
Plans to leave the study clinic within the next 24 months						
Plans to change their schedule so they no longer have the required patient volume						

Table 1: Summary of Screening by Site

PCP Participants

	Chase-Brexton Health Center	Dartmouth -Hitchcock	Annville Family Medicine	University of Utah	The Ohio State University	Total
Number of provider participants eligible but not randomized[6]	N (X.X%)					
Reasons for not being randomized[7]						
No longer interested in participating in the study	N (X.X%)					
Judgment of site/research staff						
Unable to contact						
Time commitment						
COVID-19: Illness						
COVID-19: Public health measures						
COVID-19: Other						
Other						
Number eligible and randomized[6]	N (X.X%)					

[1] Percentages are calculated based on the denominator of the number of potentially eligible provider participants.

[2] Percentages are calculated based on the denominator of the number of providers not approached for screening.

[3] Percentages are calculated based on the denominator of the number of providers approached for screening.

[4] Percentages are calculated based on the denominator of the number of providers screened.

[5] Percentages are calculated based on the denominator of the number of ineligible screens and may sum to greater than 100% if multiple eligibility criteria are not met for potential provider participants.

[6] Percentages are calculated based on the denominator of the number of eligible screens.

[7] Percentages are calculated based on the denominator of the number of provider participants eligible but not randomized.

Table 2: Cluster Level Randomizations by Site and Treatment Arm

PCP Participants

Site	Treatment Arm		Total (N=)
	EUC (N=)	STOP (N=)	
Chase-Brexton Health Center	N (X.X%)	N (X.X%)	N
Dartmouth-Hitchcock			
Annville Family Medicine			
University of Utah			
The Ohio State University			
Total			

This table presents cluster level randomizations, where a cluster consists of providers that work in teams. All sites except Dartmouth-Hitchcock work as individual providers, and therefore in those four sites, a cluster is equivalent to an individual provider.

Table 3: Individual Level Randomizations by Site and Treatment Arm

PCP Participants

Site	Treatment Arm		Total (N=)
	EUC (N=)	STOP (N=)	
Chase-Brexton Health Center	N (X.X%)	N (X.X%)	N
Dartmouth-Hitchcock			
Annville Family Medicine			
University of Utah			
The Ohio State University			
Total			

This table presents individual provider level randomizations. The actual unit of randomization is a cluster, where a cluster consists of providers that work in teams. All sites except Dartmouth-Hitchcock work as individual providers, and therefore in those four sites, a cluster is equivalent to an individual provider.

Table 4: Summary of Disposition by Site PCP Participants						
	Chase-Brexton Health Center	**Dartmouth-Hitchcock**	**Annville Family Medicine**	**University of Utah**	**The Ohio State University**	**Total**
Number of provider participants randomized	N					
Number of study completers[1]	N (X.X%)					
Number of early study terminations[2]	N (X.X%)					
Reason for early study termination						
No longer interested in participating in the study	N (X.X%)					
Judgement of site/research staff						
Plans to leave the practice						
Reduced patient panel						
Other						

[1] A provider participant is a study completer if there is no early withdrawal from the study documented on the Provider Eligibility Review eCRF (PCP).

[2] A provider participant is an early study termination if early withdrawal (and reason for withdrawal) is completed on the PCP eCRF

.

Table 5: Summary of Disposition by Treatment Arm PCP Participants			
	Treatment Arm		
	EUC (N=)	STOP (N=)	Total (N=)
Repeat of Table 4 with Treatment Arm for columns			

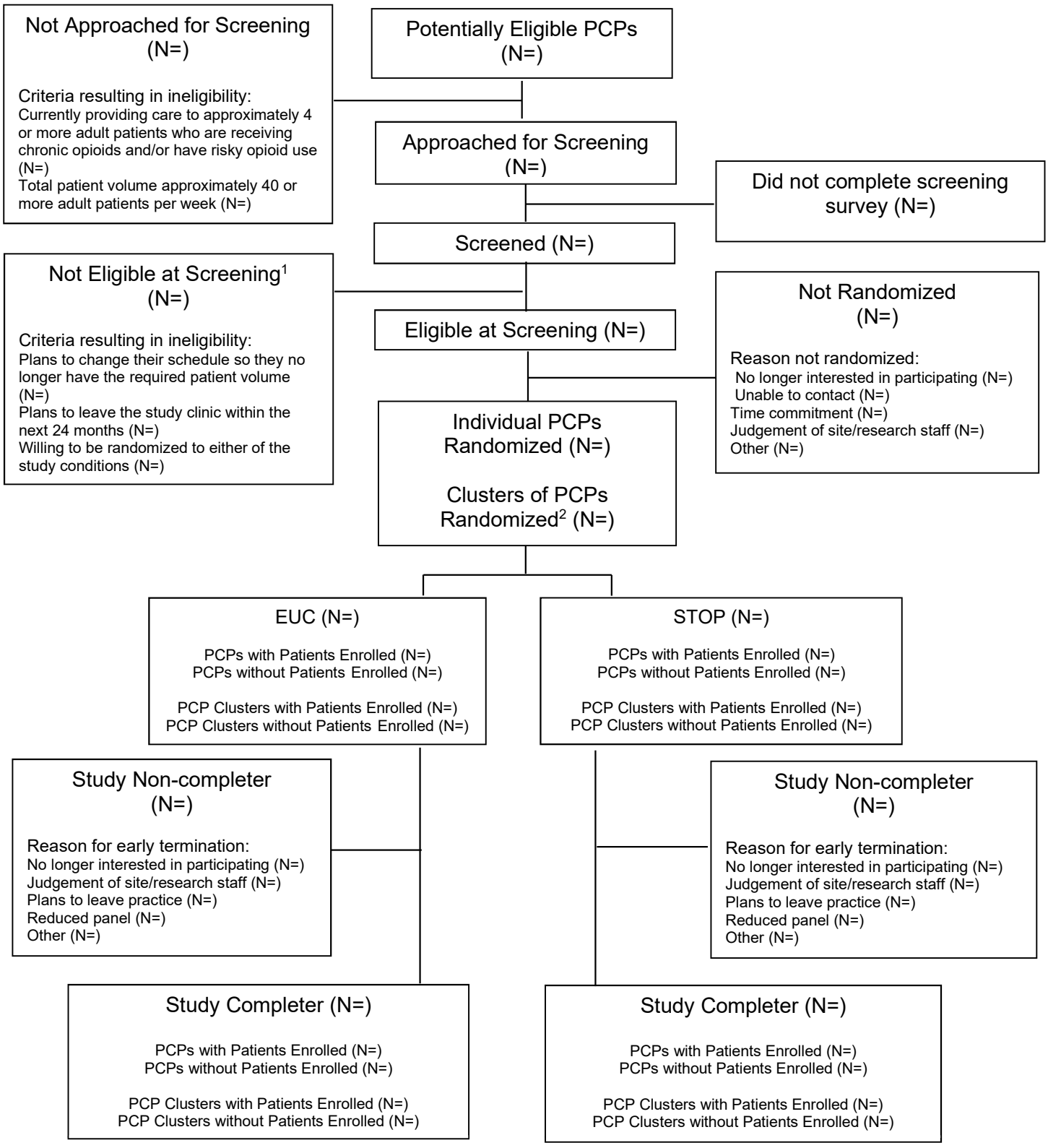
Note: All clusters with >1 PCP completed the trial, because at least one PCP remained active in the trial.

Table 6: Summary of Number of Patient Participants Enrolled per PCP Participant Cluster by Site						
	Chase-Brexton Health Center	**Dartmouth -Hitchcock**	**Annville Family Medicine**	**University of Utah**	**The Ohio State University**	**Total**
Number of provider participants randomized	N					
Number of provider participant clusters randomized	N					
Number of patient participants enrolled	N					
Number of provider participant clusters with at least one patient participant enrolled	N (X.X%)					
Number of patient participants per provider participant cluster[1]						
N	N					
Mean	X.X					
SD	X.XX					
Min	X.X					
25th Percentile	X.X					
Median	X.X					
75th Percentile	X.X					
Max	X.X					
Number of provider participant clusters						
0 patient participants	N (X.X%)					
1 patient participant						
2 patient participants						
3 patient participants						
4 patient participants						
5 patient participants						
…						
X patient participants						

[1] For provider participant clusters that have at least one patient participant enrolled.

Table 7: Summary of Number of Patient Participants Enrolled per PCP Participant Cluster by Treatment Arm			
	Treatment Arm		
	EUC (N=)	STOP (N=)	Total (N=)
Repeat of Table 6 with Treatment Arm for columns			

Figure 1: CONSORT Flow Diagram
PCP Participants



[1] Potential PCP participants may be ineligible for multiple reasons.

[2] The unit of randomization is a cluster, or PCPs that work on a team. Dartmouth-Hitchcock is the only site whose PCPs practice in teams. Dartmouth-Hitchcock randomized x clusters comprising x individual PCPs.

2 Participant Characteristics at Baseline: PCP Participants

Table 8: Summary of Baseline Characteristics by Site
PCP Participants

	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Gender						
Missing	N (X.X%)					
Male						
Female						
Transgender						
Nonbinary						
Other						
Age in years (Mean (SD))	X.X (X.XX)					
Age in years						
Missing	N (X.X%)					
< 18						
18 - < 25						
25 - < 35						
35 - < 45						
45 - < 55						
55 - < 65						
65 - < 75						
75+						
Ethnicity						
Missing	N (X.X%)					
Not Hispanic or Latino						
Hispanic or Latino						
Refused to answer						
Race						
Missing	N (X.X%)					
American Indian or Alaska Native						
Asian						
Black or African American						
Native Hawaiian or Pacific Islander						

Table 8: Summary of Baseline Characteristics by Site PCP Participants						
	Chase-Brexton Health Center (N=)	**Dartmouth-Hitchcock (N=)**	**Annville Family Medicine (N=)**	**University of Utah (N=)**	**The Ohio State University (N=)**	**Total (N=)**
White						
Other						
Multiracial						
Don't know						
Refused to answer						
Medical Profession						
Missing	N (X.X%)					
Physician (MD/DO)						
Physician Assistant (PA)						
Nurse-Practitioner (NP)						

Table 9: Summary of Baseline Characteristics by Treatment Arm PCP Participants			
	Treatment Arm		
	EUC (N=)	STOP (N=)	Total (N=)
Repeat of Table 8 with Treatment Arm for columns			

Table 10: Summary of Baseline Characteristics in Study Completers by Treatment Arm **PCP Participants**			
	Treatment Arm		
	EUC (N=)	**STOP (N=)**	**Total (N=)**
Repeat of Table 9 for Study Completers			

3 Participant Enrollment and Disposition: Patient Participants

Table 11: Summary of Prescreens by Site
Patient Participants

	Chase-Brexton Health Center	Dartmouth-Hitchcock	Annville Family Medicine	University of Utah	The Ohio State University	Total
Number of started prescreening attempts	N					
Number of completed attempts	N (X.X%)					
Number of prescreen eligible attempts	N (X.X%)					
Number of prescreen eligible patients[1]	N					
Number of ineligible prescreen attempts	N (X.X %)					
Criterion resulting in ineligibility[2]						
≥18 years old	N (X.X%)					
Risky opioid use in past 90 days						

[1] Patients may take the prescreen survey multiple times. This is the number of unique IDs entered across all eligible prescreen record attempts.

[2] Percentages are calculated based on the denominator of the number of ineligible prescreens and may not sum to 100% if multiple eligibility criteria are not met for potential participants.

Table 12: Summary of Screens by Site Patient Participants						
	Chase-Brexton Health Center	**Dartmouth-Hitchcock**	**Annville Family Medicine**	**University of Utah**	**The Ohio State University**	**Total**
Number screened	N					
Number of eligible screens	N (X.X%)					
Number of ineligible screens	N (X.X %)					
Criterion resulting in ineligibility[1]						
Inclusion Criteria						
PCP enrolled in study	N (X.X%)					
Age 18 years or older at time of prescreening						
Proficient in spoken and written English						
Risky opioid use in the past 90 days from the date of prescreening						
Access to phone that can receive text messages and access to internet						
Able to provide sufficient contact information						
Willing and able to provide informed consent						
Exclusion Criteria						
Moderate to severe OUD	N (X.X%)					
Received MOUD or engaged in opioid treatment program in past 30 days						
Receiving opioids for end of life care						
Pregnancy						
In jail, prison, or have pending legal action that could prevent participation in study activities						
Plan to leave the area or the clinical practice within the next 12 months						

Table 12: Summary of Screens by Site Patient Participants						
	Chase-Brexton Health Center	**Dartmouth-Hitchcock**	**Annville Family Medicine**	**University of Utah**	**The Ohio State University**	**Total**
Other factors that may cause harm or increased risk or preclude adherence to study						
Number of participants eligible but not enrolled	N (X.X%)					
Reasons for not being enrolled[2]						
No longer interested in participating in the study	N (X.X%)					
Judgment of site/research staff						
Unable to contact						
Time commitment						
COVID-19: Illness						
COVID-19: Public health measures						
COVID-19: Other						
Other						

[1] Percentages are calculated based on the denominator of the number of ineligible screens and may sum to greater than 100% if multiple eligibility criteria are not met for potential participants.

[2] Percentages are calculated based on the denominator of the number of participants eligible but not enrolled.

Table 13: Summary of Prescreens, Screens, and Enrollments by Site

Patient Participants

Site	Number of Completed Prescreen Attempts[1]	Number of Screens	Percent of Eligible Prescreens Screened	Number of Screen Fails	Percent of Screens Who Screen Fail	Number Eligible but Not Enrolled	Number Enrolled	Percent of Eligible Prescreens Enrolled	Percent of Screens Enrolled
Chase-Brexton Health Center	N	N	X.X%	N	X.X%	N	N	X.X%	X.X%
Dartmouth-Hitchcock									
Annville Family Medicine									
University of Utah									
The Ohio State University									
Total									

[1] Patients may prescreen multiple times and therefore be counted multiple times in this number.

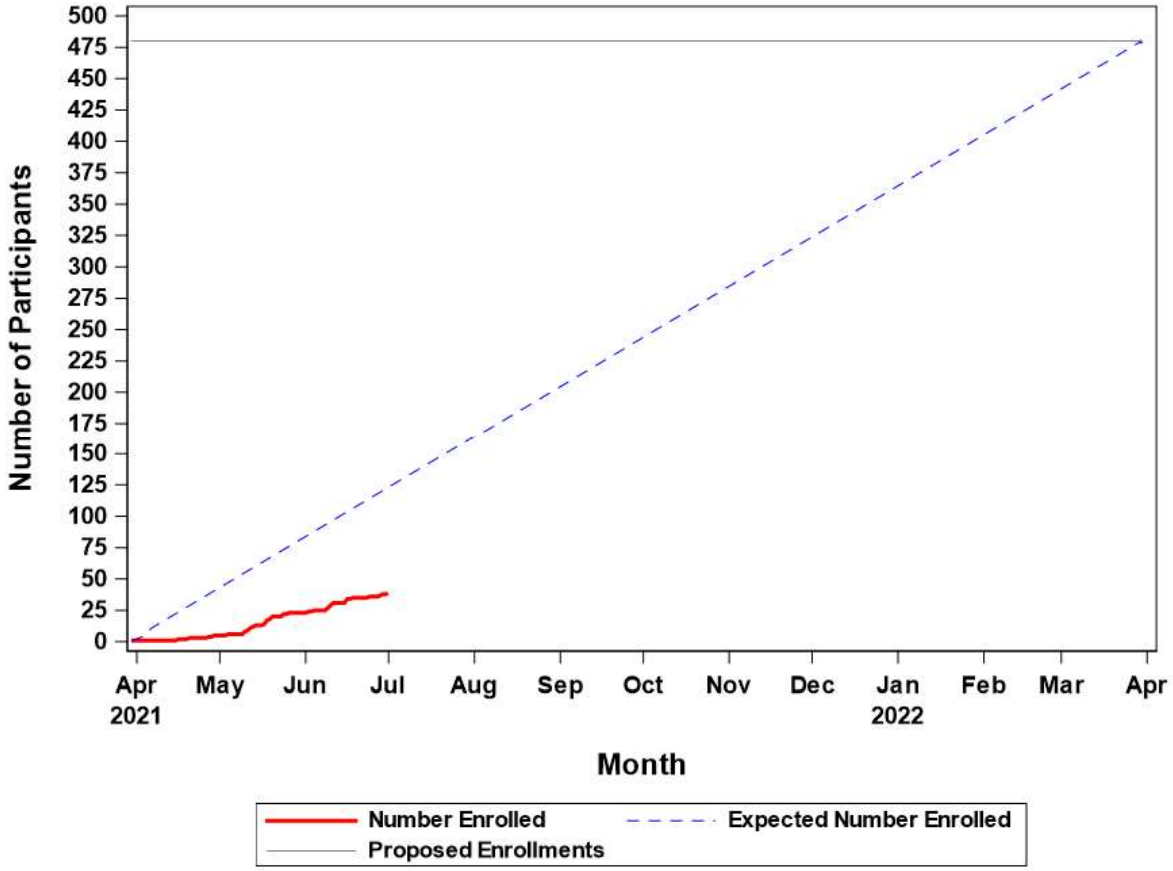
Table 14: Enrollments by Site and Treatment Arm

Patient Participants

Site	Treatment Arm		Total (N=)
	EUC (N=)	STOP (N=)	
Chase-Brexton Health Center	N (X.X%)	N (X.X%)	N
Dartmouth-Hitchcock			
Annville Family Medicine			
University of Utah			
The Ohio State University			
Total			

Figure 2: Figure of Expected versus Actual Enrollments Overall

Patient Participants



Example figure provided.

Figure 3: Figure of Expected versus Actual Enrollments by Site

Patient Participants

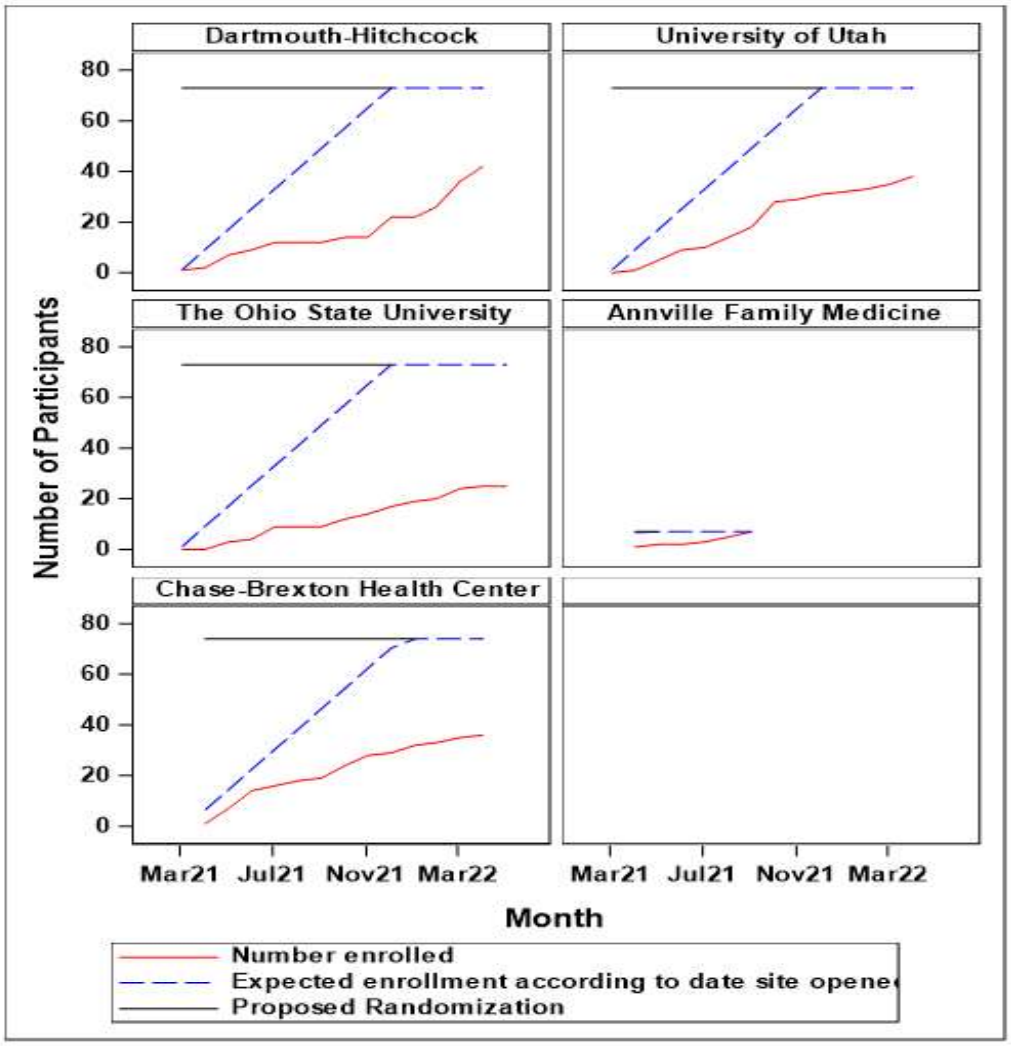


Table 15: Proposed and Actual Enrollments by Site Patient Participants						
Site	**Proposed Enrollments[1]**	**Date Site Opened for Enrollment**	**Date of First Enrollment**	**Actual Enrollments**	**Actual/ Proposed (%)**	**Date of Last Enrollment**
Chase-Brexton Health Center	N	mm/dd/yyyy	mm/dd/yyyy	N	X.X%	mm/dd/yyyy
Dartmouth-Hitchcock						
Annville Family Medicine						
University of Utah						
The Ohio State University						
Total						

[1] Proposed Enrollment = proposed number of enrollments per site based on the total sample size N.

Table 16: Summary of Disposition by Site

Patient Participants

	Chase-Brexton Health Center	Dartmouth-Hitchcock	Annville Family Medicine	University of Utah	The Ohio State University	Total
Number of patient participants enrolled	N					
Number of study completers[1]	N (X.X%)					
Number of early study terminations[2]	N (X.X%)					
Reason for early study termination						
Participant stopped participation due to practical problems (e.g. no childcare or transportation	N (X.X%)					
Participant incarcerated						
Participant withdrew consent/assent						
Participant deceased						
Participant terminated for administrative issues						
Participant terminated due to pressure or advice from outsiders						
Participant in hospital, in-patient, or residential treatment (not for substance abuse treatment)						
Clinical deterioration: new onset of psychiatric or medical condition						
Participant in detox, residential, or intensive outpatient treatment for substance abuse treatment						
Participant refused, non-specific						
Unable to contact participant						
Participant terminated due to COVID-19: Illness						
Participant terminated due to COVID-19: Public health measures						
Participant terminated due to COVID-19: Other						
Participant terminated for other reason						

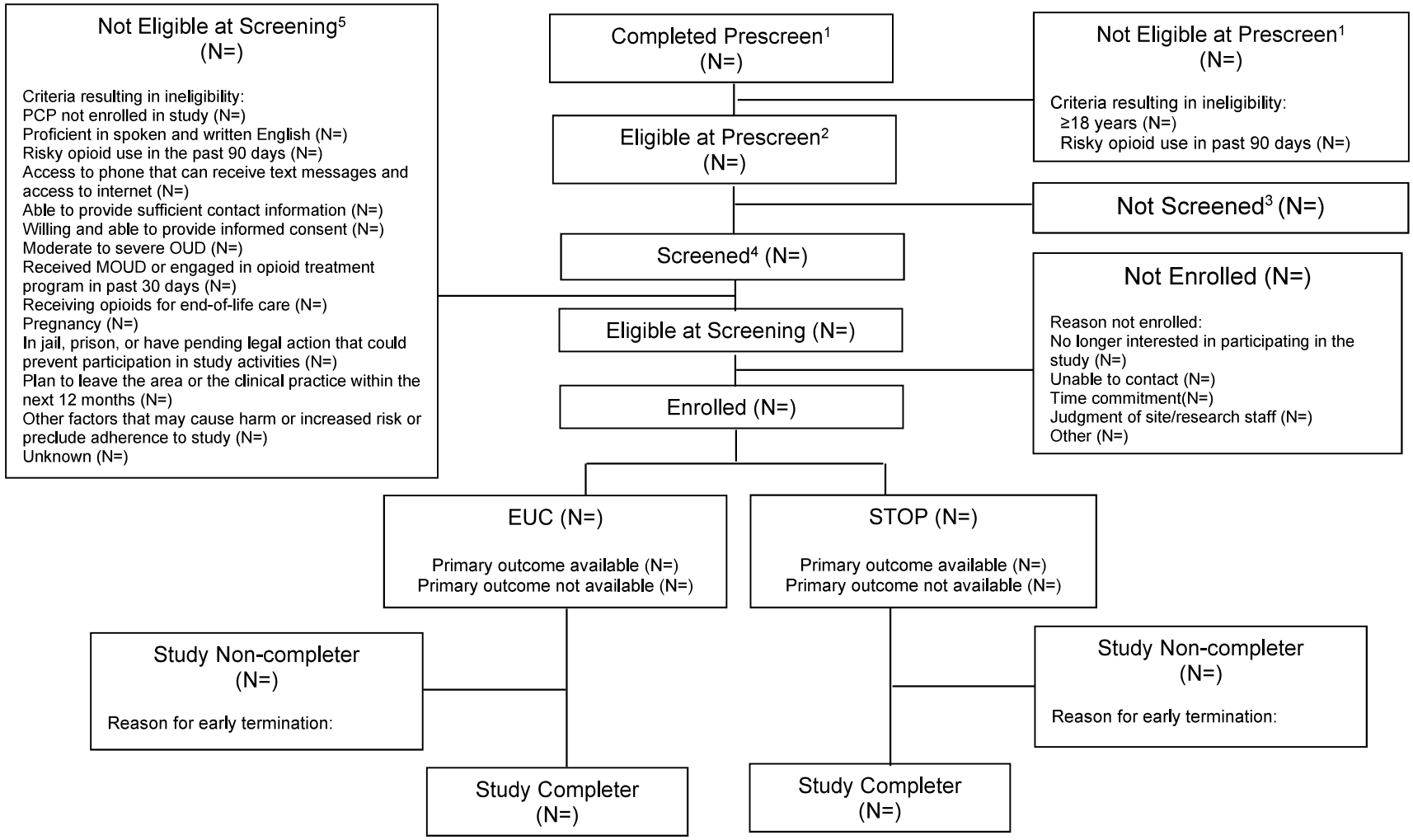
[1] A participant is a study completer if they have a completed Study Completion (STC) form indicating they have completed their last study activity.

[2] A participant is an early study termination if they have a completed STC form indicating they did not complete their last study activity.

Table 17: Summary of Disposition by Treatment Arm Patient Participants			
	Treatment Arm		
	EUC (N=)	STOP (N=)	Total (N=)
Repeat of Table 16 with Treatment Arm for columns			

Figure 4: CONSORT Flow Diagram

Patient Participants



[1] Potential patient participants may prescreen multiple times and therefore may be counted multiple times in this number.

[2] The X potential patient participants who were eligible at prescreen were from X eligible HLS records.

[3] The X potential patient participants who were eligible at prescreen but were not screened were from X eligible HLS records.

[4] There were X patient participants who were screened but not in the prescreen eligible box due to not creating a UQID at the time of prescreening eligible. These participants were ineligible at screening.

[5] Potential patient participants may be ineligible for multiple reasons.

4 Participant Characteristics at Baseline: Patient Participants

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Sex						
Missing	N (X.X%)					
Male						
Female						
Don't know						
Refused to answer						
Age in years (Mean (SD))	X.X (X.XX)					
Age in years						
Missing	N (X.X%)					
< 18						
18 - < 25						
25 - < 35						
35 - < 45						
45 - < 55						
55 - < 65						
65 - < 75						
75+						
Ethnicity						
Missing	N (X.X%)					

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Not Hispanic or Latinx						
Hispanic or Latinx						
Don't know						
Refused to answer						
Race						
Missing	N (X.X%)					
American Indian or Alaska Native						
Asian						
Black or African American						
Native Hawaiian or Pacific Islander						
White						
Other						
Multiracial						
Don't know						
Refused to answer						
Education completed						
Missing	N (X.X%)					
Less than high school diploma						
High school graduate						
GED or equivalent						

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Some college, no degree						
Associate's degree: occupational, technical, or vocational program						
Associate's degree: academic program						
Bachelor's degree						
Master's degree						
Professional school degree						
Doctoral degree						
Don't know						
Refused						
Marital status						
Missing	N (X.X%)					
Married						
Widowed						
Divorced						
Separated						
Never married						
Living with partner						
Don't know						
Refused						

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Employment						
Missing	N (X.X%)					
Working now						
Only temporarily laid off, sick leave, or maternity leave						
Looking for work, unemployed						
Retired						
Disabled permanently or temporarily						
Keeping house						
Student						
Other						
Insurance coverage						
Missing	N (X.X%)					
None						
Privately purchased						
Medicaid						
Medicare						
Both Medicaid and Medicare						
Through employer (participant's or participant's spouses or another family member's employer)						
TRICARE or other military healthcare, including VA health care						
Other						

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Spent time in jail or prison during lifetime						
Missing	N (X.X%)					
Yes						
No						
If yes for any time spent in jail or prison in lifetime, spent time in jail or prison during past 12 months						
Missing	N (X.X%)					
Yes						
No						
Risky opioid use in past 30 days at prescreening[1]						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
Binge alcohol use in past 30 days at prescreening						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Median	X.X					
Maximum	X					
Benzodiazepine use in past 30 days at prescreening						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
Stimulant use in past 30 days at prescreening						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
Marijuana use in past 30 days at prescreening						
N	N					
Mean	X.X					
SD	X.XX					

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Minimum	X					
Median	X.X					
Maximum	X					
Other drug use in past 30 days at prescreening						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
Prescription for opioids in past 6 months at prescreening						
Missing	N (X.X%)					
Yes						
No						
For participants with an opioid prescription in past 6 months at prescreening, Current Opioid Misuse Measure (COMM) score (range 0-68)						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	**Dartmouth-Hitchcock (N=)**	**Annville Family Medicine (N=)**	**University of Utah (N=)**	**The Ohio State University (N=)**	**Total (N=)**
Median	X.X					
Maximum	X					
For participants with an opioid prescription in past 6 months at prescreening, Current Opioid Misuse Measure (COMM) score (range 0-68)						
Missing	N (X.X%)					
0-8						
9+						
Alcohol use disorder score (range 0-6)[2]						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
Alcohol use disorder score (range 0-6)[2]						
Missing	N (X.X%)					
0						
1+						
Drug use disorder score (range 0-6)[2]						
N	N					

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	**Dartmouth-Hitchcock (N=)**	**Annville Family Medicine (N=)**	**University of Utah (N=)**	**The Ohio State University (N=)**	**Total (N=)**
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
Drug use disorder score (range 0-6)[2]						
Missing	N (X.X%)					
0						
1+						
Overdose risk behavior score (range 0-34)						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
Pain severity (mean; range 0-10)[3]						
N	N					
Mean	X.X					
SD	X.XX					

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Minimum	X					
Median	X.X					
Maximum	X					
Pain severity (worst pain; range 0-10)[3]						
Missing	N (X.X%)					
Mild pain (1-4)						
Moderate pain (5-6)						
Severe pain (7-10)						
Pain functioning or interference (mean; range 0-10)[3]						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
PROMIS Anxiety Short Form score (range 0-32)[4]						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Median	X.X					
Maximum	X					
PHQ-8 score (range 0-24)[5]						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
PHQ-8 score (range 0-24)[5]						
Missing	N (X.X%)					
0-9						
10+						
PROMIS Sleep Disturbance Short Form score (range 420)[6]						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	**Dartmouth-Hitchcock (N=)**	**Annville Family Medicine (N=)**	**University of Utah (N=)**	**The Ohio State University (N=)**	**Total (N=)**
Health related quality of life (QoL): Overall (range 0-100)[7]						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
Health related quality of life (QoL): Overall (range 0-100)[7]						
Missing	N (X.X%)					
0-50						
51+						
Health related quality of life (QoL): Mental health component (range 0-50)[7]						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
Health related quality of life (QoL): Physical health component (range 0-50)[7]						

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
Addiction treatment program utilization in past 12 months						
Missing	N (X.X%)					
No						
Yes						
Not sure						
Harm reduction program utilization in past 12 months						
Missing	N (X.X%)					
No						
Yes						
Not sure						
Taken medication for treatment of OUD disorder (such as buprenorphine, methadone, or naltrexone) in past 12 months						
Missing	N (X.X%)					
No						
Yes						

Table 18: Summary of Baseline Characteristics by Site Patient Participants						
	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Not sure						

[1] Risky opioid use included nonmedical use of prescribed opioids (taking a higher dose or taking an opioid more frequently than prescribed; taking pharmaceutical opioids that were not prescribed to the individual taking them) or any use of illicit opioids collected on the Healthy Living Monthly baseline survey.

[2] Alcohol (AUD) and drug use disorder (DUD) scores were measured using the Psychiatric Diagnostic Screening Questionnaire (PDSQ).There are 6 yes (1) or no (0) items for both AUD and DUD. The score for each disorder is the sum of the 6 items. Scores range from 0-6. A score of 1 or greater indicates substance use disorder (DSM-4 abuse or dependence).

[3] Pain severity and functioning (interference) were measured using the Brief Pain Inventory (BPI) Short Form. The form asks 11 questions to measure the intensity of pain, and the rate at which pain interferes with daily activities, using a 0 to 10 scale. Pain severity can be measured using the average of the four severity items or the “worst pain” single item. A worst pain item score of 1-4 indicates mild pain, 5-6 moderate pain, and 7-10 severe pain. Pain functioning (interference) is the average of the seven functioning (interference) items.

[4] The PROMIS Anxiety Short Form is an 8-item self-assessment of anxiety symptoms in the last seven days. The response values of each item are 0-4 Likert rating format (never, rarely, sometimes, often, and always) and the total score is the sum of all items. The score ranges from 0-32.

[5] Depression symptoms was assessed using the Patient Health Questionnaire (PHQ-8) Depression screening tool. The tool is an 8-item self-assessment, the response values of each item are 0-3 Likert rating format (not at all, several days, more than half the days, nearly every day) , and the total score is the sum of the 8 items. The score ranges from 0-24. A score of 5-9 indicates mild depressive symptoms, 10–14 moderate depressive symptoms, 15–19 moderately severe depressive symptoms, and 20–24 severe depressive symptoms.

[6] Sleep quality over the past seven days was assessed using the PROMIS Sleep Disturbance Short Form. The response values of first item is 1-5 Likert rating format (very good, good, fair, poor, very poor); and remaining three items item use 1-5 Likert rating format (very much, quite a bit, somewhat, a little bit, not at all). The item 3 and 4 will be reverse the direction with higher scores indicating worse sleeping quality. The total score is the sum of all items (range from 4-20).

[7] Quality of life was assessed using the Short Form-12 (SF-12).

Table 19: Summary of Baseline Characteristics by Treatment Arm Patient Participants			
	Treatment Arm		
	EUC (N=)	STOP (N=)	Total (N=)
Repeat of Table 18 with Treatment Arm for columns			

Table 20: Summary of Baseline Characteristics by Primary Outcome Availability and Treatment Arm Patient Participants						
	Primary Outcome Available (N=)			Primary Outcome Not Available (N=)		
	Treatment Arm			Treatment Arm		
	EUC (N=)	STOP (N=)	Total (N=)	EUC (N=)	STOP (N=)	Total (N=)
Repeat of Table 18 with Treatment Arm and Primary Outcome Available as columns						

Table 21: Summary of Baseline Characteristics in Study Completers by Treatment Arm Patient Participants			
	Treatment Arm		
	EUC (N=)	STOP (N=)	Total (N=)
Repeat of Table 19 for Study Completers			

5 Monthly Survey Completion: Patient Participants

Table 22: Summary of Healthy Living Monthly Assessment Completion by Site Patient Participants				
Site	**Number of Participants Enrolled**	**HLM Survey**	**Number of Participants Submitting HLM Survey[1]**	**Number of Participants Completing Risky Opioid Use Questions[1]**
Chase-Brexton Health Center	N	1-month	N (X.X%)	N (X.X%)
		2-month		
		3-month		
		4-month		
		5-month		
		6-month		
		7-month		
		8-month		
		9-month		
		10-month		
		11-month		
		12-month		
Dartmouth-Hitchcock		1-month		
		2-month		
		3-month		
		4-month		
		5-month		
		6-month		
		7-month		
		8-month		
		9-month		
		10-month		
		11-month		
		12-month		

Table 22: Summary of Healthy Living Monthly Assessment Completion by Site Patient Participants				
Site	**Number of Participants Enrolled**	**HLM Survey**	**Number of Participants Submitting HLM Survey[1]**	**Number of Participants Completing Risky Opioid Use Questions[1]**
Annville Family Medicine		1-month		
		2-month		
		3-month		
		4-month		
		5-month		
		6-month		
		7-month		
		8-month		
		9-month		
		10-month		
		11-month		
		12-month		
University of Utah		1-month		
		2-month		
		3-month		
		4-month		
		5-month		
		6-month		
		7-month		
		8-month		
		9-month		
		10-month		
		11-month		
		12-month		
The Ohio State University		1-month		
		2-month		
		3-month		
		4-month		
		5-month		
		6-month		

Table 22: Summary of Healthy Living Monthly Assessment Completion by Site Patient Participants				
Site	**Number of Participants Enrolled**	**HLM Survey**	**Number of Participants Submitting HLM Survey[1]**	**Number of Participants Completing Risky Opioid Use Questions[1]**
		7-month		
		8-month		
		9-month		
		10-month		
		11-month		
		12-month		
Total		1-month		
		2-month		
		3-month		
		4-month		
		5-month		
		6-month		
		7-month		
		8-month		
		9-month		
		10-month		
		11-month		
		12-month		

[1] The denominator is the numbers of participants enrolled.

Table 23: Summary of Healthy Living Monthly Assessment Completion by Treatment Arm

Patient Participants

Treatment Arm	Number of Participants Enrolled	Survey	Number of Participants Submitting Survey[1]	Number of Participants Completing Risky Opioid Use Questions[1]
EUC	N	1-month	N (X.X%)	N (X.X%)
		…		
		12-month		
STOP		1-month		
		…		
		12-month		
Total		1-month		
		…		
		12-month		

[1] The denominator is the number of participants enrolled.

6 Visit Attendance: Patient Participants

Table 24: Summary of Attendance at Study Visits by Treatment Arm Patient Participants

Treatment Arm	Number of Participants Enrolled	Visit	Number Attended[1]	Percentage Attended
EUC	N	Baseline	N	X.X%
		3-month		
		6-month		
		9-month		
		12-month		
STOP		Baseline		
		3-month		
		6-month		
		9-month		
		12-month		
Total		Baseline		
		3-month		
		6-month		
		9-month		
		12-month		

[1] A visit is considered attended if the Visit Documentation (V01) form indicates the visit was attended. Visits are comprised of assessments conducted by research staff and self-administered assessments and could be completed remotely or in person.

Table 25: Summary of Missed Visits by Treatment Arm
Patient Participants

	Treatment Arm		
	EUC (N=)	**STOP (N=)**	**Total (N=)**
Number of expected visits[1]	N		
Number of missed visits during active participation[2]	N (X.X%)		
Number of missed visits due to early study termination[2,3]	N (X.X%)		
Number of participants with at least one missed visit[4]	N (X.X%)		
Average number of missed visits per participant	X.X		
Reason for missed visit during active participation[5]			
Participant on vacation	N (X.X%)		
Participant illness			
Participant in hospital, in-patient, or residential treatment			
Participant incarcerated			
Site closed			
Participant withdrew consent			
Participant deceased			
Unable to contact			
Site decision/error			
COVID-19: Illness			
COVID-19: Public health measures			
COVID-19: Other			
Other			

[1] Five visits per participant are expected: Baseline, 3, 6, 9 and 12-months.

[2] Percentages are calculated based on the denominator of number of expected visits.

[3] Includes participants who missed visits prior to the Study Completion (STC) form being completed indicating early study termination.

[4] Percentage is calculated based on the denominator of number of participants enrolled.

[5] Percentages are calculated with the number of missed visits during active participation as the denominator.

7 STOP Intervention Exposure

Table 26: Summary of Primary Care Provider Intervention by Site
STOP Patient Participants

Activity	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Participants receiving the brief advice[1]	n/N (X.X%)					
Received within 10-day window	n/N (X.X%)					
Received outside 10-day window	n/N (X.X%)					
Participants receiving the Healthy Living Study Report Card[2]	N (X.X%)					
Participants receiving opioid overdose pamphlet[2]	N (X.X%)					
Participants receiving the Video Doctor[2]	N (X.X%)					
Average minutes spent discussing opioid use	X.X					

[1] Only STOP patient participants with the version of the PCP Intervention Checklist (PIC) form that asks if the brief advice was delivered are included in the brief advice delivery calculation (form updated on September 30, 2021). The denominator is the number of STOP patient participants with this version of the form.

[2] Denominator is the number of STOP patient participants.

Table 27: Summary of Nurse Care Manager Intervention by Site
STOP Patient Participants

Activity	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Participants educated on overdose prevention[1]	N (X.X%)					
Participants receiving the workbook[1]	N (X.X%)					
Participants receiving information to access naloxone[1]	N (X.X%)					
Interactions with patient participant[2]						
Month 1						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
…						
Month 12						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					
Total (Months 1-12)						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					

[1] Denominator is the number of STOP patient participants.

[2] Participants can interact with the NCM through face to face visits, video or telephone calls, and emails/texts as many times as they need for 12 months following enrollment.

Table 28: Summary of Telephone Health Coach Interactions by Site
STOP Patient Participants

Activity	Chase-Brexton Health Center (N=)	Dartmouth-Hitchcock (N=)	Annville Family Medicine (N=)	University of Utah (N=)	The Ohio State University (N=)	Total (N=)
Number of coaching sessions per participant[1]						
No sessions	N (X.X%)					
1 session						
2 sessions						
3 sessions						
4 sessions						
5 sessions						
6 sessions						
Number of coaching sessions per participant						
N	N					
Mean	X.X					
SD	X.XX					
Minimum	X					
Median	X.X					
Maximum	X					

[1] Denominator is the number of STOP patient participants.

8 Primary Outcome Analyses

Table 29: Summary of Primary Outcome Availability by Treatment Arm in ITT Population			
Treatment Arm	**Number of Participants Enrolled**	**Number with Primary Outcome Available[1]**	**Primary Outcome Availability Percentage**
EUC	N	N	X.X%
STOP			
Total			

[1] Six monthly surveys contributing to the primary outcome are expected per participant: 1-, 2-, 3-, 4-, 5-, and 6-months post baseline visit. The primary outcome is considered available if all the questions for risky opioid use (illicit and non-medical) are completed on all six of the monthly surveys.

Table 30: Summary of Risky Opioid Use Missing Data Patterns by Treatment Arm in ITT Population

Pattern[1]	HLM Survey							Treatment Arm		
	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	EUC (N=)	STOP (N=)	Total (N=)
1	X	X	X	X	X	X	X	N (X.X%)	N (X.X%)	N (X.X%)
2	X	X	X	X	X	X	O			
3	X	X	X	X	X	O	O			
4	…									
5	X	X	X	X	O	O	X			
6	X	X	O	X	X	X	X			
7	…									
8	O	X	X	O	X	X	O			
9	…									
10	O	O	O	O	O	O	O			

[1] A 'X' indicates that risky opioid use was collected at that month on the HLM survey. An 'O' indicates that risky opioid use was not collected at that month on the HLM survey. The different colors indicate 5 missing data patterns and correspond to those in Table 31: No Missing data (blue); Missing due to dropout (orange); Intermittent missing (grey); both intermittent missing and missing due to dropout (green); and all missing (yellow). If a patient participant did not complete the risky opioid use data at baseline and on all 6 of the monthly surveys after baseline, they are categorized in the 'all missing' pattern and the patient participant will be excluded from the primary outcome analysis.

Note: Table provides a representative sample of the missing data patterns that may exist. All patterns seen in the data will be presented at time of final analysis.

Table 31: Summary of Participants by Risky Opioid Use Missing Data Patterns and Treatment Arm in ITT Population

Pattern[1]	Treatment Arm		Total (N=)
	EUC (N=)	STOP (N=)	
No missing data	N (X.X%)	N (X.X%)	N (X.X%)
Missing due to dropout			
Intermittent missing			
Both intermittent missing and missing due to dropout			
All missing			

[1] The summary of the risky opioid use missing data patterns are based on the patterns reported in Table 30 for data in the baseline and Months 1-6 HLM surveys.

Table 32: Summary of Primary Outcome Analysis by Treatment Arm Using Multiple Imputation in ITT Population

Treatment Arm	Number of Participants Enrolled	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Results[1]			
			Rate Ratio[2]	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
EUC	N	X.x (X.xx)	X.xx	X.xx	X.xx	0.xxx
STOP						
Total						

[1] Results for the treatment effect are obtained from the mixed effects negative binomial model adjusted for site (stratification factor) and baseline value of the response. Missing values among the variables which contribute to the response value from Months 1-6 and missing baseline values of the response are imputed via a multiple imputation approach. The missing data due to intermittent missingness and due to dropout are imputed separately assuming a missing at random (MAR) and a missing not at random (MNAR) missing data mechanism, respectively.

[2] The rate ratio is defined as the exponentiated estimate of the treatment effect as a ratio of the mean total number of days of risky opioid use for those enrolled to STOP versus EUC within the first 180 days post-baseline.

9 Sensitivity Analyses of Primary Outcome

Table 33: Summary of Primary Outcome Analysis by Treatment Arm in Complete Case Population

Treatment Arm	Number of Participants Enrolled	Number of Participants Contributing to Analysis[1]	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Results[2]			
				Rate Ratio[3]	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
EUC	N	N (%)	X .x (X.xx)	X.xx	X.xx	X.xx	0.xxx
STOP							
Total							

[1] A participant contributed to the analysis if they are from the complete case population. A participant is a complete case if they have no missing values of the response variable during Months 1-6 and the baseline value of the response.

[2] Results for the treatment effect are obtained from the mixed effects negative binomial model adjusted for site (stratification factor) and baseline value of the response. Missing values of the variables that contribute to the primary outcome and baseline value of the response are not imputed.

[3] The rate ratio is defined as the exponentiated estimate of the treatment effect as a ratio of the mean total number of days of risky opioid use for those enrolled to STOP versus EUC within the first 180 days post-baseline.

Table 34: Summary of Primary Outcome Analysis by Treatment Arm Using Multiple Imputation Assuming Missing at Random[1] in ITT Population

Treatment Arm	Number of Participants Enrolled	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Results [2]			
			Rate Ratio[3]	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
EUC	N	X.x (X.xx)	X.xx	X.xx	X.xx	0.xxx
STOP						
Total						

[1] Assuming a missing at random (MAR) for missingness due to both intermittent missingness and dropout is used for multiple imputation of the missing data in the sensitivity analysis.

[2] Results for the treatment effect are obtained from the mixed effects negative binomial model adjusted for site (stratification factor) and baseline value of the response. All of missing values from the variables of the primary outcome from Months 1-6 and baseline value of the response are imputed via multiple imputation assuming missing at random (MAR) for both intermittent missingness and for dropouts.

[3] The rate ratio is defined as the exponentiated estimate of the treatment effect as a ratio of the mean total number of days of risky opioid use for those enrolled to STOP versus EUC within the first 180 days post-baseline.

10 Supplemental Analyses of Primary Outcome

Table 35: Summary of Primary Outcome Analysis with Individual-level Covariate Adjustment by Treatment Arm

Treatment Arm	Number of Participants Enrolled	Number of Participants Contributing to Analysis[1]	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Results[2]			
				Rate Ratio[3]	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
EUC	N	N (%)	X.x (X.xx)	X.xx	X.xx	X.xx	0.xxx
STOP							
Total							

[1] A participant contributed to the analysis if they have no missing values in the response variable and all of the covariates adjusted in the mixed effect regression model.

[2] Results for the treatment effect are obtained from the mixed effects negative binomial model adjusted for site (stratification factor) and baseline value of the response, [*list of all covariates included in the model*] are adjusted. Missing values from the variables of the response and covariates are not imputed.

[3] The rate ratio is defined as the exponentiated estimate of the treatment effect as a ratio of the mean total number of days of risky opioid use for those enrolled to STOP versus EUC within the first 180 days post-baseline.

Table 36: Summary of Primary Outcome Analysis by Sex and Treatment Arm							
		Treatment Arm		Results[1]			
		EUC (N=)	STOP (N=)				
Subgroup	Number of Participants Enrolled	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Male	N	X.X (X.XX)	X.X (X.XX)	X.XX	X.XX	X.XX	0.xxx
Female							

[1] Results are obtained from the mixed effects negative binomial model. The rate ratio and p-value for the interaction term between treatment arm and subgroup is shown. Missing values are not imputed.

Table 37: Summary of Primary Outcome Analysis by Age and Treatment Arm							
		Treatment Arm		Results[1]			
		EUC (N=)	STOP (N=)				
Subgroup	Number of Participants Enrolled	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
< 55 years	N	X.X (X.XX)	X.X (X.XX)	X.XX	X.XX	X.XX	0.xxx
≥ 55 years							

[1] Results are obtained from the mixed effects negative binomial model. The rate ratio and p-value for the interaction term between treatment arm and subgroup is shown. Missing values are not imputed.

Table 38: Summary of Primary Outcome Analysis by Race and Treatment Arm							
		Treatment Arm		Results[1]			
		EUC (N=)	STOP (N=)				
Subgroup	Number of Participants Enrolled	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Black	N	X.X (X.XX)	X.X (X.XX)	X.XX	X.XX	X.XX	0.xxx
White							
Other[2]							

[1] Results are obtained from the mixed effects negative binomial model. The rate ratio and p-value for the interaction term between treatment arm and subgroup is shown. Missing values are not imputed.

[2] Other includes American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, Other and Multiracial.

Table 39: Summary of Primary Outcome by Ethnicity and Treatment Arm							
		Treatment Arm		Results[1]			
		EUC (N=)	STOP (N=)				
Subgroup	Number of Participants Enrolled	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Not Hispanic or Latinx	N	X.X (X.XX)	X.X (X.XX)	X.XX	X.XX	X.XX	0.xxx
Hispanic or Latinx							

[1] Results are obtained from the mixed effects negative binomial model. The rate ratio and p-value for the interaction term between treatment arm and subgroup is shown. Missing values are not imputed.

Table 40: Summary of Primary Outcome Analysis by Treatment Arm in Per-Protocol Population

Treatment Arm	Number of Participants Enrolled	Number of Participants Contributing to Analysis[1]	Days of Risky Opioid Use in the 180 Days from Baseline (Mean (SD))	Results[2]			
				Rate Ratio[3]	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
EUC	N	N (%)	X.x (X.xx)	X.xx	X.xx	X.xx	0.xxx
STOP							
Total							

[1] A participant contributed to the analysis if they are from per-protocol population and have no missing values of the response variable during Months 1-6 and the baseline value of the response.

[2] Results for the treatment effect are obtained from the mixed effects negative binomial model adjusted for site (stratification factor) and baseline value of the response. Missing values from the variables of the response and baseline value of the response are not imputed.

[3] The rate ratio is defined as the exponentiated estimate of the treatment effect as a ratio of the mean total number of days of risky opioid use for those enrolled to STOP versus EUC within the first 180 days post-baseline.

11 Supportive Analyses of Primary Outcome

Table 41: Summary Statistics of Risky Opioid Use by Treatment Arm			
	Treatment Arm		Total (N=)
	EUC (N=)	STOP (N=)	
Monthly Risky Opioid Use (Days)			
1-Month			
N	N		
Mean	X.X		
SD	X.XX		
Minimum	X		
Median	X.X		
Maximum	X		
2-Month			
…			
12-Month			
N	N		
Mean	X.X		
SD	X.XX		
Minimum	X		
Median	X.X		
Maximum	X		
Quarterly Risky Opioid Use (Days)			
1-3 Months			
N	N		
Mean	X.X		
SD	X.XX		
Minimum	X		
Median	X.X		
Maximum	X		
4-6 Months			
…			
9-12 Months			
N	N		

Table 41: Summary Statistics of Risky Opioid Use by Treatment Arm			
	Treatment Arm		
	EUC (N=)	STOP (N=)	Total (N=)
Mean	X.X		
SD	X.XX		
Minimum	X		
Median	X.X		
Maximum	X		
6-Months Risky Opioid Use (Days)			
1-6 Months			
N	N		
Mean	X.X		
SD	X.XX		
Minimum	X		
Median	X.X		
Maximum	X		
7-12 Months			
N	N		
Mean	X.X		
SD	X.XX		
Minimum	X		
Median	X.X		
Maximum	X		

Table 42: Summary of Risky Opioid Use in Past 30 Days by Treatment Arm				
Treatment Arm	**Number of Participants Enrolled**		**Number of Participants Contributing to Estimate for Monthly Use[1]**	
EUC	N		N (X.x%)	
STOP				
Total				
Results[2]				
Time Duration	**Rate Ratio**	**95% Lower Confidence Limit**	**95% Upper Confidence Limit**	**p-value**
Months 1~6	X.xx	X.xx	X.xx	0.xxx
Months 7~12				

[1] A participant contributes to the monthly use estimate if they have all fixed effect covariates and at least one monthly use outcome through 12 months post-baseline.

[2] Results are obtained from a longitudinal mixed effects model. Time trends of the treatment effect are modelled using a piecewise linear function for the time variable. The results are reported with the piecewise linear function at the breaking point of month 6 to allow for different slopes for the change in risky opioid use during months 1-6 and months 7-12. In final data analysis, the growth trajectory pattern of the change in opioid use during the 12-month study period will be used to determining the breaking points used in the final model.

Table 43: Summary of Risky Opioid Use in Past 90 Days by Treatment Arm

Months 1-3

Treatment Arm	Number of Participants Enrolled	Number of Participants Contributing to Estimate during Months 1-3[1]	Results[2]			
			Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
EUC	N	N (X.x%)	X.xx	X.xx	X.xx	0.xxx
STOP						
Total						

Months 4-6

Treatment Arm	Number of Participants Enrolled	Number of Participants Contributing to Estimate during Months 4-6[3]	Results[4]			
			Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
EUC	N	N (X.x%)	X.xx	X.xx	X.xx	0.xxx
STOP						
Total						

Months 7-9

Treatment Arm	Number of Participants Enrolled	Number of Participants Contributing to Estimate during Months 7-9[5]	Results[6]			
			Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
EUC	N	N (X.x%)	X.xx	X.xx	X.xx	0.xxx
STOP						
Total						

Table 44: Summary of Risky Opioid Use in Past 90 Days by Treatment Arm						
Months 10-12						
Treatment Arm	**Number of Participants Enrolled**	**Number of Participants Contributing to Estimate during Months 10-12[7]**	**Results[8]**			
			Rate Ratio	**95% Lower Confidence Limit**	**95% Upper Confidence Limit**	**p-value**
EUC	N	N (X.x%)	X.xx	X.xx	X.xx	0.xxx
STOP						
Total						

[1] A participant contributes to months 1-3 estimate if they have all fixed effect covariates and days of opioid use at months 1-3.

[2] Results are obtained from a longitudinal mixed effects model. The rate ratio and p-value result are obtained from main effect of treatment and interaction between treatment effect and time of months 1-3.

[3] A participant contributes to months 4-6 estimate if they have all fixed effect covariates and days of opioid use at months 4-6.

[4] Results are obtained from a longitudinal mixed effects model. The rate ratio and p-value result are obtained from main effect of treatment and interaction between treatment effect and time of months 4-6.

[5] A participant contributes to months 7-9 estimate if they have all fixed effect covariates and days of opioid use at months 7-9.

[6] Results are obtained from a longitudinal mixed effects model. The rate ratio and p-value result are obtained from main effect of treatment and interaction between treatment effect and time of months 7-9.

[7] A participant contributes to months 10-12 estimate if they have all fixed effect covariates and days of opioid use at months 10-12.

[8] Results are obtained from a longitudinal mixed effects model. The rate ratio and p-value result are obtained from main effect of treatment and interaction between treatment effect and time of months 10-12.

Table 45: Summary of Risky Opioid Use During Months 7-12 by Treatment Arm						
			Results[2]			
Treatment Arm	Number of Participants Enrolled	Number of Participants Contributing to Estimate during Months 7-12[1]	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
EUC	N	N (X.x%)	X.xx	X.xx	X.xx	0.xxx
STOP						
Total						

[1] A participant contributes to months 7-12 estimate if they have all fixed effect covariates and days of opioid use at months 7-12.

[2] Results are obtained from a longitudinal mixed effects model. The rate ratio and p-value result are obtained from main effect of treatment and interaction between treatment effect and time of months 7-12.

12 Secondary Outcome Analyses (Patient Level): Binge Alcohol Use

Table 46: Summary Statistics of Binge Alcohol Use by Treatment Arm
Repeat of Table 41 for binge alcohol use days

Table 47: Summary of Binge Alcohol Use in Past 30 Days by Treatment Arm
Repeat of Table 42 for binge alcohol use

Table 48: Summary of Binge Alcohol Use in Past 90 Days by Treatment Arm
Repeat of Table 43 for binge alcohol use

Table 49: Summary of Binge Alcohol Use in Past 180 Days by Treatment Arm

Months 1-6

Treatment Arm	Number of Participants Enrolled	Number of Participants Contributing to Estimate during Months 1-6[1]	Results[2]			
			Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
EUC	N	N (X.x%)	X.xx	X.xx	X.xx	0.xxx
STOP						
Total						

Months 7-12

Treatment Arm	Number of Participants Randomized	Number of Participants Contributing to Estimate during Months 7-12[3]	Results[4]			
			Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
EUC	N	N (X.x%)	X.xx	X.xx	X.xx	0.xxx
STOP						
Total						

[1] A participant contributes to months 1-6 estimate if they have all fixed effect covariates and days of alcohol use at months 1-6.

[2] Results are obtained from a longitudinal mixed effects model. The rate ratio and p-value result are obtained from main effect of treatment and interaction between treatment effect and time of months 1-6.

[3] A participant contributes to months 7-12 estimate if they have all fixed effect covariates and days of alcohol use at months 7-12.

[4] Results are obtained from a longitudinal mixed effects model. The rate ratio and p-value result are obtained from main effect of treatment and interaction between treatment effect and time of months 7-12.

13 Secondary Outcome Analyses (Patient Level): Benzodiazepine Use

Table 50: Summary Statistics of Benzodiazepine Use by Treatment Arm
Repeat of Table 41 for benzodiazepine use days

Table 51: Summary of Benzodiazepine Use in Past 30 Days by Treatment Arm
Repeat of Table 42 for benzodiazepine use

Table 52: Summary of Benzodiazepine in Past 90 Days by Treatment Arm
Repeat of Table 43 for benzodiazepine use

Table 53: Summary of Benzodiazepine in Past 180 Days by Treatment Arm
Repeat of Table 49 for benzodiazepine use

14 Secondary Outcome Analyses (Patient Level): Stimulant Drug Use

Table 54: Summary Statistics of Stimulant Drug Use by Treatment Arm
Repeat of Table 41 for stimulant drug use days

Table 55: Summary of Stimulant Drug Use in Past 30 Days by Treatment Arm
Repeat of Table 42 for stimulant drug use

Table 56: Summary of Stimulant Drug Use in Past 90 Days by Treatment Arm
Repeat of Table 43 for stimulant drug use

Table 57: Summary of Stimulant Drug Use in Past 180 Days by Treatment Arm
Repeat of Table 49 for stimulant drug use

15 Secondary Outcome Analyses (Patient Level): Marijuana Use

Table 58: Summary Statistics of Marijuana Use by Treatment Arm
Repeat of Table 41 for marijuana use days

Table 59: Summary of Marijuana Use in Past 30 Days by Treatment Arm
Repeat of Table 42 for marijuana use

Table 60: Summary of Marijuana Use in Past 90 Days by Treatment Arm
Repeat of Table 43 for marijuana use

Table 61: Summary of Marijuana Use in Past 180 Days by Treatment Arm
Repeat of Table 49 for marijuana use

16 Secondary Outcome Analyses (Patient Level): Other Drug Use

Table 62: Summary Statistics of Other Drug Use by Treatment Arm			
	Treatment Arm		Total (N=)
	EUC (N=)	STOP (N=)	
Monthly Risky Opioid Use (Days)			
3-Month			
N	N		
Mean	X.X		
SD	X.XX		
Minimum	X		
Median	X.X		
Maximum	X		
6-Month			
…			
9-Month			
…			
12-Month			
N	N		
Mean	X.X		
SD	X.XX		
Minimum	X		
Median	X.X		
Maximum	X		

17 Secondary Outcome Analyses (Patient Level): Urine Drug Screen Results

Table 63: Summary of Positive UDS Results by Visit and Treatment Arm
Patient Participants

Visit		Treatment Arm		Total (N=)
		EUC (N=)	STOP (N=)	
Baseline Visit	Number of opioid positive UDS results[1]	n/N (X.X%)		
	Number of opioid + MOUD positive results[2]	n/N (X.X%)		
	Number of positive UDS results for any substance	n/N (X.X%)		
	Number of positive UDS results for:			
	Opiates (300 ng)	n/N (X.X%)		
	Oxycodone (100 ng)			
	Methadone (300 ng)			
	Buprenorphine (10 ng)			
	Fentanyl (20 ng)			
	Amphetamine (500 ng)			
	Barbiturate (300 ng)			
	Benzodiazepines (300 ng)			
	Cocaine (150 ng)			
	Ecstasy (500 ng)			
	Methamphetamine (500 ng)			
	Phencyclidine (PCP) (25 ng)			
	Marijuana (50 ng)			
6-month Visit	…			
12-month Visit	…			
Total	Number of opioid positive UDS results[1]	n/N (X.X%)		
	Number of opioid + MOUD positive results[2]	n/N (X.X%)		
	Number of positive UDS results for any substance	n/N (X.X%)		
	Number of positive UDS results for:			
	Opiates (300 ng)	n/N (X.X%)		
	Oxycodone (100 ng)			
	Methadone (300 ng)			
	Buprenorphine (10 ng)			
	Fentanyl (20 ng)			
	Amphetamine (500 ng)			
	Barbiturate (300 ng)			
	Benzodiazepines (300 ng)			
	Cocaine (150 ng)			
	Ecstasy (500 ng)			
	Methamphetamine (500 ng)			
	Phencyclidine (PCP) (25 ng)			
	Marijuana (50 ng)			

[1] Opioid category includes: opiates (300 ng), oxycodone (100 ng), and fentanyl (20 ng).

[2] Opioid + MOUD category includes: opiates (300 ng), oxycodone (100 ng), methadone (300 ng), buprenorphine (10 ng), and fentanyl (20 ng).

Table 64: Summary of Positive UDS Results by Visit, Prescription for Opioids, and Treatment Arm
Patient Participants

Visit	Prescription for Opioids in Past 6 Months		Treatment Arm		Total (N=)
			EUC (N=)	STOP (N=)	
Baseline Visit	Yes	Number of participants reporting having an opioid prescription in past 6 months on the COMM[1]	N (X.X%)		
		Number of opioid positive UDS results[2]	n/N (X.X%)		
		Number of opioid + MOUD positive results[3]	n/N (X.X%)		
		Number of positive UDS results for any substance	n/N (X.X%)		
		Number of positive UDS results for:			
		Opiates (300 ng)	n/N (X.X%)		
		Oxycodone (100 ng)			
		Methadone (300 ng)			
		Buprenorphine (10 ng)			
		Fentanyl (20 ng)			
		Amphetamine (500 ng)			
		Barbiturate (300 ng)			
		Benzodiazepines (300 ng)			
		Cocaine (150 ng)			
		Ecstasy (500 ng)			
		Methamphetamine (500 ng)			
		Phencyclidine (PCP) (25 ng)			
		Marijuana (50 ng)			
	No	Number of participants reporting not having an opioid prescription in past 6 months on the COMM[1]	N (X.X%)		
		Number of opioid positive UDS results[2]	n/N (X.X%)		
		Number of opioid + MOUD positive results[3]	n/N (X.X%)		
		Number of positive UDS results for any substance	n/N (X.X%)		
		Number of positive UDS results for:			
		Opiates (300 ng)	n/N (X.X%)		
		Oxycodone (100 ng)			
		Methadone (300 ng)			
		Buprenorphine (10 ng)			
		Fentanyl (20 ng)			
		Amphetamine (500 ng)			
		Barbiturate (300 ng)			
		Benzodiazepines (300 ng)			
		Cocaine (150 ng)			
		Ecstasy (500 ng)			
		Methamphetamine (500 ng)			
		Phencyclidine (PCP) (25 ng)			
		Marijuana (50 ng)			
6-month Visit	Yes/No	…			
12-month Visit	Yes/No	…			

[1] Denominator is the number of patient participants.

[2] Opioid category includes: opiates (300 ng), oxycodone (100 ng), and fentanyl (20 ng).

[3] Opioid + MOUD category includes: opiates (300 ng), oxycodone (100 ng), methadone (300 ng), buprenorphine (10 ng), and fentanyl (20 ng).

18 Safety Analyses

Table 65: Summary of Non-fatal Drug or Alcohol Overdose Events in the Past 6 Months, by Treatment Arm

Patient Participants

		Treatment Arm		
Visit		**EUC (N=)**	**STOP (N=)**	**Total (N=)**
Baseline	Number of non-fatal drug or alcohol overdoses	N		
	Number of participants with at least one non-fatal drug or alcohol overdose	N (X.X%)		
	Number of non-fatal drug or alcohol overdoses per participant			
	N	N		
	Mean	X.X		
	SD	X.XX		
	Minimum	X		
	Median	X.X		
	Maximum	X		
6-month	Number of non-fatal drug or alcohol overdoses	N		
	Number of participants with at least one non-fatal drug or alcohol overdose	N (X.X%)		
	Number of non-fatal drug or alcohol overdoses per participant			
	N	N		
	Mean	X.X		
	SD	X.XX		
	Minimum	X		
	Median	X.X		
	Maximum	X		

Table 65: Summary of Non-fatal Drug or Alcohol Overdose Events in the Past 6 Months by Treatment Arm

Patient Participants

		Treatment Arm		
Visit		**EUC (N=)**	**STOP (N=)**	**Total (N=)**
12-month	Number of non-fatal drug or alcohol overdoses	N		
	Number of participants with at least one non-fatal drug or alcohol overdose	N (X.X%)		
	Number of non-fatal drug or alcohol overdoses per participant			
	N	N		
	Mean	X.X		
	SD	X.XX		
	Minimum	X		
	Median	X.X		
	Maximum	X		

Table 66: Summary of Suicide Risk by Treatment Arm

Patient Participants

	Treatment Arm		
	EUC (N=)	**STOP (N=)**	**Total (N=)**
Number endorsing suicide risk on PSS[1] at Baseline	N (X.X%)		
Number endorsing suicide risk on PSS at 6-months	N (X.X%)		
Number endorsing suicide risk on PSS at 12-months	N (X.X%)		
Number endorsing suicide risk on PSS at either 6 or 12-months	N (X.X%)		

[1] Patient Safety Screener. PSS is administered at baseline, 6-months, and 12-months. Endorsing suicide risk on PSS is defined as a response of 'yes' to having thoughts of killing themselves over the last 2 weeks or if they attempted to kill themselves within the last 24 hours (including today) or within the last month (but not today).

Table 67: Summary of Hospitalizations by Treatment Arm Patient Participants				
		Treatment Arm		
Visit		EUC (N=)	STOP (N=)	Total (N=)
6-month	Number of hospitalizations	N		
	Numbers of participants with hospitalizations	N (X.X%)		
	Number of hospitalizations per participant			
	0	N (X.X%)		
	1			
	2			
	3			
	4			
	5 or more			
	Number of hospitalizations per participant			
	N	N		
	Mean	X.X		
	SD	X.XX		
	Minimum	X		
	Median	X.X		
	Maximum	X		
12-month	Number of hospitalizations	N		
	Numbers of participants with hospitalizations	N (X.X%)		
	Number of hospitalizations per participant			
	0	N (X.X%)		
	1			
	2			
	3			
	4			
	5 or more			
	Number of hospitalizations per participant			
	N	N		
	Mean	X.X		
	SD	X.XX		
	Minimum	X		
	Median	X.X		
	Maximum	X		

Table 68: Summary of ED Visits by Treatment Arm
Patient Participants

		Treatment Arm		
Visit		**EUC (N=)**	**STOP (N=)**	**Total (N=)**
6-month	Number of ED visits	N		
	Numbers of participants with ED visits	N (X.X%)		
	Number of ED visits per participant			
	0	N (X.X%)		
	1			
	2			
	3			
	4			
	5 or more			
	Number of ED visits per participant			
	N	N		
	Mean	X.X		
	SD	X.XX		
	Minimum	X		
	Median	X.X		
	Maximum	X		
12-month	Number of ED visits	N		
	Numbers of participants with ED visits	N (X.X%)		
	Number of ED visits per participant			
	0	N (X.X%)		
	1			
	2			
	3			
	4			
	5 or more			
	Number of ED visits per participant			
	N	N		
	Mean	X.X		
	SD	X.XX		
	Minimum	X		
	Median	X.X		
	Maximum	X		

Listing 1: Listing of Non-fatal Drug or Alcohol Overdoses by Treatment Arm Patient Participants						
Treatment Arm = EUC/STOP						
Site	**Participant ID**	**Date of Enrollment**	**Visit**	**Date of Assessment**	**Number of Overdoses[1]**	**Comments**
xxxxxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	Baseline/ 6-month/ 12-month	mm/dd/yyyy	N	xxxxxxxxxx

[1] Only the number of non-fatal drug or alcohol overdoses in the past 6 months are reported at each visit.

Listing 2: Listing of Suicide Risk by Treatment Arm							
Treatment Arm = EUC/STOP							
Site	**Participant ID**	**Date of Enrollment**	**Visit**	**Date of Assessment**	**Over the past 2 weeks, have you had thoughts of killing yourself?**	**Have you ever attempted to kill yourself?**	**If yes, when did this last happen?**
xxxxxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	Baseline/ 6-month/ 12-month	mm/dd/yyyy	Yes/ No/ Unable to complete	Yes/ No	Within the last 24 hours (including today)/ Within the last month (but not today)/ Between 1 and 6 months ago/ More than 6 months ago

All visits are included for participants who answered 'yes' to having thoughts of killing themselves over the last 2 weeks or if they attempted to kill themselves within the last 24 hours (including today) or within the last month (but not today).

Listing 3: Listing of Hospitalizations by Treatment Arm

Patient Participants

Treatment Arm = EUC/STOP

Site	Participant ID	Date of Enrollment	Date of Hospitalization	Date of Discharge	Primary Diagnosis/ Complaint	Secondary Diagnosis/ Complaint	Tertiary Diagnosis/ Complaint	Severity	Outcome
xxxxxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxx	xxxxxxxxxx	xxxxxxxxxx	Grade 1 - Mild/ Grade 2 - Moderate/ Grade 3 – Severe/ Grade 4 – Life threatening/ Grade 5 - Death	Recovering/resolving/ Recovered/resolved/ Recovered/recovered with sequelae/ Not recovered/not resolved/ Fatal/ Unknown

All hospitalizations are as reported on the ED Visits and Hospitalization (EDH) form.

Listing 4: Listing of ED Visits by Treatment Arm

Patient Participants

Treatment Arm = EUC/STOP

Site	Participant ID	Date of Enrollment	Date of ED Visit	Date of Discharge	Primary Diagnosis/ Complaint	Secondary Diagnosis/ Complaint	Tertiary Diagnosis/ Complaint	Severity	Outcome
xxxxxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxx	xxxxxxxxxx	xxxxxxxxxx	Grade 1 - Mild/ Grade 2 - Moderate/ Grade 3 - Severe Grade 4 - Life threatening/ Grade 5 - Death	Recovering/resolving/ Recovered/resolved/ Recovered/recovered with sequelae/ Not recovered/not resolved/ Fatal/ Unknown

All ED visits are as reported on the ED Visits and Hospitalization (EDH) form.

Listing 5: Listing of Deaths by Treatment Arm

Patient Participants

Treatment Arm = EUC/STOP

Site	Participant ID	Date of Enrollment	Date of Death	Source of Death Report	Type	Cause of Death	MedDRA vxx.x	
							Preferred Term	System Organ Class
xxxxxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	Medical chart/ Death certificate/ Autopsy report/ Treating physician/ Other	Primary	xxxxxxxxxx	xxxxxxxxxx	xxxxxxxxxx
					Secondary	xxxxxxxxxx	xxxxxxxxxx	xxxxxxxxxx

19 Data Quality

Table 69: Summary of Data Audits

Site	Date of Audit	Total Fields Audited[1]	Total Data Discrepancies[2]	Error Rate
Chase-Brexton Health Center	mm/dd/yyyy	N	N	x.xx%
	Subtotal			
Dartmouth-Hitchcock	mm/dd/yyyy			
	Subtotal			
Annville Family Medicine	mm/dd/yyyy			
	Subtotal			
University of Utah	mm/dd/yyyy			
	Subtotal			
The Ohio State University	mm/dd/yyyy			
	Subtotal			
Total	-			

[1] Fields reviewed at monitoring visit comparing the database to source documentation.

[2] Fields discrepant between database and source documentation.

20 Protocol Deviations

Table 70: Summary of Protocol Deviations by Site						
	Chase-Brexton Health Center	Dartmouth-Hitchcock	Annville Family Medicine	University of Utah	The Ohio State University	Total
Total number of protocol deviations	N					
Number of protocol deviations related to COVID-19	N (X.X%)					
Number of participants impacted per protocol deviation						
None	N (X.X%)					
One						
More than one						
Total number of major protocol deviations	N					
Number of major protocol deviations related to COVID-19	N (X.X%)					
Type of major protocol deviation						
No consent/assent obtained	N (X.X%)					
Unauthorized assessments and/or procedures conducted prior to obtaining informed consent/assent						
Ineligible participant randomized/inclusion/exclusion criteria not met						
Ineligible participant enrolled/inclusion/exclusion criteria not met						
Stratification error						
Safety event not reported						
Safety event assessment not conducted per protocol						
Breach of confidentiality						
Other significant deviation issues						
Other laboratory assessments issues						
Total number of minor protocol deviations	N					

Table 70: Summary of Protocol Deviations by Site						
	Chase-Brexton Health Center	**Dartmouth-Hitchcock**	**Annville Family Medicine**	**University of Utah**	**The Ohio State University**	**Total**
Number of minor protocol deviations related to COVID-19	N (X.X%)					
Type of minor protocol deviation						
Other informed consent/assent procedures issues	N (X.X%)					
Other inclusion/exclusion criteria issues						
Other laboratory assessments issues						
Study assessments/procedures not followed in accordance with the study protocol						
Inappropriate unblinding						
Other study procedures/assessments issues						
Other randomization procedures issues						
Study behavioral intervention was not provided/performed as per protocol						
Other study behavioral intervention issues						
Safety event reported out of protocol specified reporting timeframe						
Safety event not elicited, observed and/or documented as per protocol						
Other safety event issues						
Destruction of study materials without prior authorization from sponsor						
Other significant deviations issues						

Listing 6: Listing of Protocol Deviations												
Deviation Category = XXXXXXXXX												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Resolution/ Corrective Action**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Planned/ Actual IRB Report Date**
xxxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy

Major PDs are Highlighted in grey.