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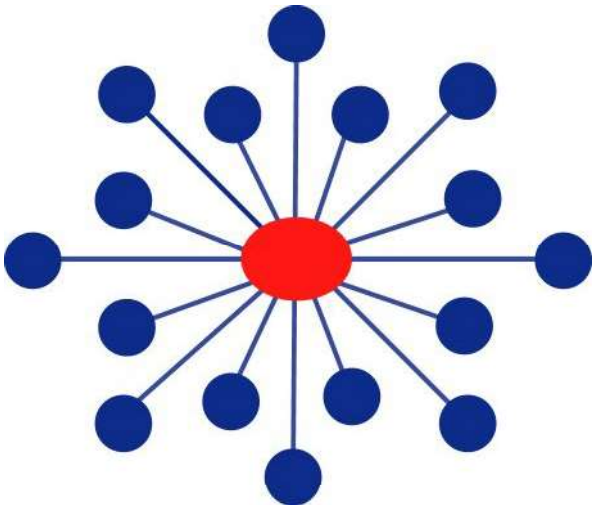

NIDA CTN Protocol 0101

Subthreshold Opioid Use Disorder Prevention (STOP) Trial (STOP Trial)

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Sponsor: National Institute on Drug Abuse (NIDA)

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CONFIDENTIAL

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CONFIDENTIALITY STATEMENT

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACASI	Audio Computer Assisted Self-Interview
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
EMA	Ecological Momentary Assessment
EHR	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
MME	Morphine Milligram Equivalents
MI	Motivational Interviewing
MITI	Motivational Interviewing Treatment Integrity
MOP	Manual of Procedures

Abbreviation	Definition
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, General Activity – a 3-item scale assessing pain intensity and interference
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
PS	Protocol Specialist
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	Short Form 12 – health related quality of life measure
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
TLFB	Timeline Follow-Back
TOPCARE	Transforming Opioid Prescribing in Primary Care
UDS	Urine Drug Screen

2.0 STUDY SYNOPSIS

2.1 Study Objectives

Concurrent to efforts to expand treatment to those currently experiencing an opioid use disorder (OUD), it is critically important to focus on the prevention of OUD among individuals with subthreshold OUD.[1-5] ***Subthreshold OUD*** is opioid use that is not severe enough to meet diagnostic criteria for moderate-severe OUD (that would require medication and more intensive treatment). As defined here, subthreshold OUD includes individuals with problem opioid use or mild OUD symptoms. Individuals with subthreshold OUD engage in ***risky opioid use*** behavior, which includes 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 them. Although a minority (18%) of the 12 million Americans with past-year illicit or nonmedical opioid use currently have an OUD, all of them are at high risk of developing OUD in the future.[5]

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 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. 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.

A 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.

The primary objective (Aim 1) 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. Our primary hypothesis 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 post-baseline (primary outcome), and at 3, 9, and 12 months post-baseline (secondary outcome), in comparison to patient participants with primary care providers assigned to EUC.

Secondary objectives capture patient participant-level outcomes (Aim 2) and provider-level outcomes (Aim 3). Patient participants having primary care providers assigned to the STOP intervention, in comparison to those with providers assigned to EUC, are hypothesized to have fewer days of non-opioid substance use (including use that increases the risk of overdose), lower incidence of moderate-severe OUD, decreased overdose risk behavior and overdose events, better health-related quality of life, better sleep, fewer symptoms of depression or anxiety, and no worsening of pain (symptoms or functioning). Providers assigned to the STOP intervention, in comparison to those assigned to EUC, are hypothesized to adopt better treatment practices for patients with subthreshold OUD. Specifically, PCPs in the STOP condition are expected to have improved prescribing practices (lower rates prescribing of high-dose opioids [>90 morphine milligram equivalents (MME)], any chronic opioids, or benzodiazepines; more prescribing of naloxone kits) and more frequent monitoring (toxicology testing, diagnosis of OUD, higher visit frequency) for patients with risky opioid use, as well as higher rates of PCP counseling patients on the risks of opioid use.

Definitions

- *Risky opioid use*: 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.
- *Subthreshold OUD*: Risky opioid use, with 0-3 DSM-5 criteria for OUD

2.1.1 Study Design and Outcomes

The study will be conducted at five sites, each having one or more participating primary care clinics. This is a cluster-randomized trial, randomized at the level of the PCP that 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. 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).

After study launch at each site, PCP participants will complete questionnaires on demographic and clinic characteristics. Patients with subthreshold OUD (as determined by research screening tools and 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. Provider practices, including prescribing and

monitoring for patient participants with subthreshold OUD, are assessed from the electronic health record (EHR).

The primary outcome (Aim 1) is days of risky opioid use in the past 180 days, assessed at 6 months. Secondary outcome measures for Aim 1 are days of risky opioid use assessed at earlier (3 months) and later (9 and 12 months) time points. Additional patient-level secondary outcomes (Aim 2) include substance use that increases opioid-related overdose risk (binge alcohol use, concurrent use of stimulants or sedatives with opioids), other drug use, drug and alcohol use disorders, overdose risk behaviors and nonfatal overdose events, pain symptoms and related functioning, mental health symptoms (depression, anxiety, suicidality), health-related quality of life, sleep, and acute health care utilization. Aim 3 provider-level outcome measures are collected from the EHR and include medications prescribed, lab tests, diagnosis of OUD and frequency of medical visits. Counseling on risk of opioid use will be provided by patient self-report.

2.1.2 Sample Size and Study Population

The sample consists of PCPs and their patients. We anticipate that the study will enroll approximately 100 PCPs. We estimate, however, that 30-40% of the enrolled PCPs will have no participating patients because we will not identify patients who meet the eligibility criteria in their panel, leaving approximately 60 PCPs who will have patients that will enroll into the study. Each of these PCPs is expected to have approximately 5 patients participating in the study, although the study can achieve patient recruitment in a variety of ways (e.g., 60 PCPs may have 5 patients enrolled each; Or 50 PCPs may have 4 patients, 5 PCPs may have 6 patients, and 7 PCPs may have 10 patients). This results in a total of approximately 300 patient participants enrolled in the study.

Original recruitment targets were based on 5 sites recruiting for the duration of the study. In October 2021, one site stopped recruiting, leaving 4 sites to continue. The sample of approximately 300 patients is thus comprised of recruitment from 5 sites for the initial 6 months, and from 4 sites for the remainder of the study.

PCPs eligible for participation will provide care to approximately 4 or more patients who receive chronic opioid treatment and/or have risky opioid use and see, on average, 40 or more adult patients (age ≥18 years) per week. The primary criteria for patient participant eligibility include: having a PCP who is enrolled in the study and having risky opioid use in the past 90 days. Patients will be excluded if they have moderate-severe OUD (4+ DSM-5 criteria); are currently receiving or have received medication for OUD (MOUD) in the past 30 days; or are receiving opioids for end of life care. Participant characteristics are anticipated to reflect the characteristics of adult primary care providers and 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.

2.1.3 Treatment/Assessment/Intervention and Duration

Treatment Intervention: STOP is a multi-component intervention with provider-facing and patient-facing elements. Providers in the STOP condition work with a nurse care manager (NCM), embedded in the clinic, who assists them with managing patient participants with subthreshold OUD. For all patient participants, the NCM provides patients with education and promotes self-management for reducing risky opioid use and for overdose prevention, reviews medications and

alerts the PCP to unsafe prescribing (e.g., high dose opioids, benzodiazepines prescribed to patients with opioid use), and as needed recommends non-pharmacological interventions for pain management, links patient participants to mental health services, and supports patient engagement in primary care. For patient participants on prescribed opioids, the NCM also provides medication monitoring (e.g., toxicology testing, pill counts), the level of which is adjusted based on the needs of the patient and concerns of the PCP. The NCM additionally monitors to ensure that the PCP regularly assesses patients for OUD.

Patient participants in the STOP condition receive Step 1 counseling. In Step 1, patients receive brief advice from their PCP and/or a "video doctor" (approximately 2 minutes of counseling modeled on the PCP's brief advice). Participants are additionally offered 2 telephone health coaching sessions (approximately 2- and 4-weeks after the baseline visit). Coaching is conducted via phone and/or HIPAA compliant video chat software by telephone health coaches, who are trained health professionals. Health coaches attempt to conduct two sessions with patient participants in the STOP condition, which focus on substance use behavior, stress/mood management, and quality of life issues. The sessions also emphasize opioid use and overdose risk and incorporate motivational interviewing (MI) techniques. Patient participants who may benefit from additional coaching (for example, those who do not improve or who experience clinical worsening of unhealthy opioid use) will be offered Step 2 enhanced telephone health coaching. In Step 2, the telephone health coach provides patient participants with approximately 4 additional sessions (approximately once/week) over the telephone (with or without video). The telephone health coach will conduct a clinical assessment of motivation to reduce risky opioid use. For patient participants with low motivation to change current opioid use behaviors, the coach will conduct additional MI. As patient participants increase their readiness to change, specific behavioral strategies for relapse prevention will be presented within a cognitive behavioral therapy (CBT) framework.

Study Assessments and Study Duration: The estimated time from initiation of enrollment to completion of data analysis is 44 months. Each site is anticipated to begin enrolling provider participants approximately 1-2 months before initiating the intervention, and to complete patient participant enrollment within approximately 26 months. Data will be collected from patient participants for 12 months following the baseline assessment, and data will be collected from providers for the entire period during which their clinical site is engaged in the intervention (anticipated to be 37 months). Limited patient participant assessments will be completed monthly, while more comprehensive assessments will be completed at baseline and quarterly. Sites will thus complete data collection approximately 12 months after the completion of recruitment. Data analysis is anticipated to be completed 6 months after the end of data collection.

2.1.4 Safety Reporting

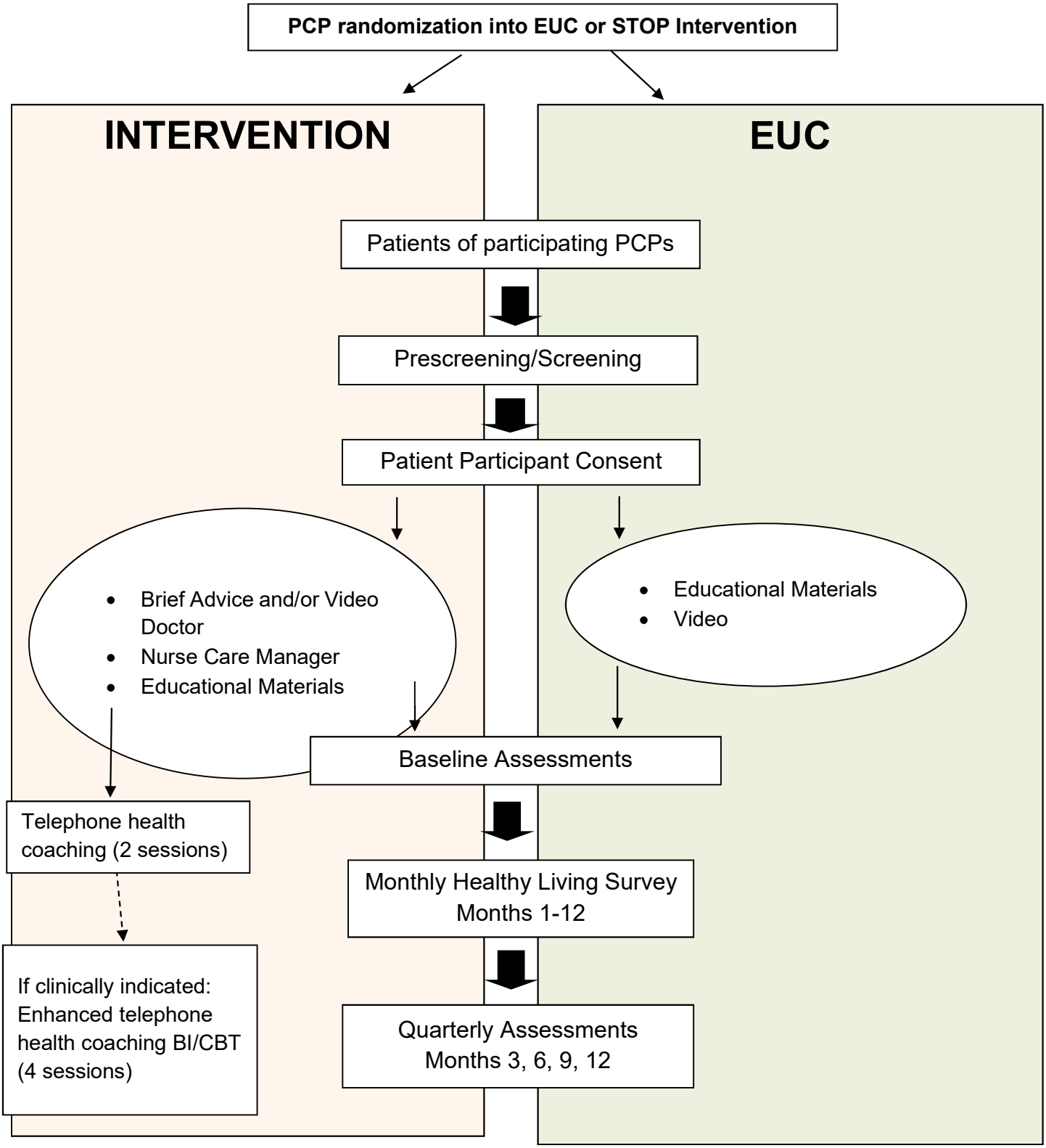
This is a minimal risk study. Therefore, no causally related Adverse Events and Serious Adverse Events are anticipated. Safety reporting will be limited to reporting the following Safety Events: Emergency Department (ED) visits, hospitalizations, overdose events, suicidal ideation, and deaths. These Safety Events will be reported on separate case report forms (CRFs). The sites will follow local standard operating procedures (SOPs) for managing any medical or psychiatric emergencies.

2.1.5 Analyses

Demographic variables and baseline distributions of potential confounding variables will be summarized by treatment group. The primary outcome will be analyzed with a mixed effects generalized linear model with a negative binomial distribution. The model will include PCP random intercepts, fixed clinic effects, a fixed treatment effect, and the baseline value of the response variable. A secondary analysis will expand the model to include multiple time points for the response variable and treatment by time interactions. The mean number of days of use will be visualized by treatment group with 95% confidence intervals. Similar models will explore secondary outcomes.

3.0 STUDY SCHEMA

3.1 Figure 1: Basic Study Schema



3.2 Key Research Site Roles

Each site will designate individuals in the following roles:

- **Site Principal Investigator** (MD; DO; PhD). The Site PI will be responsible for working with the research team to facilitate the conduct of the study at the study site.
- **Site Clinical Champion** (NP; PA; MD; DO; Licensed Behavioral Health Clinician). The Clinical Champion will be a clinic provider who advocates for the study among their colleagues in the study clinic(s), assists with training of participating PCPs, and provides ongoing support to the PCP participants and NCM in carrying out the study interventions.
- **Research Coordinator**. One or more Research Coordinators (RCs) will be assigned to each site to coordinate and help with oversight of study activities.
- **Research Assistant**. One or more research assistants (RAs) will be assigned to each site to conduct recruitment, enrollment, and data collection.
- **Nurse Care Manager** (RN; LPN with RN supervision). A full-time nurse care manager (NCM) will be assigned to each site to carry out the STOP intervention. The position can be split (e.g., 50:50, 40:60) and if the site has a cluster of practices, the NCM can practice at more than 1 site to make the system workable and support the PCPs and patients. If the position is split, both NCMs will do weekly reporting jointly to the technical assistance (TA) team (as if one site) and both will attend the training program.
- **Practice Manager**. The site practice manager will be tasked with assisting research staff with administrative tasks at the sites throughout the course of the study.

Required qualifications of the nurse care manager (NCM):

- Registered Nurse (RN). This can be diploma, BSN or MSN. LPN with RN supervision
- Willingness to enroll 3-5 patients per week.
- Willingness to provide weekly reporting.
- Willingness for regular interactions with the technical assistance team.
- Enthusiasm and energy/leadership ability to lead the team and for working with patients with addiction and pain as well as providers and clinical leaders in the system and community, as relevant.

Preferred qualifications of the NCM: prior behavioral health, pain or addiction experience, and adequate experience to function as the nurse manager of the program.

Telephone health coaches will be centrally located and serve all participating sites. Because the telephone health coaches are not located at a study site, this is not considered a site role. Coaches will be social workers, counselors, or individuals with other professional training that qualifies them to deliver the STOP counseling intervention. Preferred qualifications of telephone health coaches include prior experience working with patients who have subthreshold substance use disorders, and in health coaching and behavior change interventions. A Research

Coordinator will be hired to work with the coaches to manage administrative tasks (e.g., participant scheduling, tracking and retention) and monitor fidelity of health coaching sessions.

4.0 INTRODUCTION

4.1 Background and Significance to the Field

The United States is experiencing an opioid crisis that is driven by a high prevalence of untreated opioid use disorder (OUD). Concurrent to efforts to expand treatment to those currently experiencing an OUD, it is critically important to focus on the *prevention of OUD* among individuals with subthreshold OUD.[1-5] ***Subthreshold OUD*** is opioid use that is not severe enough to meet diagnostic criteria for moderate-severe OUD (that would require medication and more intensive treatment). As defined here, subthreshold OUD includes individuals with problem opioid use or mild OUD symptoms. Individuals with subthreshold OUD engage in ***risky opioid use*** behavior, which includes 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 them. An estimated 12 million Americans have past-year risky opioid use. Another 5 to 8 million individuals are receiving long-term opioid therapy.[6] While a minority (18%) of individuals with illicit or prescription opioid exposure are thought to currently have a moderate-severe OUD, all of them are at high risk for this condition.[5]

Opioid-related research has primarily focused on treatment interventions for individuals who have already developed moderate-severe OUD. Little is currently known about the trajectories of individuals who have subthreshold OUD, including how likely, and within what timeframe, they may develop a more severe OUD or experience opioid-related overdose. OUD prevention efforts have focused on regulatory efforts and published guidelines about prescribing opioid analgesics, particularly by primary care physicians.[7] There is increasing concern that curbing prescribing could be contributing to the opioid crisis when opioid tapers are not accompanied by interventions that actively engage patients and providers in preventing the development or worsening of subthreshold OUD, treat underlying pain, and provide access to effective treatment and overdose prevention strategies for individuals who already have a moderate-severe OUD.[8, 9]

Individuals with subthreshold OUD may experience few symptoms or consequences of their opioid use, and rarely seek addiction services.[5, 10] However, these individuals are frequently encountered in primary care settings where they receive routine medical care and, in some cases, prescription opioids for pain management. Although prevalence of subthreshold OUD in primary care settings varies based on the patient population, a prior 5-site study conducted in the Clinical Trials Network (CTN) (CTN-0059) found prevalence of risky opioid use to be 5-10% among adult primary care patients.[11, 12] Prevalence of subthreshold OUD is much higher (21-29%) among patients who are receiving prescribed opioids.[13]

Definitions

- *Risky opioid use*: 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.
- *Subthreshold OUD*: Risky opioid use, with 0-3 DSM-5 criteria for OUD.

The important role of primary care. Primary care clinics are optimally positioned to identify and provide early intervention for individuals at risk for developing moderate-severe OUD because they are the largest prescribers of opioid analgesics,[14] and they are often the only point of health care contact for individuals whose opioid use is not yet severe enough to require intensive addiction treatment.[15] Yet there has been almost no research on interventions to halt the progression to OUD among primary care patients with risky opioid use.

Prior approaches to reducing risky subthreshold drug use in primary care patients have relied on single-contact brief interventions that are not well integrated with medical care.[16-19] Brief interventions have had mixed results for reducing drug use, and the limited number of trials of brief intervention approaches have not informed care for the large population of patients with subthreshold OUD.[16, 17, 19, 20] The "Quit Using Drugs Intervention Trial" (QUIT) Protocol is one of the only brief interventions for drug use with experimental efficacy among U.S. adults.[21-25] Additionally, one study using similar strategies as drug use brief interventions, but focused on overdose risk rather than consumption alone, showed efficacy for reductions in opioid misuse and overdose risk behavior.[26]

The promise of collaborative care. In contrast to brief intervention approaches, collaborative care interventions have been consistently shown to improve patient outcomes and increase guideline adherence and quality of care for a wide range of diseases, particularly behavioral health conditions. Collaborative care is a team-based approach to managing chronic health conditions in primary care. Collaborative care is grounded in the Chronic Care Model (CCM) for chronic disease management,[27, 28] which seeks to improve patient outcomes through integrative systems changes, including organizational support, clinical information systems, delivery system redesign, decision support, self-management support, and community resources. Collaborative care teams typically consist of a primary care provider (PCP) working with a care manager who maintains a registry to proactively track and manage care delivery, and a health coach who supports patients in disease self-management.[29] Collaborative care approaches have been found effective for the care of a number of chronic diseases, including substance use disorders and depression.[21, 30-33] The "Massachusetts Model" for office-based OUD treatment is a collaborative intervention utilizing a nurse care manager, and is currently being studied in a pragmatic trial conducted within the CTN (PROUD Trial, CTN-0074).

Preliminary studies. STOP is a collaborative care model that combines elements of two evidence-based interventions: (1) *Transforming Opioid Prescribing in Primary Care (TOPCARE*),[33] a provider-facing intervention that relies on a nurse care manager using population management skills to improve opioid prescribing practices for patients receiving opioids for chronic pain; and (2) *Quit Using Drugs Intervention Trial (QUIT)*,[21] a patient-facing intervention utilizing brief advice and motivational counseling to reduce moderate-risk illicit drug use. In STOP, counseling is tailored for patients with subthreshold OUD use by incorporating elements of an emergency department intervention that employed motivational interviewing to reduce risky opioid use and overdose risk.[34]

TOPCARE was tested in a cluster RCT [33] *(Trial Registration ClinicalTrials.gov ID NCT01909076, Protocol ID DA034252, http://www.clinicaltrials.gov (Lasser and Liebschutz, PIs))* that demonstrated improvement in guideline concordant care by PCPs (AOR, 6.0; 95% CI, 3.6-

10.2), and reduced opioid prescribing (AOR, 1.6; 95% CI, 1.3-2.1). The TOPCARE cluster RCT tested whether a bundle of interventions for primary care practices can improve guideline adherence for chronic opioid therapy (COT). PCP participants and their 985 patients at 4 urban primary care practices were randomized to the multicomponent TOPCARE intervention (nurse care manager working with a registry for population management, clinical decision support tools, and academic detailing) or clinical decision support tools alone. The TOPCARE intervention improved guideline concordant care (urine drug screening and controlled substance agreements, 65.9% vs. 37.8%; P < .001; AOR, 6.0; 95% CI, 3.6-10.2), but not early refills (20.7% vs. 20.1%; AOR, 1.1; 0.7-1.8).[33] Intervention patients were more likely than controls to have either a 10% dose reduction or opioid treatment discontinuation (AOR, 1.6; 95% CI, 1.3-2.1; P < .001). In adjusted analyses, intervention patients had a mean (SD) morphine daily dose 6.8 (1.6) milligrams lower than controls (P < .001). TEACH (Targeting Effective Analgesia in Clinics for HIV) *(Trial Registration ClinicalTrials.gov ID NCT02564341, Protocol ID H-33269/DA037768, http://www.clinicaltrials.gov (Liebschutz, PI))* extended the TOPCARE approach to clinical centers for treating HIV-infected patients. Initial results (manuscript under review) reveal a marked improvement in provider guideline adherence and no difference in viral suppression (88% vs. 84%, AOR 1.14 (0.63, 2.04)).

QUIT demonstrated efficacy for reducing moderate-risk drug use in two trials *(Trial Registration ClinicalTrials.gov ID NCT01942876, Protocol ID DESPR DA022445, http://www.clinicaltrials.gov and P30DA027828-02S1/S2 (Gelberg, PI))*.[21, 23] The QUIT multi-component brief intervention approach is the only screening and brief intervention (SBI) for drug use in primary care settings that has exhibited efficacy among U.S. adults.[21, 35, 36] QUIT is a primary care-integrated approach consisting of 1) brief advice (<4 minutes) by the patient's own primary care provider, that leverages the trusted doctor-patient relationship; 2) video doctor: 2 minute video modeled on the provider's brief advice; and 3) health coaches who proactively reach out to patients at approximately 2 and 4 weeks after the primary care visit, to support and enhance substance use reduction behavior change. Coaches use motivational interviewing (MI) and cognitive behavioral therapy (CBT) techniques and focus on quality of life issues and referral to resources. In the initial trial (R01DA022445), QUIT reduced patients' highest scoring drug use by 33% (10.5 to 7 days/mo. at 3-months),[21] and by 44% (11 to 6.5 days/mo.) in the QUIT replication study (P30DA027828-02S1/S2).[23] While not powered for drug-specific analyses, participants in QUIT had fewer days of risky opioid use (11.6 days/mo. in control vs. 3.8 days/mo. in QUIT, at 3-months).[21]

STOP further draws on the Safety and Prevention Outcomes Study (SPOS) *(Trial Registration ClinicalTrials.gov ID NCT01894087, Protocol ID R49CE002099, http://www.clinicaltrials.gov (Bohnert, PI))*, which specifically targeted prescription opioid misuse among patients presenting to the emergency department. The SPOS trial achieved significantly lower levels of risky opioid use and overdose risk behaviors with a 30-minute motivational interviewing intervention, in comparison to brief educational pamphlets.[37] Specifically, the level of opioid misuse, from the Current Opioid Misuse Measure, was reduced by 50% at 6 months in the intervention group, compared to a 39.5% reduction in the comparison group. Similar reductions were seen in overdose risk behavior, which decreased by 40.5% in the intervention group, in comparison to a 14.7% reduction in the comparison group.

Study rationale. Our hypothesis is that the STOP intervention can decrease the quantity and frequency of illicit and nonmedical opioid use among primary care patients with subthreshold OUD, thereby reducing their risk for important health outcomes including the development of moderate-severe OUD and opioid-related overdose. STOP is a collaborative care model consisting of (1) a practice-embedded nurse care manager (NCM) who provides patient education and supports the primary care provider (PCP) in engaging and monitoring patients who have risky opioid use; (2) brief advice delivered to patients by their PCP; and (3) remote coaching of patients by telephone health coaches to motivate and support behavior change.

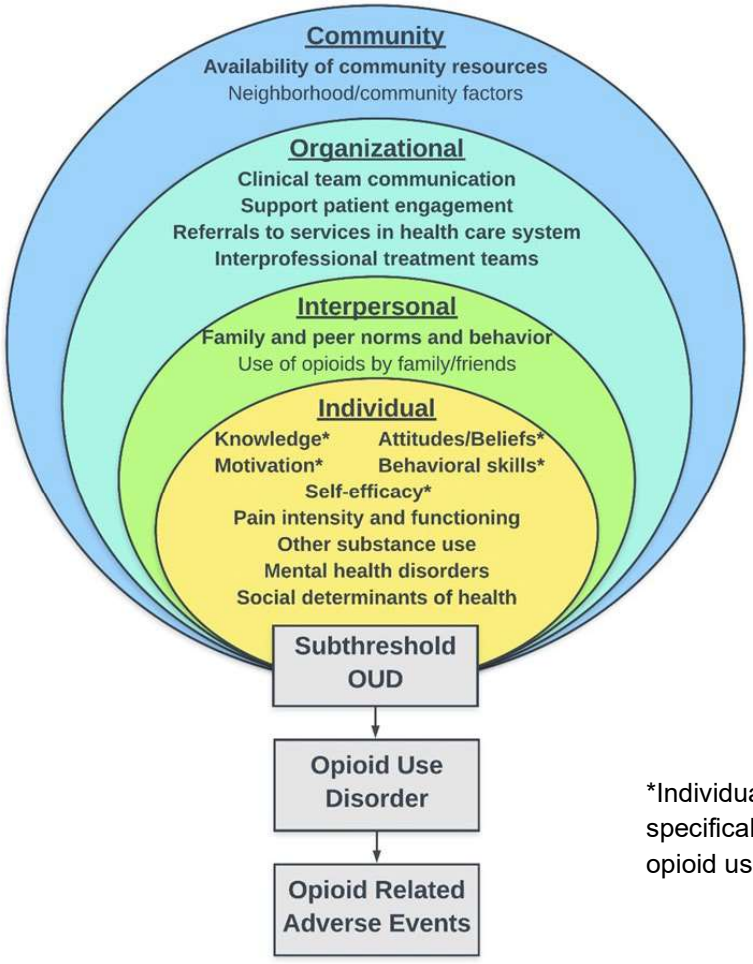
There have been no prior studies examining the efficacy of a collaborative care approach to prevent progression of subthreshold OUD; our study will close this evidence gap. The proposed research directly addresses the dual objectives of the Helping to End Addiction Long-term[SM] (HEAL) initiative to prevent opioid misuse and addiction by intervening with patients who are at high risk for OUD, while enhancing clinical practice for pain management by supporting primary care providers in providing guideline-recommended care to patients receiving opioids for chronic pain. STOP draws upon interventions that independently show promise for addressing subthreshold OUD and integrates them into a single model that can be implemented in regular primary care practice. The study poses minimal risk to participants and has the potential to make a significant contribution to scientific knowledge and medical practice regarding interventions to prevent the highly morbid condition of OUD.

Sustainability. Our proposed study is the culmination of years of work within the CTN to increase the capacity of medical settings to screen for drug use (CTN-0059), integrate screening into the EHR (CTN-0062) and treat OUD in primary care settings (CTN-0074). Although this is an efficacy trial, the STOP intervention is designed for delivery in routine primary care practice and works with patients and their PCPs in the context of existing clinical care. If our trial shows positive results, we will further test STOP in a subsequent multi-site implementation-effectiveness trial that will characterize the cost effectiveness of the intervention and barriers and facilitators of its implementation, which will inform health system and payor decisions about adopting the STOP model more broadly. Attesting to the potential sustainability of the model, in the TOPCARE study, 2 of the 4 participating clinics continued the intervention by funding the nurse care manager role after the study ended. Behavioral health counseling such as the telephone health coaching provided in STOP is increasingly covered by insurance, including by the Screening, Brief Intervention, and Referral to Treatment (SBIRT) billing codes and other models of reimbursement for collaborative care models. At study close, we will facilitate dissemination of the STOP intervention by developing a guide for its implementation into practice.

Conceptual model. The STOP stepped-care intervention integrates patient- and provider-facing interventions and is informed by Wagner's Chronic Care Model,[28] Ewart's Social Action Theory,[38] Social Ecological Frameworks for health promotion,[39] and the opioid use literature. As depicted in Figure 2, subthreshold OUD is influenced by multiple factors, including (1) patient-level individual factors such as knowledge, attitudes, beliefs, motivation, behavioral skills, self-efficacy, pain intensity, physical functioning, social determinants of health (e.g., homelessness, poverty, trauma), mental health disorders, and other substance use; (2) interpersonal factors such as perceived approval of risky opioid use by members of one's social system (e.g., family and peers), and use of opioids by family/friends; (3) organizational factors such as utilization of clinical

information systems to enhance communication and efficiency, decision support for evidence-based care, and use of interprofessional treatment teams; and (4) community factors such as availability of community resources (e.g., housing, food assistance, transportation, health/mental health programs), and other neighborhood/community factors (e.g., drug availability, violence, community poverty rates). While STOP does not directly intervene on all of the factors that impact a patient's risky opioid use, it is designed to address each level of the social ecological framework. Table 1 maps the STOP intervention components to the Social Ecological Framework's 4 levels of influence. Addressing each of these multiple systems of influence enables individuals to reduce their risky opioid use, which can in turn lead to reduction in moderate-severe OUD and opioid-related events, such as overdose and death. Bold items in Figure 2 denote targets of the STOP intervention.

4.2 Figure 2: Social Ecological Framework of Risky Opioid Use



*Individual factors that specifically impact risky opioid use

4.3 Table 1: Mapping of the STOP Intervention Components to the Social Ecological Framework's 4 Levels of Influence

Levels of Influence	STOP Intervention Components
1. Individual	• Brief advice from PCP enhances knowledge about the health risks of opioids and increases motivation to reduce opioid misuse. • Video Doctor reinforces PCP message. • Telephone health coach provides counseling that increases motivation, self-efficacy, and skills to reduce opioid misuse. Stepped-up health coaching sessions utilize MI/CBT to target knowledge, motivation, attitudes, beliefs, and behavioral skills for treatment refractory patients, with specific emphasis on reducing opioid misuse and related risk behaviors, managing chronic pain, and/or preventing substance-related relapse. • Nurse Care Manager provides individualized patient education (including overdose prevention, risk reduction, and self-management skills), assessment, and ongoing monitoring.
2. Interpersonal	• Telephone health coach educates patients on how to talk with peers about opioid use and overdose prevention (including normative behavior); teaches assertive communication with family and peers and ways to maintain their own appropriate opioid use despite others' misuse. • Nurse care manager provides Overdose Education and Naloxone Distribution (OEND), including education to members of patient participants' social networks, and coaches patient participants on communicating their needs effectively to their clinical care team.
3. Organizational (Clinic level)	• Telephone health coach suggests clinic resources and proactively links patients to the Nurse Care Manager for referrals when patients spontaneously raise barriers to reducing opioid misuse (e.g., physical or mental health problems). • Nurse Care Manager evaluates patients for OUD and opioid-related risk behaviors and provides ongoing monitoring that is communicated back to the clinical team; makes referrals to specialty care services patients may require (e.g., mental health or substance use disorder treatment), and links patients who develop OUD to treatment (office-based buprenorphine or referral to opioid treatment program).
4. Community	• Telephone health coach recommends community and/or online resources and proactively links patients to the Nurse Care Manager and/or clinic social workers for assistance when patients spontaneously raise barriers to reducing opioid misuse (e.g., social determinants of health, family/friend factors, community/neighborhood factors). • Nurse Care Manager makes referrals to community services that may benefit patients such as physical activity programs for pain (e.g., yoga, Tai Chi), peer support for substance use (e.g., 12-step and other groups), and addiction treatment resources.

5.0 OBJECTIVES

5.1 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.

5.2 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) 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.

5.3 Exploratory Objectives

The study has the following 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 TOPCARE study, 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.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This cluster randomized trial, conducted in primary care clinics and randomized at the level of the PCP, will compare the STOP intervention to enhanced usual care (EUC) for 12 months. Patients who are eligible and enroll will receive the intervention according to the assignment of their PCP. 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. In the **STOP arm**, PCPs and their enrolled patient participants can receive the STOP intervention, consisting of a NCM, brief advice (delivered by PCP and/or video doctor) about health risks of opioid misuse, and telephone health coaching via phone and/or HIPAA compliant video chat software (2 sessions conducted approximately 2 and 4 weeks after the baseline visit; 4 additional sessions utilizing MI/CBT if clinically indicated). Patient participants in either arm who are found by clinical providers to have developed a moderate-severe OUD (DSM-5 criteria) at any time during the study can be offered medication for OUD (MOUD) and linked to treatment by clinical staff in the EUC arm, and the NCM in the STOP arm, to formal assessment and MOUD treatment.

Patients will be recruited to participate in a "healthy living study" and informed that the purpose of the study is to improve health behaviors including but not limited to changes in substance use. To reduce assessment reactivity, all assessments of substance use will also include questions about other health behaviors (e.g., exercise and diet). This strategy was used in the QUIT trial, which was portrayed to participants as a 'living well study' to promote healthy lifestyles.[21]

Patient participants will be asked to complete an electronic questionnaire ("healthy living survey" that asks about exercise, diet, and drug/alcohol use) once every 30 days, for 12 months, to assess opioid and other substance use. Additionally, more detailed assessments of health status, symptoms, and behaviors will be completed at baseline and quarterly (every 3 months), for 12 months. Urine Drug Screens, collected at baseline and at 6 and 12 months, are used to verify the self-reported drug use data. Assessments of secondary outcome measures, including mental health/suicide risk and SUD symptoms, prescription opioid misuse behaviors, health-related quality of life, sleep and pain, will be completed at baseline and re-administered no more frequently than once every 3 months to decrease participant burden (see Assessment schedule in Section 11). Prescribed medications (opioids, other controlled substances, naloxone) and PCP behaviors (prescribing of opioids, benzodiazepines, and naloxone kits, OUD diagnosis, visit frequency, toxicology testing) are extracted from the electronic health record (EHR) to measure PCP participant outcomes. PCP counseling on opioid use will be obtained via patient self-report.

The outcome measures must use self-reported information about substance use because routinely collected biological measures do not reliably detect intermittent and low-level drug use, which may have extinguished days prior to the collection of the sample. Further, biological measures are unable to provide information about misuse of prescribed medication (i.e., taking the prescribed medication more frequently than instructed). To reduce social desirability bias, all substance use assessments will be self-administered using electronic questionnaires.

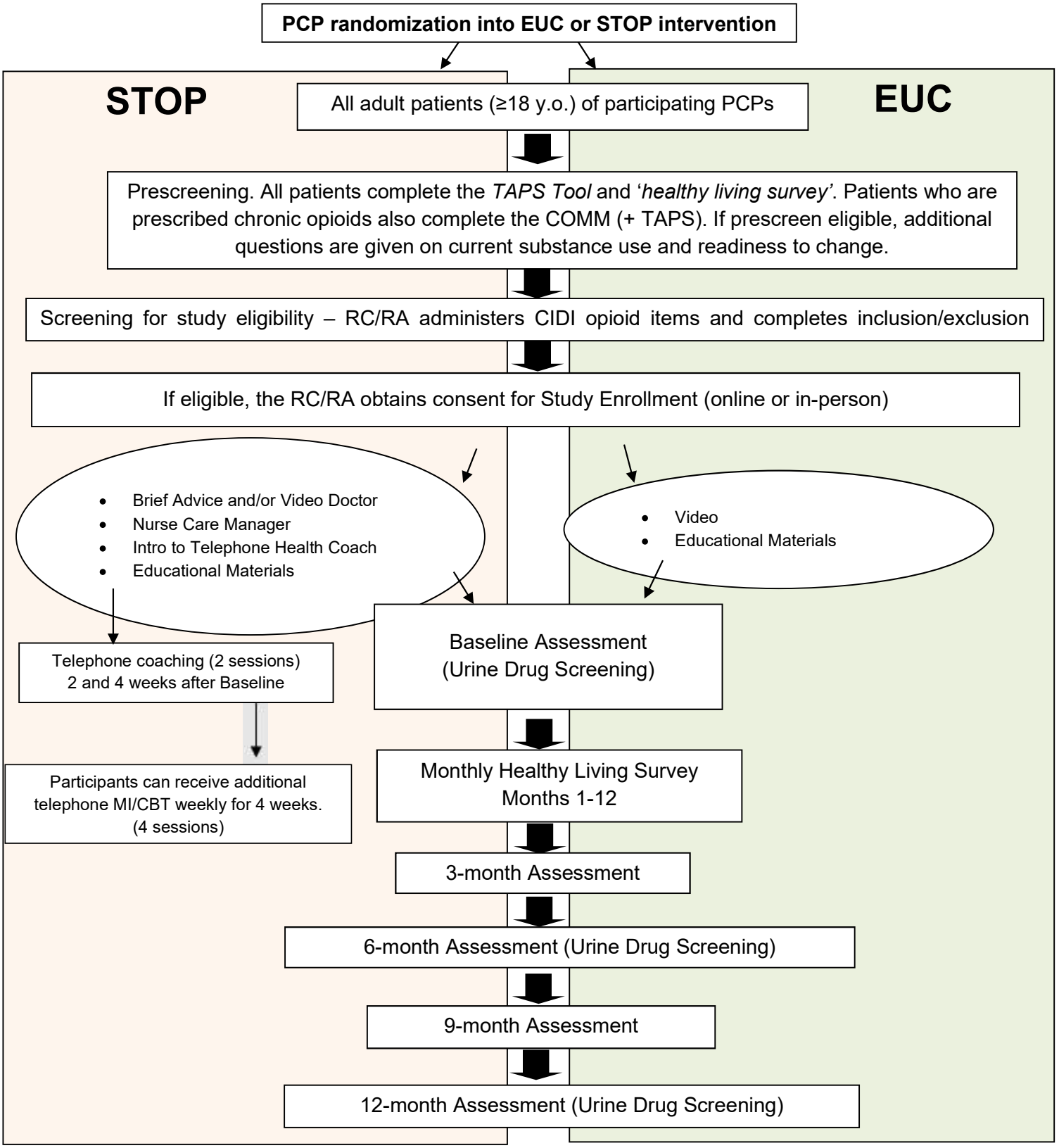
Rationale for the cluster randomized design: The proposed trial will randomize PCPs to either STOP or EUC. Randomizing clusters that are smaller than the practice level introduces potential for contamination that may reduce the observed intervention effect size. However, this strategy was used in the study team's previous trials (TOPCARE and TEACH randomized PCPs within clinics; QUIT randomized patients within clinics) that nonetheless had significant findings.[21, 33] Randomization at the clinic level would reduce contamination, but would require a much larger number of practice sites and would not be feasible with the resources available for this study. Randomizing at the patient level for this collaborative care intervention would increase contamination, as PCPs would find it challenging, and may be unwilling, to follow a study protocol that requires them to deliver different treatments to patients who have the same condition of subthreshold OUD.

6.2 Duration of Study and Visit Schedule

PCPs are enrolled just before the start of patient recruitment (approximately 1-2 months prior to intervention initiation), in order to allow time to randomize PCPs, and participate in training and study preparation activities. PCPs continue participation until the last patient participant completes 12 months of follow-up. Therefore, the total duration of participation for PCPs is up to 37 months [approximately 1 month prior to recruitment; approximately 24 months of recruitment; 12 months following enrollment of the last patient].

Patients deemed eligible will provide consent and enroll. During their baseline visit, they will view the Video Doctor and complete baseline assessments. Intervention patient participants may receive brief advice from their PCP either during a PCP visit that is integrated with the baseline visit, or within 10 business days after the baseline visit. Intervention patient participants may also meet with the Nurse Care Manager. The target dates for the first and second telephone health coaching sessions will be within approximately 2 weeks and 4 weeks of the baseline visit, respectively. If initial attempts to conduct either of these coaching sessions are unsuccessful, attempts to complete these calls will continue for approximately 3 weeks after the intended date of the session. Patient participants complete an electronic self-administered "healthy living survey" (including substance use and other health behavior) once every 30 days, for 12 months. Quarterly follow-up assessments are conducted online and by phone at 3, 6, 9, and 12 months. Therefore, the total duration of patient participation in the study is 12 months.

6.3 Figure 3: Study Design



7.0 OUTCOME MEASURES

7.1 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, and the COMM.[40, 41] Collecting data on self-reported days of use in the past 30 days is aligned with timeline follow-back methodology, and was used in the QUIT trial.[21] 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 Secondary Outcome Measure(s)

7.2.1 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. H1.2. 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, 9, and 12 months.
        iii. In the past 180 days, assessed at 12 months.
    b. 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.
    c. 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.

d. H2.3. Days of stimulant 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.
e. H2.4. Days of marijuana use:
    i. In the past 30 days, measured at baseline and monthly.
    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.
f. H2.5. Days of other drug use (not including opioids, benzodiazepines, stimulants, and marijuana).
    i. In the past 30 days, assessed at 3, 6, 9, and 12 months
g. 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.
h. H2.7. Prescription opioid misuse behaviors, among participants receiving prescribed opioids:
    i. Days of taking prescribed opioids for symptoms other than for pain, measured at baseline and monthly for 12 months.
    ii. Days of taking pain medication belonging to someone else, measured at baseline and monthly for 12 months.
    iii. COMM score, assessed at screening and at 6 and 12 months.

Urine Drug Screens are used to verify self-reported drug use. Urine Drug Screens are conducted 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)
    c. Exploratory Objective 3. Overdose death is expected to be a rare event in this population 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. 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 are measured using patient 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.

7.2.2 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 will be for the period beginning 12 months prior to start of the intervention, through 12 months after the last patient participant is enrolled.

a. 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.
b. 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

c. H3.3. Prescriptions for naloxone: number of patient participants receiving at least 1 prescription

d. H3.4. Urine Drug Screens: number ordered and completed for each patient participant

e. H3.4. Diagnosis of OUD: number of patient participants receiving a new diagnosis of OUD during the study period.

f. H3.4. Primary care visits: number of scheduled visits per patient participant

7.3 Other Outcome Measures

The following additional measures will be collected to assess exploratory outcomes, characterize domains from our conceptual model, 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).

a. Demographic characteristics and insurance status.

b. 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.

c. Social support will be assessed using the PROMIS instrumental and emotional health short forms.

d. Patient engagement in primary care (Exploratory Objective 1): Number and frequency of kept appointments and missed appointments for primary care visits.

e. 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.

f. PCP knowledge and attitudes regarding substance use, subthreshold OUD, and opioid management, assessed at baseline and at the end of the intervention period.

g. 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, days of 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.

h. Patient participant-completed assessments will measure 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.

7.4 Study Timeline

Due to delays encountered during the COVID-19 pandemic, after receiving CCTN approval of the protocol, approximately 16 months of trial preparation activities will elapse prior to commencing PCP enrollment in the main study (see Estimated Project Timeline, Table 2). Trial preparation will include obtaining Institutional Review Board (IRB) approval, developing the data collection systems, conducting a pilot study (described below), developing the Manual of Procedures (MOP), conducting all staff training, and endorsing sites. Recruitment of patient participants was originally expected to take approximately 12 months; however, due to the recruitment challenges posed by the COVID-19 pandemic, up to 12 additional months of recruitment at selected sites may be added to the original study timeline to provide sites additional time for recruitment. Follow-up assessments will be conducted for approximately 12 months after completion of the recruitment phase. Two months will be allowed for database lock after the last patient's final visit; therefore, database lock is projected to occur at approximately month 67.

7.4.1 Pilot Study

A pilot study will be conducted at one study site and is further described in Section 10.5. The purpose of the pilot is to refine study procedures for recruitment, enrollment, and baseline assessments, and it will primarily focus on evaluating the feasibility and acceptability of screening, enrollment, and assessment procedures. There is no randomization of PCPs for the pilot study. The pilot is expected to begin approximately 4 months following CCTN approval of the protocol, and to be completed in approximately 15 weeks. In addition to the formal pilot study, we will conduct telephone health coaching only with up to 10 patients at the pilot site in order to inform the training of health coaches for the main study.

7.4.2 Table 2: Estimated Project Timeline

	Study Month																				
	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45	46-48	49-51	52-54	55-57	58-60	61-63	64-67
Protocol development																						
IRB approval																						
Sites selected																						
Database and eCRF development for pilot																						
Hire and train Pilot site research team																						
Pilot site initiation activities																						
Pilot																						
Database and eCRF modifications for main study																						
Hire and train remaining sites' research teams																						
Site initiation activities for full study																						
PCP participant enrollment																						

	Study Month																				
	1-3	**4-6**	**7-9**	**10-12**	**13-15**	**16-18**	**19-21**	**22-24**	**25-27**	**28-30**	**31-33**	**34-36**	**37-39**	**40-42**	**43-45**	**46-48**	**49-51**	**52-54**	**55-57**	**58-60**	**61-63**	**64-67**
Patient participant enrollment																						
Intervention																						
Patient participant follow up																						
Data cleaning and data lock																						

8.0 STUDY POPULATION

The sample consists of PCPs and their patients. We anticipate that approximately 100 PCPs and approximately 300 patient participants will participate. The unit of randomization is the PCP, and randomization will be stratified by site. The study population includes patients who are receiving prescribed opioids for pain and those who are using illicit opioids; there are no predetermined targets for the number of patients enrolled from each of these groups. Each site will continue enrolling patient participants until approximately 300 patient participants have been enrolled across all sites. PCPs are only offered study participation if they plan to remain in the practice until the study is completed.

8.1 Inclusion and Exclusion Criteria

Participants include both PCPs and their patients. Individuals must meet all of 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.

8.1.1 PCP Inclusion and Exclusion Criteria

PCP 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.

PCP 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.

8.1.2 Patient Participant Inclusion and Exclusion Criteria

Patient Participant 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[a].
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.

[a.] 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?

Patient Participant 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 age 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.

8.1.2.1 Patient Participant Inclusion and Exclusion Criteria for Additional Pilot Telephone Health Coaching for Training Purposes Only

Patient Participant Inclusion Criteria

1. Received prescription opioids in the past six months and/or are known to have risky opioid use or OUD
2. Age 18 years or older at time of screening
3. Proficient in spoken and written English, as determined by patient self-report and research staff evaluation
4. Access to phone, per patient self-report
5. Willing and able to provide informed consent

Patient Participant Exclusion Criteria

1. 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.

Patients will not need to meet the other inclusion or exclusion criteria listed above in Section 8.1.2 in order to qualify for the additional pilot health coaching sessions.

8.2 Strategies for Recruitment and Retention

8.2.1 Recruitment of PCPs

The Site PI and/or Clinical Champions will work with clinic staff to identify potentially eligible PCPs. EHR data may be used to produce a list, organized by PCP, of patients who have been on chronic opioid treatment. All potentially eligible PCPs will be approached by the Site PI or other study affiliated personnel to assess their interest in study participation. All interested and potentially eligible PCPs will be invited to a meeting at the practice site, which may include a meal (breakfast or lunch) to increase the likelihood of attendance.

Study affiliated personnel will attend the meeting to describe the study in detail, answer questions, and ascertain interest in the study. PCPs who are interested in participating will complete the Screening survey to make a final determination of eligibility for enrollment. If eligible, PCPs will continue with consent, (see Informed Consent Procedures, Section 10.2.2) and the Baseline survey. PCPs who are unable to attend the group meeting will meet individually with study affiliated personnel to replicate the same process as in the group. PCPs will be enrolled in the study just before the start of the patient recruitment and/or after the intervention begins to allow for PCPs who are eligible after the first group of PCPs are enrolled. Sites will be able to continue enrolling eligible PCPs until approximately 6 months before the end of patient recruitment.

8.2.2 Recruitment of Patients

Recruitment procedures are further detailed in Section 10. Research staff will attempt to contact all adult patients of participating PCPs. Recruitment materials will direct participants to an online site where they may complete an initial eligibility prescreening survey to assess minimum eligibility

criteria. Patients will be provided information on how to access the online site, which may be accessed directly or through electronic links provided in correspondence and/or a study specific website. Patients receiving COT as well as patients with conditions such as alcohol use, tobacco use and benzodiazepine use will be prioritized for prescreening throughout the study. These patients will be identified through review of EHR data and/or by clinical staff.

Both males and females will be recruited. Based on our prior studies in primary care, we anticipate that at least one-third of patient participants will be female, and that their race and ethnicity will reflect the demographic characteristics of English-speaking patients from the participating clinics. This study does not to seek to enroll prisoners. If a participant later meets the Office for Human Research Protections (OHRP) definition of a prisoner (as stated in 46 Subpart C) after baseline enrollment, sites may keep such individuals in the study and collect follow-up data only if they have IRB and OHRP approval to do so. Data may be collected either in person or by electronic means, provided that data collection follows the procedures approved by OHRP and the local IRB.

Anticipated number of patients screened: The study will enroll approximately 100 PCPs from a total of 5 sites. We estimate, however, that 30-40% of the enrolled PCPs will have no participating patients (because we will not identify patients who meet the eligibility criteria in their panel), leaving approximately 60 PCPs who will have patients that will enroll into the study. Each of these PCPs is expected to have approximately 5 patient participants participating in the study (see Table 3).

We expect that approximately 15-20% of the sample will be comprised of patient participants who are receiving prescribed opioids. Based on urine toxicology data collected in the TOPCARE study, we anticipate that approximately 30% of patients who are receiving prescribed opioids will have unhealthy opioid use. Participating PCPs are expected, on average, to have approximately 8 long-term opioid patients, and so we anticipate that 1-2 of these patients will be eligible. PCPs with more than 8 patients on long-term opioids will contribute more from this group (risky opioid use of prescribed opioids). Patients with illicit/non-prescribed opioid use are anticipated to constitute the remainder of the sample. In our prior studies, between 3.9% and 6.6% of adult primary care patients screened positive for illicit opioid use.[12, 21]

In the general patient population (not limited to those patients on prescribed long-term opioids), we anticipate that PCPs will have approximately 1100 patients in total (this panel size is slightly lower than the national average (1200-1900/PCP), to accommodate some less than full-time providers [42]). Approximately 42% of patients are expected to be screened for the study. Of the approximately 460 general patients who we anticipate being able to screen, we conservatively estimate that 1% (total of 5 patients) will be eligible. We expect to enroll approximately 75% of those deemed eligible (a conservative estimate, given that in our prior trials the rate of enrollment of eligible patients was 81-84%[21, 37]). Thus, in total, each PCP is anticipated to have approximately 1 patient on prescribed opioids, and 4 patients with risky use of illicit/non-prescribed opioids, participating in the study.

8.2.3 Table 3: Anticipated Patient Participant Screening and Enrollment for each of the 60 PCPs Having Patients in the Study

	PCP Panel Size ~ 1100 patients	
	Prescribed Opioids (N=8)	General Patient Population (N=1100)
Number Screened (42% of panel)	5	460
Percent Eligible	30%	1%
Number Eligible	1-2	5
Agree to Enroll (75% of eligible)	1	4
Anticipated Enrollees	1 + 4 = 5	

Procedures for study retention: Patient participants will provide detailed contact information in a locator form at the baseline visit, which will be updated by research staff whenever the information changes and reviewed and updated at each quarterly assessment. Patient participants will be informed that if their contact information changes between study visits, they will receive an incentive if they contact the research team and provide the updated information. Research staff will attempt to contact patient participants approximately once/month during the study period. Patient participants will receive electronic notifications and reminders to complete questionnaires. In addition, research staff may contact patient participants by phone, text, email, letter, and/or in person to ask them to complete assessments. The dates of follow-up assessments that are to be conducted by phone will be scheduled at the time of the current study visit.

To lower potential barriers to participating in study visits, assessments may be completed remotely (electronically by text/online and by phone). Because of the expected difficulty of maintaining high follow-up rates in the study population, adequate compensation for time and inconvenience is critical. Monetary incentives will be provided for each post-visit study activity, including for completing the baseline and quarterly assessments, monthly questionnaires, and urine drug screens. During the first 6 months of study participation, patient participants will also receive a bonus for completing consecutive assessments, paid monthly. For example, if a patient participant has completed their Month 1 assessment, and they go on to complete their Month 2 assessment, they will receive a bonus payment in addition to the standard incentive for completing the Month 2 assessment. If they do not complete their Month 1 assessment, then in Month 2 they are not eligible for the bonus payment. Patient participants who miss a monthly assessment will be notified that they can still receive the incentive if they complete the assessment in the subsequent month. Incentives will be paid in the form of either a debit card or gift card. The amount of each incentive payment will be specified on the informed consent documents and reviewed with patients as part of the consent process.

9.0 SITE SELECTION

9.1 Number of Sites

Approximately 5 sites will be selected to participate in the study. Each site will have approximately 5 primary care clinics serving adult patients. For sites with more than 1 participating clinic, the clinics must share the same administrative infrastructure and be geographically proximal (approximately 1 hour or less on average to travel between sites).

A site survey designed specifically for this study, followed by interviews and site visits, will be used to arrive at the final site selection. Sites will be selected based on the capacity and patient volume to support enrollment of the target population. Research experience and successful participation in prior studies is desirable as it provides evidence of the feasibility of study implementation. Participating clinics must be primary care clinics serving adult patients. Each site is expected to have approximately 7-30 eligible primary care providers who will meet eligibility criteria and agree to participate. Across 5 sites, each site will have approximately 16 PCPs. Sites need to have capacity to provide referrals to opioid treatment program(s), and have a fully functional electronic health record system, including clinical notes, laboratory tests, and prescribed medications. Sites will need to provide a clinical champion to facilitate the implementation of the intervention and conduct of the research and provide space for the NCM. To ensure that there is sufficient contrast between the STOP and EUC conditions, the participating clinics should not be currently using a collaborative care model dedicated to managing primary care patients receiving opioid prescriptions.

Additional characteristics that will make sites desirable for this study are as follows:

- Located in an area with higher than average prevalence of opioid use, to ensure a sufficient pool of eligible patients for recruitment. We use rates of opioid overdose deaths and opioid prescribing as markers of opioid prevalence.
- Capacity to provide office-based buprenorphine treatment.
- Able to provide space in or near the clinic for recruitment, consent, and research activities.
- A diverse, representative sample of participants is desirable to enhance the external validity of the findings. However, it will only be feasible to conduct assessments and the intervention in English.

9.1.1 Rationale for Site Selection

The selection of study sites is based on the applicability of the expected findings to patients in the community, as well as cost and feasibility. Study participants will be recruited from primary care sites. We will seek to select sites that serve a diverse group of patients with a mix of race/ethnicity and socio-economic status. Primary care sites will be selected based on the site characteristics delineated above.

10.0 STUDY PROCEDURES

10.1 Screening and Informed Consent Procedures

10.1.1 Prescreening

Patients aged 18 or older of participating PCPs will be asked to complete prescreening questionnaires. The prescreening questionnaire is electronic and self-administered. The following modes of contacting patients for prescreening and screening may be used: 1) messages through the clinic's EMR/patient portal, email, text message, fliers and posters, and/or mailed letters; 2) research staff outreach in-person or by telephone; 3) clinical staff referring patients to the research staff. Patients can be recruited before, during or after any type of clinic visit, and/or without an upcoming appointment. Details of the RC/RA interaction with the patient participant will be specified in the Manual of Procedures (MOP). Figure 4 describes the prescreening and enrollment process.

Before initiating the prescreening questionnaire, patients will view written information online that briefly describes the study and informs them that participation is voluntary. There is no incentive provided for prescreening. Individuals will be informed that if they are eligible and choose to enroll in the study, they will receive incentives for participation.

Prescreening is anonymous and confidential; therefore, a waiver of consent will be obtained from the IRB. Patients with prescreening results indicating that they may be eligible for the study will be guided to complete the Healthy Living Monthly and Readiness to Change assessments, and, if still eligible, provide contact information and construct a unique identifier that can be used to retrieve their prescreening responses. Patients who are eligible after these initial surveys will be contacted by the RC/RA for further screening (CIDI, and eligibility review) and consent. A modest incentive may be offered to patients who prescreen eligible if the RC/RA is able to reach them for screening, in order to increase the chance that screening will be completed. For patients who have an upcoming PCP appointment that will be integrated with the baseline visit, the RC/RA should attempt to screen and consent them prior to this appointment. If a patient is participating in a telehealth visit with their PCP, the RC/RA will attempt to contact the patient prior to their telehealth visit to determine study eligibility.

10.1.2 Methods for Remote Screening and Enrollment

1. Individuals who are prescreened online and provide contact information will be contacted by a RC/RA within approximately one week of completing prescreening. At this contact, the RC/RA will explain the next steps for screening and enrollment. At this time, the RC/RA will also inquire about whether the patient has an upcoming scheduled appointment with their participating PCP. Refusals and inability to participate will be recorded by the RC/RA in the Participant Tracking Log.
    a. The patient agrees to continue screening over the phone:
        i. If the patient does not have an upcoming PCP appointment, the RC/RA will conduct screening, and if eligible, will request permission to obtain electronic consent from the participant for participation. After enrollment,

the RC/RA can continue with baseline activities, including the video doctor and RC/RA-administered assessments, as time allows. The PCP will be asked to follow-up with the patient participant within 10 business days after the baseline to deliver the brief advice. All baseline activities should be completed as soon as possible, preferably within 30 days of prescreening.

ii. If the patient does have an upcoming PCP appointment in the next 30 days, the RC/RA will conduct screening, and if eligible, will request permission to obtain electronic consent from the participant for participation prior to their PCP appointment. The RC/RA should wait to enroll the participant and conduct the rest of the baseline activities until after the PCP appointment. If the patient misses or reschedules their PCP appointment, then the RC/RA can complete baseline activities and ask the PCP to follow-up to provide brief advice within 10 business days of the baseline visit.

b. The patient does not want to continue with remote screening and provide consent:

i. If the patient does not have an upcoming PCP appointment in the next 30 days, the RC/RA will schedule another time within the 30 day screening window (either in-person or remote) to continue screening and if eligible, complete enrollment procedures. Once enrolled, the RC/RA can continue with the baseline activities (video doctor and RC/RA-administered assessments). The PCP will be asked to follow-up with the patient participant within 10 business days after the baseline to deliver the brief advice.

ii. If the patient does have an upcoming PCP appointment in the next 30 days, the patient will be instructed to arrive to their appointment 30 minutes early to conduct screening, and if eligible, provide consent for participation before seeing their provider. The RC/RA should wait to enroll the participant and conduct the rest of the baseline activities until after the PCP appointment. If the patient misses or reschedules their PCP appointment, then the RC/RA can complete baseline activities and ask the PCP to follow-up to provide brief advice within 10 business days of the baseline visit.

c. Patients who prescreen eligible, but screen ineligible are not eligible to participate in the study. If they screen ineligible due to moderate or severe OUD or receipt of MOUD, the RC/RA will provide the patient with overdose prevention information (including printed and/or electronic materials); a list of community and/or clinic resources for OUD treatment; contact information for a social worker or behavioral health staff in the patients clinic, if available; an ineligible patient letter patients can provide to their PCP (for moderate to severe OUD patients only); and will suggest that patients speak with their primary care provider.

2. Individuals who prescreen eligible and contact the RC/RA themselves will follow the same process outlined above for a) remote screening and consent, b) in-clinic screening and consent, or c) ineligible status.
3. If a prescreened eligible patient has an upcoming PCP appointment, but is not reached by the RC/RA prior to their PCP appointment, the patient can complete screening and consent any time within 30 days of prescreening.
4. Individuals who prescreen eligible but are not screened by the RC/RA within 30 days, will need to begin the process for determining eligibility again after the 30 day window. Please refer to the MOP for additional details and Section 10.2.2 for consent procedures.

10.1.3 Methods for In-Person Prescreening, Screening and Enrollment

1. RC/RAs will approach patients in the clinic and follow the RC/RA in-clinic recruitment script. They will then offer patients the prescreening questionnaire on a tablet if they have not already completed it (in the past 30 days). Assistance may be provided by the RC/RA if this is requested by the patient. If the patient is not able or willing to use the tablet, paper CRFs will be available. All paper assessments will be stored as source documentation. Patients with prescreening results indicating that they may be eligible for participation in the study will be informed of this by the RA, who will meet with them in a private area to conduct screening, and if eligible obtain consent. Enrollment procedures and baseline activities can continue after the PCP appointment, as needed, or preferably within 30 days of prescreening.
2. If an individual screens ineligible due to moderate or severe OUD or receipt of MOUD the RC/RA will provide the patient with overdose prevention information (including printed and/or electronic materials); a list of community and/or clinic resources for OUD treatment; contact information for a social worker or behavioral health staff in the patients clinic, if available; an ineligible patient letter patients can provide to their PCP (for moderate to severe OUD patients only); and will suggest that patients speak with their primary care provider.

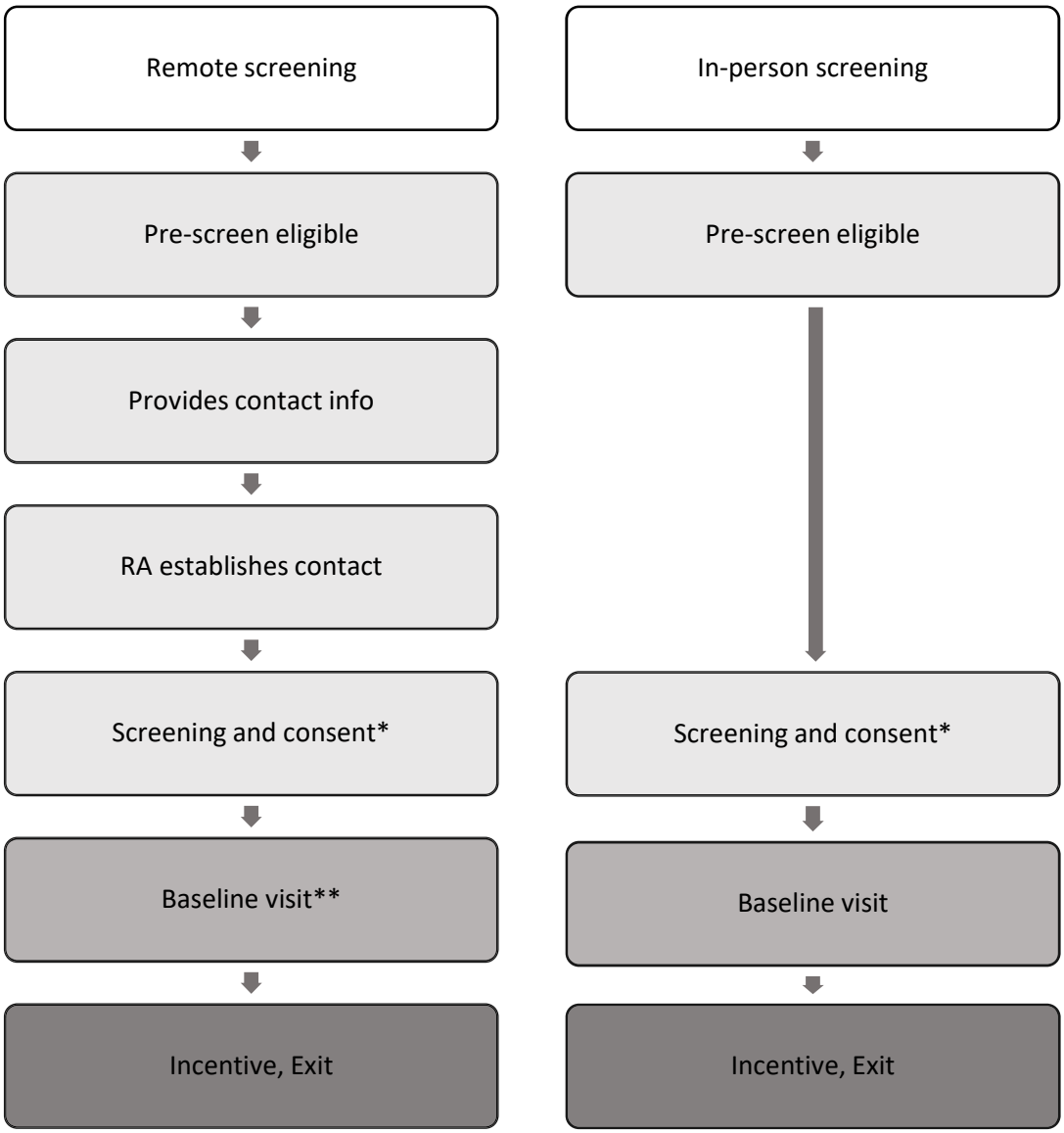
10.1.4 Methods for Telehealth Prescreening, Screening and Enrollment

1. If a patient completes the prescreener prior to a telehealth visit, the RC/RA will attempt to reach out to them prior to the telehealth visit and conduct screening and consent. If eligible and the patient enrolls in the study, the RC/RA will provide the patient's PCP with the patient's screening results as indicated in the local SOP.
2. If a patient does not complete the prescreener prior to their telehealth visit, the RC/RA may call the patient prior to their scheduled telehealth visit to inquire about their interest in participating. If a patient is interested, the RC/RA will text or email the prescreener survey to the patient, and either stay on the phone with the patient as they complete it or have the patient call them back when finished.
    a. If the patient is ineligible, the RC/RA will thank them for their time using an IRB approved script.

b. If the patient's prescreening results indicate that they may be eligible, the RC/RA will conduct screening, and if eligible obtain consent.

c. If an individual screens ineligible due to moderate or severe OUD or receipt of MOUD, the RC/RA will provide the patient with overdose prevention information (including printed and/or electronic materials); a list of community and/or clinic resources for OUD treatment; contact information for a social worker or behavioral health staff in the patients clinic, if available; an ineligible patient letter patients can provide to their PCP (for moderate to severe OUD patients only); and will suggest that patients speak with their primary care provider.

Figure 4: Patient Prescreening and Enrollment



*If a patient has a PCP appointment and there is not enough time to read the full study consent before their PCP visit, the RC/RA may obtain verbal consent instead using a brief IRB approved consent script. In such cases, patients will read and sign the full consent after their PCP visit.

**Research staff are encouraged to complete the baseline visit as soon as possible after enrollment, preferably within 30 days of prescreening.

10.2 Prescreening and Assessment of Study Eligibility

The prescreener will include tools to assess study eligibility and a general health behavior questionnaire called the "healthy living survey," which includes questions about general health behavior (exercise, diet) as well as substance use. The purpose of including questions that are not about substance use is to partially mask the topic of the study for potential participants, and those questions will not be used to determine eligibility. For all patients, the prescreening tool includes the Tobacco, Alcohol, Prescription medication, and other Substance Screening Tool (TAPS Tool). The TAPS Tool is a brief screening and assessment instrument that was developed and validated in CTN-0059. For patients who have received a prescription for opioid medication in the 6 months prior to date of prescreening, based on patient self-report, the prescreening tool will additionally include the Current Opioid Misuse Measure (COMM).[43, 44] The study will utilize three items from the COMM, items 9, 14, and 15, to determine eligibility. Prior to each of these three questions, there will be an instruction line informing patients that the questions are only asking about their opioid pain medications.

Prescreening is considered positive if the patient has a TAPS score $\geq$1 for heroin and/or prescription opioids, and/or a positive response to COMM items 9, 14, or 15. The TAPS Tool requires at least 1 day of unhealthy opioid use in the past 90 days to achieve a score of $\geq$1, and the COMM requires opioid misuse behaviors to have occurred in the past 30 days.

Individuals with a positive prescreen for risky opioid use, but do not meet the other eligibility criteria, will receive from the RC/RA additional information about overdose prevention and OUD treatment. This may include specific information about linkage to clinic resources that can assist them with initiating MOUD treatment, as detailed in the MOP and site specific standard operating procedures (SOPs).

Prescreening forms will not include identifying information for those who are ineligible; however, if a patient prescreens eligible, they will be asked to create a unique ID (referred to as 'study ID' in patient participant facing materials) and leave their contact information for the RC/RA to reach them. Individuals who are interested and screen eligible will undergo the informed consent process described below. Patients who do not qualify for the study will receive no further intervention, but the anonymous prescreening data will be kept to allow comparison to those who do qualify.

Because the prescreener is anonymous, the research staff will not know who has already completed it. Therefore, patients may receive an invitation to take the prescreener more than once, but they will be instructed to not complete it more than once in a 30 day period.

10.2.1 Screening for Eligibility

Patients who are interested in enrolling and have prescreening results suggesting study eligibility will meet with research staff by phone or in-person in a private area of the clinic, to complete the information needed for assessment of eligibility. Research staff will administer the CIDI opioid items and complete a checklist of inclusion/exclusion criteria to make a final determination of eligibility for enrollment. If the screener assesses that the patient is eligible, they can move onto informed consent and enrollment.

Patients who prescreen eligible but screen ineligible, may receive another invitation to reinitiate the prescreening and screening process, but should be encouraged not to take the prescreener more than once every 30 days.

10.2.2 Informed Consent Procedures

The study includes PCPs and patients as participants. All participants will give informed consent for study participation.

Informed Consent for PCP Participants

PCPs will be recruited and enrolled prior to the enrollment of patients (see recruitment of PCPs, Section 8.2.1). 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. The study investigators will not inform personnel outside of the study whether providers have chosen to participate and if so, to which group they have been randomized. PCPs will be allowed to inform others about their participation, if they choose to.

Informed Consent for Patient Participants

Patients are not informed of the PCP's study intervention assignment prior to enrollment. They are informed that their PCP is participating in a healthy living study and that they will receive either the STOP intervention elements (including nurse care manager, telephone health coaching) or EUC. Screening, enrollment, and consent can be completed any time within 30 days of prescreening eligible.

Informed consent will be obtained from patients before their baseline visit using an IRB-approved informed consent form on paper and/or electronically. A brief verbal consent will be available as a backup for patients enrolling before a PCP appointment who do not have time to read and discuss the full consent form before their PCP appointment. In such cases, patients will be read an IRB-approved verbal consent script and will be asked to provide verbal consent for participation in all study activities that take place during the PCP appointment (PCP brief advice and/or video doctor). Following the PCP appointment, and prior to completion of the baseline assessments, these individuals will sign the full consent which covers participation in all study activities. Consent forms will be in compliance with the pertinent sections of 45 CFR 46. Because of the low risks associated with the study, the consent form will be as brief as possible within the constraints of adequate human subjects protections. The consent form will include a description of all significant elements of the study. We also will obtain permission to audio record some telephone health coaching sessions for intervention fidelity monitoring purposes. Given the multi-site nature of the trial, it is possible that ancillary studies will be proposed before or after the study begins recruitment. For this reason, during the informed consent process, we also will seek permission to contact the participant in the future about other study opportunities.

Research staff will be available to answer questions about the consent form while patients are reviewing the document. Patients will read the informed consent document (or have it read to them, if this is preferred) and express verbally their understanding of the key elements of the study (e.g., description of the treatment condition, duration of follow-up). They then indicate their

consent to participate in the study by signing (either written or electronic) the informed consent form.

10.2.3 HIPAA Authorization and Medical Record Release Forms

Health records may be used preparatory to research, to identify individuals who are potentially eligible for study participation and to determine the timing of a potential participant's next PCP visit. For patient participants, a HIPAA disclosure will allow the study to access protected health information in the patient's medical record. Health records will be used for the collection of some study outcome measures (e.g., prescriptions and care received in the study clinic). This study will have a single IRB. Sites will be responsible for communicating with their local IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance.

10.3 Randomization

After providing written/electronic informed consent, PCPs will be randomly assigned in a 1:1 ratio to (1) STOP Intervention, or (2) Enhanced Usual Care (EUC). 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). Randomization will be stratified by site and will occur at each site prior to the intervention start date. The randomization procedure will be conducted through a process set up by the CTN Data and Statistics Center (DSC), and the randomization sequence will be unknown to staff. The DSC statistician will review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan.

Patient participants receive the intervention to which their PCP is assigned. While randomizing at the PCP level introduces the possibility of contamination that has the potential to reduce the observed intervention effect size, this strategy is similar to our study team's previous studies (TOPCARE randomized PCPs, QUIT randomized patients) that had significant findings. Contamination could arise if patient participants change PCPs or make appointments with PCPs in the opposite treatment arm, or if PCPs drop out of the study (which would force a change in PCP upon their patients). These instances of contamination will be recorded, and the contamination data may be summarized with the study findings.

After the baseline PCP encounter, differences in clinical care received by the patient participant are driven primarily by the NCM, who interacts directly with the patient participant and provides advice to the PCP about the patient participant's management. To guard against contamination, NCMs will be instructed to communicate only with PCP and patient participants who are in the intervention condition. To facilitate this, NCMs will have a list of patients who are enrolled in the study and have a PCP assigned to the intervention condition. In the relatively unlikely event that a patient participant in the EUC group has a visit with STOP intervention PCP after the baseline visit (for example, if the intervention PCP is covering for the patient's regular provider), the NCM will not interact with the patient participant.

10.4 Baseline Assessment

PCP participants complete self-administered (SA) questionnaires at baseline. These are completed as paper or electronic questionnaires prior to the beginning of the intervention period.

For patient participants, the baseline assessments are broken up into two parts: 1) a few baseline assessments are administered as part of the prescreener survey, for participants who prescreen eligible and 2) the remaining baseline assessments are administered during the baseline visit. The specific assessments are detailed in Table 6. Details regarding all assessments are in Section 11. Assessments are electronically self-administered or RA-administered as indicated; those that are RA-administered will be given in a private area of the clinic or may be done by phone.

Assessments that are most sensitive to change based on the brief advice delivered by the video doctor and/or PCP are included at the end of the prescreener survey for patients who prescreen eligible. So as not to interfere with time-pressured clinical workflows, patient participants can complete assessments that are less sensitive to change after the baseline visit. These assessments may be completed up to three weeks after the baseline visit, but most often will be done on the same day or within one week. The assessments administered after the baseline visit include questionnaires on demographics, mental health, sleep, social supports and health-related quality of life, and health services utilization. If possible, a urine sample will also be collected (either in-person or remotely) at the baseline visit.

10.5 Pilot Study

A pilot study will be conducted in 1 study site prior to initiation of the trial. The pilot site may participate in the main study, following completion of the pilot. The purpose of the pilot is to assess whether any adaptations are needed to facilitate patient recruitment, enrollment, or the collection of the baseline assessment, and only patient participants are enrolled in the pilot study. Eligibility requirements for patient participation are the same as for the main study, with the exception of the requirement that patients have a PCP who is participating in the study. The study procedures for patient recruitment and enrollment in the pilot will be the same as those detailed above for the main study.

Procedures for enrolled patient participants in the pilot will be the same as those used for the main study, except that pilot study activities will be limited to no more than four coaching sessions and two follow-up assessments, conducted at approximately 2- and 4-weeks post-baseline. Pilot study patient participants will not receive the full EUC or STOP intervention. Four telephone health coaching sessions (one per week after the baseline visit) may be conducted in order to test the mechanics of carrying out the sessions. Pilot patient participants may also be asked to participate in interviews, which may include cognitive interviews and question testing techniques that are intended to gather information about the feasibility and acceptability of the study procedures, assessments, and the STOP intervention. Interviews may also include assessing the acceptability of assessment procedures, and incentive payments for patient participants. The NCM and PCP brief advice components of the intervention will not be piloted, because introducing these practices into the clinic prior to the intervention start date is likely to contaminate the study (i.e., the NCM and PCPs would begin using their skills to manage opioid use with their other patients, who have not yet been enrolled). Given that both the PCP and NCM components have been tested in prior large trials (QUIT and TOPCARE), little new information is likely to be gained from a pilot. Instead, training of the NCMs will include role plays of clinical scenarios that will serve to build provider skills, while simultaneously refining the content and delivery of the clinical intervention. Training sessions, which are described in Section 12 and further detailed in a training

plan, will be led by members of the research team who have experience teaching and implementing these protocols with clinical staff.

The informed consent document used in the pilot will reflect the limited study activities for these participants. Individuals participating in the pilot will receive a monetary incentive for participation. The research team may enroll up to a limit of 50 patient participants. The higher number of pilot patient participants will be used if there is a need to adapt and test alternative approaches to the recruitment, enrollment, and assessment procedures, or if additional interviews are needed to inform feasibility and acceptability.

10.5.1 Additional Telephone Health Coaching for Training Purposes

In addition to the pilot activities described above, the pilot site will also recruit up to ten patients to participate only in the telephone health coaching component of the pilot study. The purpose of this activity is to collect additional information and feedback on the coaching sessions, in order to better inform training activities for the health coaches in the main study. Patients will be offered a total incentive of $50 to participate in this activity. Participants will receive up to four coaching sessions and the content and structure of the sessions will be the same as what is described in Section 10.6. No data will be entered into eClinical for this activity. Patients will be asked to verbally consent to recording of the coaching sessions, and research staff will document consent at the bottom of the script. The inclusion criteria for this activity are listed in Section 8.1.2.

Patients may be referred to participate in this activity by their PCP or other clinical staff at the pilot site. Research staff may also invite participants who prescreen eligible for the pilot study, but are not eligible (i.e., screen ineligible) for the pilot study, or those who screen eligible but do not wish to enroll. Participants receiving telephone health coaching only will provide verbal consent to participate in the coaching sessions using an IRB approved verbal consent script. They will not complete any self-administered forms or surveys; they will be contacted by the RC/RA approximately two weeks after completing their last coaching session in order to participate in a brief feedback interview over the phone.

10.6 Study Treatments

Interventions used in the study are described below. Training, supervision, and fidelity monitoring procedures for the interventions are described in Section 12, and in more detail in the Training Plan.

Patient participants in either arm who develop a moderate-severe OUD, based on the clinical judgment of the PCP, NCM, or telephone health coach at any time during the study can be offered clinical care to address OUD. This care may include office-based treatment using medication for OUD (MOUD) and referrals to addiction treatment. In the EUC arm, clinical care for OUD is facilitated by clinical staff (for example, PCPs, behavioral health providers, or social workers), while in the STOP arm clinical care for OUD is facilitated by the NCM or other clinical staff. Clinical guidelines for identifying OUD will be provided in the study MOP, and procedures for linking patients to OUD treatment will be included in the site operating procedures (SOP).

10.6.1 Enhanced Usual Care (EUC)

In the **EUC arm**, PCPs will conduct primary care as usual, without the support of the NCM. At the baseline visit, patient participants receive educational materials and view a short video. The educational materials include information about preventing opioid-related overdose, including how to obtain a naloxone kit; and a handout on cancer prevention. The video content will feature information on cancer prevention. It will be viewed on a tablet or desktop computer and will be approximately 2 minutes long. All EUC patient participants receive the same video, which is not tailored to the responses given on their questionnaires. There is no study intervention after the baseline visit.

There are no limitations placed on primary care treatment as usual. The EUC condition enhances usual care by providing patient participants with an OD prevention educational handout. This is done for safety reasons, because the current standard of care in most primary care clinics is to offer no universal screening for opioid use or OD prevention interventions in primary care. The local research teams at each site will ensure that information on naloxone is detailed and specific, and that the pamphlet gives clear guidance on how to access naloxone. The content will be further detailed in the manual of procedures and/or site standard operating procedures.

10.6.2 STOP Intervention

In the **STOP arm**, enrolled patient participants will receive the intervention components of brief advice from their PCP and/or a video doctor, printed educational materials, and will be asked to interact with the NCM and receive telephone health coaching. The roles of the intervention team members are summarized in Table 4 and further detailed below.

Telephone Health Coaches, Nurse Care Managers and research staff will use a HIPAA compliant communication software called QliqSOFT to coordinate care for STOP intervention patient participants.

Baseline primary care visit

Patient participants in the STOP arm will receive brief advice, consisting of PCP-delivered counseling and/or viewing a “video doctor.” For in-person visits, the video doctor can be completed either in-person or remotely. For telehealth visits, the video doctor will be sent via email or text to the patient participant. They will additionally receive an educational pamphlet about opioid overdose prevention and an introduction to the role of the NCM and telephone health coaches.

PCP brief advice

Brief advice can be delivered by the patient participant’s PCP as part of the baseline visit or within 10 business days. Before providing the patient participant with the brief advice, PCPs will receive a printed summary report from the RC/RA or clinical staff. The summary advises the PCP that their patient participant screened positive for risky opioid use, lists the patient participant’s screening results (TAPS Tool +/- COMM) and gives a suggested counseling script. The counseling script will include specific advice on opioid-related risks, (e.g., developing addiction, physiologic dependence, and overdose prevention), will inform patient participants of resources

to help them reduce their risk (NCM and telephone health coaching), and will include a recommendation to reduce their risk behavior. PCPs will be trained in using this script to deliver counseling, which is intended to last approximately 3 minutes. In the QUIT trial, two-thirds of the interventions lasted at most 3-4 minutes; only three (1.5%) required more than 10 minutes. PCPs will not be incentivized for delivering this counseling.

Video Doctor: The video doctor should be completed as part of the baseline visit. If the patient participant sees their PCP during the baseline visit, they will view the Video Doctor after they see their PCP and before they complete the baseline assessments. If the patient participant does not see their PCP as part of the baseline visit, the RC/RA will show them the Video Doctor after consent and enrollment. For telehealth or remote visits, the video link may be sent via email or text to the patient participants. The video is a recording of a provider delivering brief advice about opioid use that includes the same elements covered in the summary report outlined above, and will be specific to use of illicit or prescribed opioids. The video may also include an introductory message from the site NCM and the telephone health coach(es).

Patient participants in the STOP intervention will receive an educational pamphlet, which includes information about preventing opioid-related overdose, including how to obtain a naloxone kit. Patient participants will also receive a printed handout with information about the NCM and telephone health coaching sessions, including the benefits and expectations of their participation, schedule of research visits and telephone health coaching sessions, and contact information. When possible, the NCM will introduce themselves to the patient participant in-person during the course of the baseline visit. The NCM may reach out to the patient participant following the baseline visit (by phone, email, text message, or via the patient portal) to introduce themselves.

10.6.3 Table 4: Summary of Intervention Provider Roles and Timing of Patient Contacts

Team member	PCP	NCM	Telephone Health Coach
Role and responsibilities	• Brief advice • Discusses opioid use in context of overall health	• Health education • Risk reduction counseling • Overdose prevention and naloxone provision • Self-management skills • Education on non-pharmacologic pain management • Referrals and support for pain, mental health, SUD treatment, other services. • Supports engagement in primary care • Uses motivational enhancement strategies to engage patients in SUD treatment when indicated	Telephone Health coaching: • Offers support • Risk reduction counseling • Suggests strategies for overcoming barriers • Enhances motivation for behavior change • Encourages engagement w/ primary care and behavioral health providers in the clinic • Encourages utilization of community and/or on-line resources to support behavior change Enhanced coaching: • Evidence-based counseling (MI/CBT) focused on substance use behavior change
Timing of patient contacts	1. Baseline visit or within 10 business days 2. Readdress in follow-up primary care visits	1. Baseline visit 2. Ongoing monitoring and engagement in conjunction with PCP. Meets on an approximately monthly basis for patients prescribed chronic opioids and as needed for all patients	1. Telephone Health Coaching: Week 2 and Week 4 (approximately) following baseline visit 2. Enhanced coaching: For individuals who may benefit from further intervention: Weeks 7,8,9,10 (approximately)
Location	Clinic, telehealth, or telephone	Clinic (contacts are in-person +/- by telephone)	Telephone and/or video

Nurse Care Manager

The Nurse Care Manager (NCM) is a central element of the intervention, as the nurse works closely with the PCP to assess, educate, and manage patient participants with risky opioid use. For all patient participants in the STOP condition, it will include facilitating linkage to needed specialty care, including pain (e.g., physical therapy), mental health (pharmacotherapy) and addiction, as indicated. NCMs will provide health education and counseling on risk reduction, overdose prevention and self-management skills. For patient participants on COT, the role will include monitoring opioid prescribing and risks. Details of the NCM intervention are outlined in Table 5 below. Patient participants will be asked to participate in an initial visit with the NCM, which will occur on the same day as the baseline visit if possible. The NCM continues working with patients in the STOP condition throughout their 12 months of study participation. Following the initial visit with the NCM, the frequency of visits depends on patient participant needs. For all patients of intervention PCPs, the NCM can provide care management and usual nursing care. For all patients of PCPs in the EUC arm, the NCM cannot provide any care management. They can perform nursing activities distinct from what they do for enrolled intervention patients. For example, they can assist with clinic-wide initiatives such as immunization clinic (e.g., flu shots), or other nursing care (triage, wound dressing, etc.). The NCM may also work with all patients of the clinic who are receiving medication for OUD, as these patients are not eligible for our study.

Table 5: Nurse Care Manager Intervention

Nurse: Patient Participant ratio[1]
• Approximately 50 patient participants/1.0 FTE NCM (panel will increase over the course of the study, as patient participants are enrolled).
Roles/Duties
• Integrating into work flow: Prior to the start of the study, NCM will coordinate with existing practice staff to ensure smooth transition of duties and integration into usual work flow for patients of intervention PCPs.
• Reviewing panel of patient participants with risky opioid use, including those on COT: Meet with PCP to review patient participant panel to identify high risk or problem patient participants; and as patient participants are enrolled into the study, to review with PCP before or after PCP visit.
• Review charts and prescription drug monitoring program (PDMP) for presence of treatment agreements, urine drug screens and risk factors.
• Engage and assess patient participants: Conduct initial and ongoing evaluations for substance use and opioid use disorder, pain, mental health symptoms, social supports, overdose risk, suicidality, and barriers to treatment engagement and adherence.
• Conduct urine drug testing and pill counts (for patient participants on COT).
• Educate and counsel patient participants: Provide health education on substance use and disease or symptom self-management, including the relationship of opioid use to pain.
• Provide opioid risk reduction and overdose prevention counseling, ensure that patient participant is offered naloxone kit and training. Teach self-management skills for pain and other triggers for opioid use.
• Support engagement in care: Outreach to patients in between scheduled PCP visits or if patient cancels/no shows to visits to offer counseling and support.
• Refer patient participants to appropriate clinic and community resources, support ongoing engagement in primary care.
• Meet with PCPs: Review patient participants, help interpret urine drug screen results.
• Track prescriptions for patient participants and when appropriate, prepare prescriptions for PCPs to sign for naloxone and/or COT.
• Management of patient participants with substance use disorder: Refer patient participants with any active substance use disorder to treatment within or outside of the practice, as appropriate.
• Documentation: the NCM will document all patient participant interactions, changes to care and incidents in the EHR as a progress note.
• Provide care management and usual nursing care to all patients of intervention PCPs.
Patient Participant Tracking
• Each practice will choose an approach to track patient participants with subthreshold OUD. Templates of recommended fields will be supplied by the study. Options include: 1) Use EHR if possible, 2) local database (Excel, Access, etc.), or 3) develop a clinic registry.

[1] In addition to study participants, nurses may manage up to 50 patients who are receiving COT or MOUD and have a PCP in the STOP intervention condition but are not participating in the study.

Telephone Health Coaching

The STOP protocol includes one-on-one telephone behavioral coaching targeting risky opioid use. Patient-facing interventions based on Motivational Interviewing (MI) and Cognitive Behavioral Therapy (CBT) will utilize phone follow-ups to improve patient participant motivation and self-efficacy to change health behavior [45-47] and behavioral outcomes.[45, 48] MI and CBT are evidence-based treatments for behavioral health conditions, including opioid and other substance use, and can effectively be delivered via telephone and in as few as 2 sessions, with increased efficacy when up to 4 sessions are delivered. They are commonly integrated to optimize potency.

Consistent with our Social Ecological Framework of Unhealthy Opioid Use, telephone health coaching will target multiple levels that impact subthreshold OUD. These include individual patient factors (knowledge, motivation, self-efficacy, behavioral skills), interpersonal factors (education on communication skills and limit setting), organizational factors (within clinic resource referral), and community factors (community and/or on-line resource referral).

All patient participants in the STOP arm will be offered telephonic health coaching sessions with or without video at approximately 2- and 4-weeks post-baseline. Patient participants who may benefit from additional coaching (for example, those who do not improve or who experience clinical worsening of unhealthy opioid use) may receive up to 4 additional coaching sessions from the telephone health coach. Coaching is delivered from a centralized call center, by staff that receive standardized training and supervision. To the extent possible, calls will be scheduled at the patient participant's convenience (e.g., evenings, weekends). Patients may chose not to participate in health coaching.

Basic Coaching (Step 1):

All patient participants in the STOP arm will be offered the Step 1 coaching, which is conducted by telephone health coaches, who are trained health professionals. The coaches will assess the patient participant's current opioid use and other needs and provide appropriate referrals and resource links. The coaching approach is supportive and informed by MI techniques, which seek to increase the patient participant's motivation and self-efficacy to improve health behaviors.

The content of the Step 1 coaching focuses on the domain areas of substance use behavior, stress/mood management, and quality of life issues, with a particular emphasis on risky opioid use and overdose prevention. Sessions will be tailored to address risky use of other substances and provide brief recommendation to quit/reduce risky opioid use. For patient participants who endorse readiness to change, coaching will address behavioral skills acquisition, as well as behavior change plan development and implementation. Telephone health coaches will make referrals to clinic social work/behavioral health or other clinic services, or referrals to clinic/community resources, in response to barriers to opioid use reduction raised by patient participants or need for additional services. Timing of coaching sessions will be based at the patient participant's convenience, including evenings and weekends. Patient participants will be given approximately $3 per completed call for reimbursement of cell phone costs.

Step 1 coaching will include 2 sessions, each 20 to 30 minutes in length. The first will occur approximately 2 weeks post-baseline and the second will occur approximately 4 weeks post-baseline. While these are ideal windows, if initial attempts to complete the counseling sessions are unsuccessful, further attempts to engage patient participants will be made for up to 3 weeks after the target date for each call.

Enhanced Coaching (Step 2):

Patient participants who may benefit from additional coaching following the Step 1 sessions will be offered up to 4 additional sessions with a telephone health coach. Patient participants will be referred for these coaching sessions by the NCM or PCP, or at the discretion of the telephone health coach, based on clinical criteria which may include ongoing or escalating nonmedical or illicit opioid use, overdose risk behavior, symptoms of OUD, OD episodes, and/or consequences of opioid and other substance use. This determination will typically be made during or after the first or second Step 1 coaching session. These criteria will be further detailed in the MOP, and training on their application will be provided as specified in the training plan.

The telephone health coach will provide patient participants with approximately 4 sessions of coaching over the telephone for Step 2. Calls with or without video will occur approximately weekly and each call will be approximately 30-40 minutes in length. An assessment of motivation to reduce risky opioid use will be conducted by the clinician using MI-based "rulers" (e.g., "On a scale of 0 to 10, how motivated are you to reduce your risky opioid use right now?"). For patient participants with low motivation to change current unhealthy behaviors, the coach will conduct additional MI to increase motivation and self-efficacy. As patient participants increase readiness to change, specific behavioral strategies for relapse prevention and pain self-management will be presented by the coach within a CBT framework. These coaching sessions will ideally start within two weeks of the patient participant's referral into Step 2 and occur once a week for four consecutive weeks. Circumstances in which a participant may receive more or less than 4 sessions (for example, the participant refuses further coaching, or is unable to fully complete one of the sessions and wants to schedule a make-up to receive the intended content) will be detailed in the manual of procedures. If initial attempts to initiate the telephone health coaching sessions are unsuccessful, further attempts to engage participants will be made for up to 10 weeks after the referral. This time period reflects usual care practices in terms of being able to re-engage with care at a later time, balanced against the need to deliver the treatment prior to assessing outcomes in the study. Following the initial session, the subsequent 3 coaching sessions will ideally be completed weekly (one session/week). If one of these sessions is missed or delayed, further attempts to re-engage the patient participant will be made for up to 3 weeks after the target date for each session. Timing of calls will be based at the patient participant's convenience, including evenings and weekends. Patient participants will receive approximately $3 per call for reimbursement of cell phone costs.

10.7 Premature Withdrawal of PCP or Patient Participants

10.7.1 Withdrawal of PCP Participants

All PCP participants will be followed for the duration of the study unless they withdraw consent, or the investigator or sponsor decides to discontinue their enrollment for any reason. PCP

participants may withdraw voluntarily from the study at any time. Reasons for the investigator or sponsor terminating a PCP participant from the study may include, but are not limited to, the PCP breaking the study blind, lack of funding, or DSMB early termination of the study for safety or effectiveness reasons.

10.7.2 Withdrawal of Patient Participants

All patient participants will be followed for the duration of the study unless they withdraw consent, die, or the investigator or sponsor decides to discontinue their enrollment for any reason. Patient participants may withdraw voluntarily from the study at any time. Reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to, the patient participant becoming a threat to self or others, lack of funding, or DSMB early termination of the study for safety or effectiveness reasons. Treatment will be discontinued if there is evidence that continuing in the study would be harmful to the patient participant. Patient participants who withdraw or discontinue early may be replaced with other eligible individuals, if the site is still in the enrollment phase.

10.8 PCP Participant Follow-Up

PCP participant follow up will occur until the last patient participant completes 12 months of follow-up. Therefore, the total duration of participation for PCPs is up to 37 months [approximately 1 month prior to recruitment; 24 months of recruitment; 12 months following enrollment of the last patient]. Approximately six months after the last patient participant is enrolled in the study, PCPs will be asked to complete a second set of assessments, for which they will be compensated. 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.

Provider behavior, including prescriptions for opioids and other controlled substances are assessed from the electronic health record (EHR). 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.

10.9 Patient Participant Follow-Up

Follow-up assessments will be conducted for approximately 12 months following the baseline visit. Most follow-up assessments will be self-completed electronically by participants. Assessments that require an interviewer will typically be done by phone but may be done in person. The full list of assessments and assessment schedule is detailed in Section 11. Patient participants will receive a monetary incentive for the completion of each follow-up visit, the amounts of which are specified in the MOP and consent documents. All assessments are confidential, and collected using the patient participant's unique study ID.

Once per month, patient participants will receive an electronic message (by text and/or email) instructing them to fill out a brief survey. The survey questions will consist of general health behaviors (for example, exercise frequency, duration, and diet), followed by assessment of the

days of risky opioid use (use of illegal or non-prescribed opioids or use of prescribed opioids at a higher dose or frequency than prescribed) and days of other substance use. Surveys can be completed by text message and/or online. Patient participants have a one-month window to complete each monthly survey. This means the prior month's survey can be completed at the time of the current month's survey if the prior month's survey was missed.

On a quarterly basis, (at approximately 3, 6, 9, and 12 months post-baseline), patient participants will be contacted by the RC/RA to complete additional assessments. These assessments include both self-administered (usually completed online, but may be done on paper), and interviewer-administered (completed by phone) questionnaires which may be completed by participants remotely (i.e., no required travel to the research site). If a patient participant has missed the prior follow-up assessment, the RC/RA will only complete the assessment items that are currently due (e.g., if a patient participates in their 6-month follow-up after skipping the 3-month follow-up, they will complete the 6-month assessment items only).

Patient participants will submit a biologic sample (urine) for urine drug screening at 3 times during the study period, if possible. These samples will be requested as part of baseline, 6-month, and 12-month assessments. The location and processes for sample collection will be specified in the MOP and the site standard operating procedures. The results of the urine drug screen will not be shared with the participant's medical providers.

10.9.1 Follow-up with Prisoners (as defined by OHRP)

Prisoners will not be enrolled in this study. If a participant later meets the OHRP definition of a prisoner as stated in 45 CFR 46 Subpart C after baseline enrollment, sites may keep such individuals in the study and collect follow-up data only if they have IRB and OHRP approval to do so. These procedures must be compliant with 45 CFR 46 Subpart C. Data may be collected either in person or by electronic means, provided that data collection follows the procedures approved by OHRP and the IRB of record.

10.10 Blinding

10.10.1 Type of 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 the purpose of the research is to study health behaviors, not limited to opioid use.

10.10.2 Maintenance of the Blind

Most assessments are self-administered (SA) by patient participants. It is not feasible to blind research staff because the delivery of some intervention components require their involvement (e.g., showing educational video vs. video doctor to the participant, intervention specific CRFs). Patient participants may be able to deduce the assignment of their PCP, (e.g., through conversation with other patient participants in the study), but this information will not be

volunteered by clinical or research staff. To assess the success of the blind, patient participants will be asked at the end of the study what they considered to be the goal of the research.

10.10.3 Breaking the Blind

We do not anticipate any situations that would require unblinding patient participants. The patient participant's PCP will be aware of their study condition and will be able to administer any emergency medical treatment as needed without specifically informing the patient participant of their assignment.

10.11 Patient Participant Compensation

Incentives will be paid in the form of a debit card (e.g., ClinCard) or gift card for each of the following study activities:

- Baseline visit (compensation may be given in two parts: 1) following completion of RA-administered assessments and 2) following completion of the participant self-administered assessments).
- Monthly surveys (12 total).
- Quarterly assessment visits (phone or in-person) at 3, 6, 9, and 12 months (4 total)
- Urine drug screen that occurs after the baseline visit (2 total), if collected.

Bonuses for completing consecutive assessments will be paid monthly over the first 6 months. Patient participants will additionally receive a small payment (approximately $3) for each telephone health coaching session, to cover the potential cost of using a cell phone for the call. Patient participants will receive an incentive each time they contact the research team to inform them of any changes to their contact information (patient participants may receive this incentive no more than four times during the study period), the details of which will be described in the MOP.

11.0 STUDY ASSESSMENTS

The selected assessment battery attempts to balance the value of comprehensive data against the costs of data collection in terms of staff time, feasibility of completion in the context of primary care practice, financial cost, and assessment reactivity. The study is testing the efficacy of a relatively low-intensity behavioral intervention, and so assessment reactivity (i.e., the therapeutic effects of assessment) must be balanced against the need to collect detailed information about opioid use. Therefore, assessments have been limited to those that contribute directly to the objectives of the study.

To partially mask the purpose of the study and further minimize the impact of assessments on substance use behavior, questionnaires about substance use will be accompanied by questionnaires about other health behaviors, specifically exercise and diet. This strategy was used in the QUIT trial, which was conveyed to patients as a "healthy living study." Information that is most likely to be impacted by stigma or social desirability bias, such as substance use and overdose behavior, will be participant self-administered to decrease the potential for biased reporting. Self-administered assessments will be delivered electronically, and audio guidance may be made available to assist individuals with lower literacy to complete them without assistance.

11.1 Table of Assessments

Table 6 (patient participants) and Table 7 (PCP participants) list assessments and the schedule on which they are administered.

11.1.1 Patient Participant Assessments

Table 6 indicates those assessments that are self-administered (SA) versus administered by research staff (RA). To increase the feasibility of collecting baseline data, the baseline assessments are divided into those that must be completed prior to the baseline visit, and those that may be completed after the baseline visit. Assessments that must be gathered prior to the baseline visit are those that are most likely to change based on the brief advice delivered by the PCP and/or video doctor. SA assessments are typically self-completed by patient participants but may in some cases be RA-administered if the patient participant is unable or unwilling to self-complete.

11.2 Table 6: Schedule of Patient Participant Assessments

Assessment/Activity	Done By[3]	Screening for Eligibility	Baseline		Monthly (1-12)	3 Months	6 Months	9 Months	12 Months	As Needed	Visit Window
			Pre-PCP Encounter	Post-PCP Encounter							
Enrollment											
Master Enrollment Log++	RA		X								N/A
Informed Consent/HIPAA	RA		X**								N/A
Inclusion/Exclusion Checklist	RA		X**								N/A
Demographics	RA		X								N/A
Locator Information Form	RA			X							(-) 1 / (+) 3 weeks
Screening Assessments											
Healthy Living Eligibility Screener	SA	X*									(-) / (+) 1 week
TAPS Tool	SA	X*					X		X		(-) 1 / (+) 3 weeks
COMM[2]	SA	X*					X		X		(-) 1 / (+) 3 weeks
CIDI for opioids	RA	X					X		X		(-) 1 / (+) 3 weeks
Measures of Primary and Secondary Outcomes											
Days of opioid use in past 30 days (Healthy Living Monthly Survey)	SA		X[1]		X						(-) / (+) 4 weeks
Days of non-opioid substance use in past 30 days (Healthy Living Monthly Survey)	SA		X[1]		X						(-) / (+) 4 weeks
PDSQ - drug and alcohol sections	SA			X			X		X		(-) 1 / (+) 3 weeks
Overdose Risk Behavior Questionnaire	SA			X			X		X		(-) 1 / (+) 3 weeks
Non-Fatal OD Questionnaire	SA			X			X		X		(-) 1 / (+) 3 weeks
Brief Pain Inventory (BPI)-short form	SA			X		X	X	X	X		(-) 1 / (+) 3 weeks
PROMIS anxiety short form	SA			X			X		X		(-) 1 / (+) 3 weeks
Patient Health Questionnaire (PHQ-8)	RA			X			X		X		(-) 1 / (+) 3 weeks
Patient Safety Screener (PSS)	RA			X			X		X		(-) 1 / (+) 3 weeks
Short Form 12 (SF-12) Measure	SA			X			X		X		(-) 1 / (+) 3 weeks
Patient Reported ED visits and hospitalizations	SA			X			X		X		(-) 1 / (+) 3 weeks
Days of non-opioid substance use in past 90 days (TLFB) binge alcohol, benzodiazepine, stimulants, marijuana, other drug	RA					X	X				(+) 3 weeks
Days of opioid use in past 90 days (TLFB)	RA					X	X				(+) 3 weeks
Exit survey on PCP-Delivered Opioid Counseling***	RA			X							(+) 1 week
Chart Abstraction	RA								X		N/A
Marijuana Use Assessment	SA			X					X		(-) 1 / (+) 3 weeks
E-Cigarette and Vaping	SA			X			X		X		(-) 1 / (+) 3 weeks

Assessment/Activity	Done By[3]	Screening for Eligibility	Baseline		Monthly (1-12)	3 Months	6 Months	9 Months	12 Months	As Needed	Visit Window
			Pre-PCP Encounter	Post-PCP Encounter							
PROMIS Sleep 4a	SA			X			X		X		(-) 1 / (+) 3 weeks
Other Measures											
Patient Experience Questionnaire	SA					X	X	X	X		(-) 1 / (+) 3 weeks
Readiness to change	SA		X[1]			X	X				(-) 1 / (+) 3 weeks
PROMIS instrumental and emotional health short forms	SA			X			X		X		(-) 1 / (+) 3 weeks
Addiction treatment and harm reduction program utilization	SA			X			X		X		(-) 1 / (+) 3 weeks
Urine Drug Screen	RA			X			X		X		(-) 1 / (+) 3 weeks
Assessment of blinding	RA								X		N/A
Study Administration											
Inventory – Supplies Form	RA									X	N/A
Recruitment Log	RA									X	N/A
Missed Visit and Visit Documentation Form	RA			X		X	X	X	X	X	(-) 1 / (+) 3 weeks
Monthly Survey Link	RA									X	N/A
Progress Note Checklist++	RA									X	N/A
Protocol Deviation	RA									X	N/A
Visit Compensation Log++	RA									X	N/A
RA recorded ED visits and hospitalizations	RA									X	N/A
Mental Health Follow-Up Assessment	RA									X	N/A
Study Completion Form	RA									X	N/A
Death Form	RA									X	N/A

[1] Assessment completed within the prescreener survey but is considered a baseline assessment if the participant screens eligible and is enrolled into the study.

[2] Adapted COMM provided to individuals receiving any opioid therapy in the past 6 months.

[3] RA – Research Assistant or Research Coordinator Administered; SA – Self Administered++ = Not captured in eClinical

** = Completed as part of pre-screening for study eligibility*

*** = May be done after the baseline visit, if there is not enough time to complete before.*

**** = Survey is only given to patients who have an integrated PCP and baseline visit*

Note – TLFB at 3 and 6 months cannot be completed earlier than or on the target visit date.

Note – All participant-facing documents will be reviewed/approved by the IRB. Minor edits may be made to assessments (e.g., grammar, punctuation, directions, system programming, etc.) as needed. Assessments will only be submitted for re-review if information to be collected is changed (e.g., addition of new questions.).

11.2.1 PCP Participant Assessments

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). These assessments are adapted from the TOPCARE and TEACH studies.[33, 49]

11.2.1.1 Table 7: PCP Participant Assessments

Topic	Description	Screening	Baseline	End of Intervention
RC/RA Only: Provider Eligibility Review	To document PCP inclusion criteria that the RC/RA extracts from the clinic data. To be completed prior to the PCP completing their Baseline Assessment package	X		
Inclusion/Exclusion Checklist	To document eligibility of PCPs	X	x	
Demographics	Age, gender, race, ethnicity		x	
Education	Years since completing training, addiction training, pain training, certification, licensures		x	
Individual PCP Practice characteristics	Current position, number of patients seen for visits per month		x	
Organizational function	PCP views on organizational leadership, change capacity, management, resources Instrument: ORCA Context items		x	
Assessment and treatment of pain, COT management	Confidence in assessing and treating pain, identifying substance use disorder, negotiating medication agreements, urine toxicology interpretation, clinical practices for managing patients on opioid therapy, barriers to pain treatment. Instrument: Modified TOPCARE survey		x	x
Substance use and misuse in patients: knowledge and attitudes	Estimate number (%) of patients on opioids, number (%) of patients with substance misuse (incl. opioid, tobacco, alcohol, other). Rate concern about misuse of prescribed opioids and impact of substance use on prescription of opioids, beliefs about substance use problems in community, attitudes toward patients with substance use and addiction treatment. Instrument: Modified ASIP survey		x	x
Management of risky opioid use, OUD, overdose prevention	Views on interventions to reduce risky opioid use and risk behavior, clinical practices for managing patients on opioid therapy, availability and effectiveness of specialists (pain, addiction, mental health, palliative care) and non-pharmacological therapies, knowledge about opioid overdose risks. Instrument: Adapted items from TOPCARE survey; OEND questionnaire		x	x
Feedback on intervention (Intervention PCPs only)	Acceptability, value, feasibility of STOP intervention in practice Instrument: Adapted items from QUIT			x

11.3 Patient Participant Assessments

11.3.1 General Measures

11.3.1.1 Inclusion/Exclusion Checklist

This form lists each inclusion and exclusion criterion to document eligibility and is completed by research staff. Eligibility is assessed continually as appropriate. Only participants who continue to meet study eligibility criteria are allowed to continue with the screening process, and randomization (for PCPs only). Because presence of a moderate-severe OUD is an exclusion criterion in this study, as part of screening for eligibility research staff will administer the CIDI opioid items (details on the CIDI are given below). Individuals with a CIDI opioid score of 4+ (indicating moderate-severe OUD using DSM-5 criteria) will not be eligible to enroll in the study.

11.3.1.2 Locator Form

A locator form is used to obtain information to assist in finding participants during the study. This form collects the participant's current address, email address, and phone numbers. In order to facilitate locating participants if direct contact efforts are unsuccessful, addresses and phone numbers of others such as friends and family who may know how to reach the participant are collected. To facilitate contacting individuals who cannot be reached by phone or email, the form will also collect information on other locations that are frequented by the participant (for example, programs, clinics, shelters, drop-in spaces), as well as professionals who are involved with their care (for example, case managers, clinicians, outreach workers). This information will be collected at screening and will be updated at each study visit. Participants will be asked to notify the research team if there are any changes in their contact information between study visits and will receive a modest incentive for doing so. Individuals are eligible to receive this incentive up to 4 times during their study participation. No information from the locator form is used in data analyses, nor is this information captured in the database that includes information from the study assessments.

11.3.1.3 Demographics Form

The Demographics form collects information about demographic characteristics of the participant, including biological sex, date of birth, ethnicity, race, education, employment status, and marital status. Self-reported information on insurance status will also be collected. To minimize assessment reactivity, only those substance use assessments that are required to inform primary and secondary outcome measures are collected. We will adopt PhenX toolkit items for collecting these measures to the extent possible, but will not include the full battery of the Substance Abuse and Addiction Collection of the PhenX Toolkit (http://www.phenxtoolkit.org/).

11.3.1.4 Study Completion Form

This form tracks the participant's status in the study. It is completed at the month 12 follow-up visit, or once the month 12 follow-up visit window lapses for participants who do not complete this final follow-up. If the participant withdraws consent, dies or is removed from the study per judgement of study staff, this form will be completed at the time of termination from the study. This form is used in data analyses to address variables such as treatment retention and completion. This form also provides a location for the site PI attestation of review of all study data.

11.4 Protocol Specific Assessments

11.4.1 Healthy Living Eligibility Screener

A brief self-administered questionnaire about health behaviors, not including substance use, will be administered along with substance use screening and assessment questionnaires. This questionnaire, called the "healthy living survey," is used to partially mask the primary focus of the study from participants, and does not contribute to our outcome measures. This strategy was used in the QUIT intervention study to reduce assessment reactivity and social desirability bias on self-reported substance use measures.[21, 23] The healthy living survey includes questions about nutrition and frequency of exercise in the past 30 days.

11.4.2 Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool

The TAPS Tool consists of a 4-item screen for tobacco, alcohol, illicit drugs, and nonmedical use of prescription drugs, followed by a substance-specific assessment of risk level for individuals who screen positive. The TAPS Tool was developed and validated, in self-administered and interviewer-administered versions, in 2,000 adult primary care patients in CTN-0059. In that study, the TAPS demonstrated good sensitivity and specificity for detecting problem use of tobacco, alcohol, and 5 classes of drugs, including heroin and prescription opioids.[50] At a score of 1+, the self-administered TAPS had 85% sensitivity and 97% specificity for detecting any past-month opioid use (heroin and/or nonmedical use of prescription opioids, measured by 30-day timeline follow-back).[51]

11.4.3 Modified World Mental Health Composite International Diagnostic Interview (CIDI)

The CIDI has been used widely in epidemiologic and clinical research to assess substance use disorders, including opioid use disorder (OUD) based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4).[52-56] The CIDI items for opioid use will be used as the measure of OUD severity. As in prior studies, (including CTN-0059),[50, 57] the CIDI will be adapted for DSM-5 so that only the existing CIDI items that map onto the DSM-5 OUD classifications will be administered (omitting the item on legal problems and including the one on craving). Classification of the severity of OUD are based on the standard diagnostic thresholds: 2-3 criteria signifies mild OUD, 4-5 signifies moderate OUD, and 6+ signifies severe OUD. The CIDI opioid items are administered during screening for study eligibility, and at the 6-month and 12-month study visit. Only individuals with fewer than 4 criteria at the time of screening are eligible for enrollment.

11.4.4 Current Opioid Misuse Measure (COMM)

The COMM is a 17-item self-administered questionnaire that is widely used to monitor pain patients receiving opioid therapy.[43, 44] The COMM is designed to detect aberrant behavior associated with misuse of opioid medications, and has been validated in approximately 500 chronic pain patients receiving opioid therapy. We will be adapting the COMM to include an instruction line at the beginning of the survey and before items 9, 14, 15, and 16 to clarify the questions are asking about opioid pain medications. Because the COMM is only intended for use

in individuals who are taking prescription opioids, in our study it will be administered only to individuals who self-report being prescribed opioid medications.

11.5 Measures of Primary and Secondary Outcomes

11.5.1 Days of Opioid Use (Healthy Living Monthly Survey)

The primary outcome of days of risky opioid use will be measured at baseline and every 30 days using items based on the Addiction Severity Index [40,41] and the COMM: “During the past 30 days, on how many days did you use [drug name]?” The question will be asked separately for heroin/illicit opioids and for nonmedical use of prescribed opioids. For patients with a current opioid prescription, items from the COMM will also be asked. To inform the primary outcome: a) “During the PAST 30 DAYS, on how many days did you need to take pain medications belonging to someone else?” and b) “During the PAST 30 DAYS, on how many days have you had to take more of your medication than prescribed?” The extent of overlap between these different types of risky use will also be measured, when applicable. The number of days of risky use for an individual will be the sum of days for each of these questions minus the overlap. Overlap between illicit use and nonmedical use will be calculated so that every individual will have a calculated number of days of risky use. To inform secondary outcomes, the following items, adapted from the COMM, will also be administered: c) “During the PAST 30 DAYS, on how many days did you borrow pain medication from someone else?” and d) “During the PAST 30 DAYS, on how many days did you use your pain medication for symptoms other than for pain (e.g., to help you sleep, improve your mood, or relieve stress)?”. The assessment is self-administered using a computerized form. This approach to measuring days of drug use was used for assessing the primary outcome in the QUIT trial, where it demonstrated feasibility and sensitivity to change, including for opioid use.[21]

11.5.2 Days of Non-Opioid Substance Use (Healthy Living Monthly Survey)

Days of non-opioid substance use are measured using the same approach as days of opioid use, with one question asking about the use of each substance type in the past 30 days. Substances queried include alcohol (binge drinking; 4+ drinks/day for women, 5+ drinks/day for men), benzodiazepines, illicit stimulants (cocaine or methamphetamine), prescription stimulants (amphetamines), marijuana, and other drugs.

11.5.3 Timeline Follow-Back (TLFB)

The Timeline Follow-Back procedure (Sobell et al., 1988) will be used to elicit the patient participant’s self-reported use of substances (opioids and other drugs, binge alcohol), diet and exercise ($\geq$20 min) in the past 90 days.[58] The TLFB will be administered by the RC/RA by phone or in person as part of the 3-month and 6-month assessment battery, to document the patient participant’s self-reported use of substances for each day since the previous TLFB assessment.

11.5.4 Psychiatric Diagnostic Screening Questionnaire (PDSQ)

The PDSQ is a brief self-administered instrument to assess DSM-4 Axis I disorders, including alcohol use disorder (AUD) and drug use disorder (DUD). It is the only brief questionnaire assessing DSM-4 substance use disorder that has been validated for self-administration. The PDSQ was validated in more than 3,000 in both medical and mental health outpatient settings.[59-

61] There are 6 items assessing AUD and 6 items for DUD, all using a yes/no response format and a 2-week timeframe. The PDSQ is used for baseline and follow-up assessments of AUD, DUD, and depression. Because the PDSQ does not specify drug class (for example, it does not distinguish between cocaine vs. opioid use disorder) the CIDI, rather than the PDSQ, is used to measure DSM-5 OUD. The drawbacks to the PDSQ—namely, that it assesses DSM-IV rather than DSM-V SUDs, and is not specific to drug class—are counterbalanced in this study by the benefits of having a brief instrument that has been validated for self-administration.

11.5.5 Overdose Risk Behavior Questionnaire

Overdose risk behavior is assessed using a 9-item self-administered questionnaire that was developed by a group of opioid researchers based on knowledge of overdose behavioral risk factors, [62] and used in 3 prior studies to capture overdose risk behavior.[62-64] These questions measure the frequency, in the past 6 months, at which individuals used alone; used in a new place/environment; used other substances (alcohol, benzodiazepines, stimulants) within 2 hours of opioids; used more than one opioid; used more than the usual amount; and used inhaled or injected opioids. The total risk score is an aggregation of responses to the individual questions. The overdose risk behavior questionnaire is self-administered.

11.5.6 Non-Fatal Overdose Questionnaire

Non-fatal overdose is assessed using a single-item question developed and used in prior research.[65] The questionnaire is self-administered using the timeframe of the past 6 months.

11.5.7 Brief Pain Inventory Short Form (BPI)

The BPI is a self-administered questionnaire that measures the “sensory” dimension of pain (intensity, or severity) and the “reactive” dimension of pain (interference with daily function) experienced in the past 24 hours. The form asks a series of questions to measure the intensity of pain, and the rate at which pain interferes with daily activities, using a 0 to 10 scale. The BPI short form has been validated as a tool to assess the severity of pain and the impact pain has on an individual’s quality of life. Participants will complete the 4 items addressing pain symptoms (#3-6 of the short BPI instrument) and the 7 items on pain-related functioning (#9 A-G of the short BPI instrument).

11.5.8 Depression and Suicidality (PHQ-8 and PSS)

Assessment of depression symptoms and suicidality is accomplished with the Patient Health Questionnaire (PHQ-8) depression screening tool, and the Patient Safety Screener (PSS). The ninth item of the PHQ-9 is about suicidal ideation, which is queried separately in our study as part of the PSS. The PHQ-8 has been validated as a measure of depression, independent of the PHQ-9.[66] The PSS is a validated screening instrument that was used in the ED-SAFE study. It consists of one item about suicidal ideation in the past two weeks, followed by one item about lifetime suicide attempts, in a yes/no format. Individuals reporting a suicide attempt are asked when this last occurred. The PSS is administered by research staff for safety reasons, to allow for rapid assessment and response for patients with suicidality (following safety procedures specified in the site’s standard operating procedures).

11.5.9 PROMIS Anxiety Short Form

The PROMIS anxiety short form (8a) is an 8-item self-assessment of anxiety symptoms in the past 7 days.[67] The tool assesses the severity of symptoms on a Likert scale. The PROMIS anxiety short form has been validated in adults with multiple sclerosis, and found to perform similarly to more lengthy anxiety assessments.[68]

11.5.10 Health-Related Quality of Life (SF-12)

The Short Form 12 (SF-12) Measure is broadly used in clinical research and is part of the CTN DSC recommended assessment battery that measures overall functional health and well-being. The questionnaire begins by asking to rate one's overall health on a scale of 1 to 5, followed by two items on daily living activities. Additional questions address physical and emotional health as well as pain interference during the past 4 weeks. The SF-12 is a validated tool for measuring health-related quality of life.

11.5.11 Participant Reported ED Visits and Hospitalizations

Acute care admissions (hospital, emergency department) are a meaningful outcome for health systems and policymakers and will be measured using a self-administered questionnaire. Patient participants will report the number of ED visits and number of hospitalizations (detox admissions and non-detox admissions) in the past 6 months.

11.5.12 Chart Review

A structured chart review will be conducted by research staff to assess the following secondary outcome measures. Each measure is extracted for the period 12 months prior to the baseline visit, and 12 months after the baseline visit. Patient participants give consent for gathering this information when they enroll in the study.

- Prescription of opioid medications, including medication name, dose, frequency, and number of pills to be dispensed. This will be converted into MME by day (assuming maximum medication used) over the 12-month period.
- High-dose opioids (defined as >90 MME daily).
- Prescriptions for benzodiazepines, converted into standard medication (e.g., diazepam) equivalent dose, and converted into daily doses. It will also allow calculation of overlap of opioids and benzodiazepines.
- Prescription of naloxone kits: date of prescription.
- Monitoring of patient participants with opioid use: toxicology testing, diagnosis of OUD.
- Primary care visits and missed appointments at the study clinic.
- Number of visits to a study PCP randomized to the opposite treatment arm

11.5.13 Exit Survey on PCP-Delivered Opioid Counseling

Patient participants will complete a brief RC-administered exit survey at the baseline visit only if the patient had a PCP appointment integrated with their baseline visit. The exit survey asks patient participants about the substance use counseling elements they received from their PCP and is

based on a questionnaire that was used in a prior study *(Trial Registration ClinicalTrials.gov ID NCT02893514, Protocol ID DA040830, (McNeely, PI))* to assess delivery of drug use brief intervention by PCPs.

11.5.14 Marijuana Use Assessment

This survey assesses participants' recreational and medical cannabis/marijuana use frequency over the past 12 months, including reasons for use (e.g., to address medical/psychological concerns, to replace other substances or medications), method of administration, and perceived harm or benefit associated with use.

11.5.15 E-Cigarette and Vaping Assessment

This survey will determine how often in the previous six months a participant vapes, and if so, did the device contain either nicotine or marijuana/THC.

11.5.16 PROMIS Sleep 4a Assessment

Patient participants will complete this assessment (PROMIS Item Bank v1.0, Sleep Disturbance Short Form 4a) to provide information on sleep quality over the past seven days.

11.6 Measures of Readiness to Change

Readiness to change substance use behavior is frequently measured in behavioral intervention trials with patients who are not treatment-seeking. While studies have not shown consistent effects, readiness appears to be associated with higher consequences of substance use, while confidence to change is associated with future reductions in consumption.[69] Participants will complete two related items; one item asks about readiness, another asks about confidence to change opioid, other drug, and alcohol use behavior. These items are self-reported on a scale of 1-10, where 1 indicates lowest and 10 indicates highest readiness.

11.6.1 PROMIS Instrumental and Emotional Health Measures

Two PROMIS forms are selected to measure the social support domains of emotional and instrumental support that participants receive. The measure of instrumental support (PROMIS Item Bank v2.0, Instrumental Support Short Form 4a) is 4 items that ask about the availability of someone to help if the participant is confined to bed, needs to be taken to the doctor, is sick and needs assistance with daily chores, and running errands if needed. The emotional support instrument (PROMIS Item Bank v2.0, Emotional Support Short Form 4a) asks about the frequency with which the participant is available to listen to them when they need to talk, to confide in, to make them feel appreciated, and to talk with them when they have a bad day.

11.6.2 Addiction Treatment and Harm Reduction Services Utilization

A self-reported questionnaire will collect information on the number of weeks of participation in any addiction treatment program or in any harm reduction program, and number of weeks taking MOUD (buprenorphine, methadone, naltrexone). MOUD received in the study clinic is additionally assessed through chart review, as indicated above.

11.6.3 Patient Experience Questionnaire

A self-reported questionnaire will collect information from patient participants about their interactions with care providers in the past 3 months. Individuals assigned to the STOP intervention will complete all items of the questionnaire (pertaining to PCP, nurse care manager, and telephone health coach), while individuals assigned to EUC will complete only the PCP section. The questionnaire addresses the 'individual' level of influence in our conceptual model by assessing patient satisfaction and comfort with the patient-facing intervention components. For participants who report receipt of opioid counseling, they will complete additional items about how they perceived the counseling in relation to the reason they sought care, how helpful it was to them, what they learned, and if it made them think about changing their opioid use behavior. The questionnaire is administered with the quarterly assessments at months 3, 6, 9, and 12. Because the telephone health coaching intervention ends by month 6, the telephone health coach-specific items are not administered in the month 9 and month 12 assessments.

11.7 Fidelity Measures

Fidelity monitoring is discussed in Section 12. Only the fidelity assessment that is completed by study participants is presented here. The remaining fidelity assessments are completed by study staff (NCMs, telephone health coaches, research staff) or PCPs, and are discussed in the fidelity monitoring section.

11.7.1 Exit Survey on PCP-Delivered Opioid Counseling

For fidelity monitoring of the PCP brief advice, which can be provided at the baseline visit for patient participants who have an integrated PCP and baseline visit, patient participants will complete a RC-administered exit survey.

11.7.2 Assessment of Blinding

At the end of the 12-month study visit, or at the patient participants last study visit if they withdraw early, the RC/RA will ask patient participants what they considered to be the primary objective of the study and record the verbatim and categorical response. The response categories include: opioid study; drug/alcohol study; exercise study; weight loss study; healthy lifestyle study; other.

11.7.3 Qualitative Interviews

A designated interviewer(s), who is qualified and appropriately trained, will conduct qualitative interviews with up to 30 participating patients assigned to the STOP intervention to understand how they engaged with the NCM, health coach, and PCP. Approximately 6 patient participants will be interviewed at each site. A purposeful sampling approach will be used to select patient participants in the following categories: a) patient participants who utilized both the NCM and health coach; b) patient participants who utilized the NCM but not the health coach; c) patient participants who utilized the health coach but not the NCM; d) patients who received brief advice within the 10 business day window; and e) patients who did not receive brief advice within the 10 business day window. Interviews will be approximately 30-45 minutes in length, and will be audio

recorded. Individuals invited to participate in interviews will complete a separate informed consent for this activity, and will receive an additional incentive payment for their participation.

11.8 Clinical and Safety Assessments

The study is of a behavioral intervention embedded in primary care. Each of the research sites have established practices for managing medical and psychiatric emergencies, and the study staff will utilize these procedures. Patient participants' medical providers will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action. Pregnancy is an exclusion criterion for study enrollment.

11.8.1 Mental Health Follow-Up Assessment

This CRF/eCRF must be completed by the RC/RA if the patient participant endorses suicidal thoughts on the PSS at the 6-month and 12-month assessments to document that the appropriate actions were taken as guided by site-specific SOPs.

11.8.2 Death Form

This form will be used to capture patient participant deaths that occur during the study. This form will document when and where the death had occurred, the primary and secondary causes of death, the source for the cause of death, and any additional supplementary narrative on the circumstances surrounding the death of the patient participant. The RC/RA entering the form will also be instructed to upload any supporting documentation, such as an autopsy, death, or discharge note.

11.8.3 RA-recorded ED Visits and Hospitalizations

This form will be used to capture information regarding a participant's ED visit or hospitalization during the course of the study post baseline. The form will document the admission dates of ED visits or hospitalization, the dates that the RC/RA was notified of these visits, diagnoses, outcomes, and discharge dates. The RC/RA is expected to submit this form for every ED visit and hospitalization that they become aware of after the baseline visit.

11.9 Drug Use Measures

11.9.1 Urine Drug Screen

Urine drug screens are conducted at baseline and at the 6- and 12-month assessments. The drug screens conducted for the study are for verification of self-report, and results will not be shared with the clinical team. Urine samples may be collected on-site or off-site. For urine samples that are collected off-site they must be sent to the research site for testing. If research staff are not allowed on site due to COVID-19 restrictions, the NCM may conduct the urine drug screen testing or it may be skipped.

Study personnel will ship or give patient participants urine specimen cups labeled with study ID and prepaid packaging to ship back to the research site. All urine specimens are tested using an FDA-approved dip card following all the manufacturer's recommended procedures. Fentanyl dipsticks are not FDA cleared; therefore, results cannot be used for clinical care. Results can only be used to add to the data system to characterize a study population. The urine drug screen

includes the following drugs: opioids, oxycodone, fentanyl, barbiturates, benzodiazepines, cocaine, amphetamine, methamphetamine, marijuana, methadone, buprenorphine, phencyclidine (PCP) and ecstasy (MDMA).

11.10 Administrative Forms

Missed Visit and Visit Documentation Form: This form is designed to capture whether or not a visit occurred, reasons for any visit that is missed, and specific information regarding the details of a visit that is completed (e.g., where did the visit occur). This assessment will be completed directly in the electronic data capture system at every protocol-specific visit. Submission of this form indicating the visit did not occur will remove the requirement for all assessments scheduled for that visit. Active tracking and follow-up should be performed for all missed visits.

Monthly Survey Link Form: This form is used as needed in instances where the RC/RA needs to retrieve a Healthy Living Monthly survey link for a specific participant and time point, in the case a participant no longer has access to the survey link (e.g., participant deleted the text message and/or email they received to complete the monthly survey).

Protocol Deviation: This form should be entered into the electronic data capture system whenever a protocol deviation occurs. This form will document a description of the deviation, how it occurred, the corrective action taken to resolve the specific deviation, as well as a description of the plan implemented to prevent future occurrences of similar deviations.

11.11 Out-of-Window and Missed Assessments

Research staff are expected to make all reasonable efforts to obtain survey and UDS assessments from participants within the windows outlined in Tables 6 and 7 above. However, given that all study assessments can be collected remotely, research staff have limited control over whether and when participants complete assessments. Therefore, if research staff make reasonable and timely efforts to collect assessments within window, but participants choose to skip an assessment or complete it late, the study team would not consider this to be a deviation from the procedures outlined in this protocol.

12.0 TRAINING, SUPERVISION, AND FIDELITY MONITORING

12.1 Research Staff Training

Research staff will be trained as specified in a comprehensive Study Training Plan developed by the Lead Node, CCC, DSC, and Protocol Development team. Additional details and guidance for study procedures will be provided in a Manual of Procedures (MOP) and in local site SOPs. The Investigative Team is also responsible for the development of instructional material and delivery of the training.

CTN-0101 research staff training will be primarily conducted via webinar and/or telephone conferences. Additional details on training for the Primary Care Providers, Clinical Champions, Nurse Care Managers and Telephone Health Coaches can be found below. Required training for all study staff will include Human Subjects Protection (HSP) and Good Clinical Practice (GCP), as well as protocol-specific training as needed (e.g., assessments, study visits and procedures, safety and Safety Event reporting, data management and collection, and quality assurance). Research staff collecting and entering data in the Electronic Data Capture (EDC) system will complete training on electronic case report form (eCRF) data entry and data management and integrity. All study staff will be required to complete the study-specific training plan for their assigned study role as well as satisfy any training requirements per local institutions. Tracking of training completion for individual staff as prescribed for assigned study role(s) will be documented, endorsed by the site PI and LN, and audited by the CCC. As changes occur in the prescribed training, the Training Plan and training documentation tracking forms will be amended to reflect these adjustments.

The Lead Node is primarily responsible for development and delivery of study-specific training related to the study intervention(s) and procedures. The CCC is responsible for the development and delivery of non-intervention training, including regulatory and laboratory procedures, safety and Safety Event reporting, quality assurance and monitoring, etc. The DSC is responsible for training related to data management (DM), the EDC system, and good data management practices. Other parties will contribute as needed based on the subject matter and material to be covered. The various sub-teams will collaborate to deliver quality instructional material designed to prepare research staff to fully perform study procedures based on the assigned research roles and responsibilities.

12.2 Primary Care Provider Training

PCPs randomized into the STOP Intervention will attend remote trainings conducted online, via webinar, or in person. The Clinical Champion will play a leading role in training PCPs at their clinic and may provide additional coaching and support. Trainings will focus on the PCP role in delivering brief advice and collaborating with the Nurse Care Manager to counsel and manage the care of patient participants with subthreshold OUD. Training will include discussion and demonstration of common scenario(s) encountered by PCPs who are caring for patient participants with subthreshold OUD. PCPs will also be provided documentation guidance for entering opioid information and counseling into patient charts.

12.3 Clinical Champion Training

PCP clinical champions (approximately one per site) will be invited to a training led by members of the investigative team. The primary goal of clinical champion training is to prepare them to be a well-informed resource who can further educate and provide guidance to their PCP colleagues. The training will educate Clinical Champions about the study, including the roles of PCPs and all members of the research team. It will include content on delivering brief advice to patients with substance use, management and monitoring of patients receiving prescription opioids, identifying and assessing OUD, treatment of OUD, and overdose prevention. Additional remote trainings for clinical champions may be conducted to address areas of need that are identified by members of the research team, participants, or clinical staff throughout the study period.

12.4 Nurse Care Manager Training

The NCMs will undergo training initially and receive ongoing support. Training will emphasize the NCM role with patient participants who are using illicit opioids, as well as their role in the management of patient participants who are receiving prescription opioids from their PCP. The details are noted in Table 8 below.

12.4.1 Table 8: Outline of NCM Training

Initial Training
• Prior to live training, the NCMs will receive online training, including SCOPE of Pain (http://www.scopeofpain.org/) or a similar free continuing education activity on managing pain medications, as well as motivational interviewing such as SAMHSA-endorsed free on-line program https://attcnetwork.org/node/2892. They will be assigned readings on managing patients with opioid and other substance use, overdose prevention, non-pharmacologic pain modalities and pain management in primary care.
• All NCMs will be invited to a live training conducted either in-person or remotely. For example, the training may include the following activities: • 8 hours didactic on subthreshold OUD, overdose prevention and risk reduction, motivational interviewing, pain management treatments, the relationship between pain and opioid use, and identifying OUD. • 4-8 hours of interactive workshops on study protocol and potential scenarios, focused on strategies for engaging and motivating behavior change in patients with subthreshold OUD.
Ongoing Technical Assistance and Clinic Site Visits • Technical assistance will occur with co-investigators and nurse consultants o Approximately weekly phone calls with each site (together or separately depending on scheduling) for 6 months, then every other week until study end. • Local clinic site visit by a technical assistance team nurse or physician trainer early after start of the NCM with: o Any staff who work with intervention PCP o Admin/leadership meeting. o One on one with NCM, walk through details. o One on one with clinical champion and site PI.

12.5 Telephone Health Coach Training

Telephone health coaches will have an approximate 4-day in-person or virtual training in the content and procedures involved in the behavior change coaching, with special focus on building competence in MI and CBT techniques. Special emphasis will be paid to education about opioids and opioid use (including subthreshold OUD, OUD), assessing patient participants' readiness to change risky opioid use behaviors, and determining treatment foci (e.g., additional MI vs. CBT focused on risky opioid use vs. CBT focused on pain management). Telephone health coaches will be trained to refer patient participants to clinic and local community resources or to provide local information and referral hotlines if needed. In addition, they will be trained to assess patient participants for continued unhealthy opioid use or clinical worsening of symptoms that would result in initiation of enhanced (i.e., Step 2) coaching. Training activities will include didactic presentations, group discussions, and experiential learning through role play and use of practice patients. Following the training, telephone health coaches will conduct mock sessions with each other, which may be digitally audio recorded and coded for fidelity by the trainers. Health coaches who meet performance criteria will be cleared to conduct sessions with patient participants. Those who require additional training, practice, and supervision will continue to conduct mock sessions and have all recordings reviewed and coded by the trainers until cleared. In-person learning community sessions will be held every 2-4 weeks to debrief jointly, problem-solve challenging patient participants, and monitor and provide supervision on every patient participant.

All telephone health coaches will complete suicide assessment and triage training. Solicitations of patient participant discomfort and suicidal ideation will be made by telephone health coaches when indicated during telephone sessions.

12.6 Fidelity Monitoring

PCP brief advice: In the STOP arm, at the baseline visit or within 10 business days, PCP participants will be asked to complete an Intervention Checklist that indicates the content of their counseling and any referrals made. Patient participants will complete a post-baseline visit exit survey that asks them about the substance use counseling elements they may have received from their PCP. These instruments are based on tools that have been used in prior NIDA-funded studies *(Trial Registration ClinicalTrials.gov ID NCT02893514, Protocol ID DA040830, http://www.clinicaltrials.gov, (McNeely, PI); Trial Registration ClinicalTrials.gov ID NCT01942876, Protocol ID DESPR DA022445, http://www.clinicaltrials.gov (Gelberg, PI))* to assess delivery of drug use brief intervention by PCPs.

NCM: The NCM will document the delivery of intervention components on a fidelity checklist, and track interactions with patient participants, PCPs, and telephone health coaches (THCs). Monitoring may include:

- Number of interactions with PCP and route (in-person, phone, electronically).
- Number of interactions with THC.
- Number of new patient visits.
- Number of follow up patient participant visits.
- Number of contacts via phone or electronically, and whether contact was successful

- Duration and content area(s) covered in each patient session.

Health coaching: To facilitate fidelity monitoring, all health coaching sessions will be recorded by the research staff providing the coaching, with oral permission from participants during each call. Additionally, health coaches will track, for each patient participant, the number of contacts attempted, number of successful contacts, and the duration of each coaching session. They may also complete a checklist of content area(s) covered in each coaching session.

Given the content and the relatively brief course of coaching sessions, the focus of fidelity monitoring for adherence to the chosen therapeutic style will be on the use of motivational interviewing (MI) skills, rather than cognitive behavioral therapy (CBT). The primary source of the rating scale is the Motivational Interviewing Treatment Integrity (MITI) Scale 4.1. We will follow the strategy of Haddock and colleagues to integrate elements of CBT techniques into the fidelity monitoring.[70] Additionally, we will use a study-specific rating tool for the content of the sessions, based on the treatment manual, to ensure that the core domains/topics are covered during the session.

- Coders: The study team will include individuals responsible for coding sessions. The coders will be trained by the investigators. The coders will all code the same recordings until sufficient inter-rater agreement (>80%) is achieved.
- Frequency of Sessions Coded. For the first 3 months of intervention delivery, all sessions will be reviewed and MITI coded in real time. Coders will provide results of coding to the investigator responsible for supervising the telephone health coaching intervention, who can integrate them into 1:1 supervision. Once a level of consistency has been achieved for each telephone health coach, we will continue with bi-weekly in-person supervision but may only code a random 10% of the sessions for independent ratings of adherence to the intervention.
- Use of Coding for Improving Session Delivery. Individuals delivering the coaching, along with members of the investigator team will participate in weekly learning community calls to debrief on and jointly problem solve challenging cases, and monitor/provide supervision on every intervention case.

13.0 CONCOMITANT THERAPY/INTERVENTION

13.1 General

Patients must meet the inclusion and exclusion criteria at the time of enrollment, including the requirements that they are not currently taking medication for treatment of opioid use disorder or enrolled in an opioid treatment program. Participation in the trial does not prohibit initiating any medications or treatments.

14.0 STATISTICAL DESIGN AND ANALYSES

14.1 General Design

14.1.1 Study Hypothesis

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 includes 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.

14.1.2 Secondary Objectives

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

The patient-level secondary objective (Aim 2) is to examine the impact of STOP on the important patient participant outcomes of moderate-severe OUD, overdose risk behavior and overdose events, alcohol and other drug use, health-related quality of life, mental health, pain symptoms and functioning, sleep, and acute health care utilization. We hypothesize that 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. Lower prescription opioid misuse behaviors, among participants receiving prescribed opioids.

H2.8 Lower incidence of moderate-severe OUD.

H2.9 Lower rates of non-opioid drug use disorder and 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 prescribing practices and monitoring of patient participants with subthreshold OUD. 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).

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: toxicology testing, diagnosis of OUD, and higher visit frequency.

14.1.3 Exploratory Objectives

The study has the following 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 TOPCARE study, 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 counseling to support patients 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 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. Data on deaths of study participants will be obtained from the EHR and from other

administrative data kept by the health system or government entities. 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) may utilize these services. Through the involvement of 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.

14.2 Primary and Secondary Outcomes (Endpoints)

14.2.1 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 the Addiction Severity Index and COMM.[40, 41] Collecting data on self-reported days of use in the past 30 days is aligned with timeline follow-back methodology, and was used in the QUIT trial.[21] 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 frequently or at higher doses than instructed on the prescription (e.g., taking 2 tablets when the prescription indicates a dose of 1 tablet), or taking pharmaceutical opioids that were not prescribed to them. Prescribed 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).

14.2.2 Secondary Outcome Measure(s)

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. H1.2. Days of risky opioid 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 12 months.
    b. 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.
    c. 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.
    d. 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.
    e. 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.
    f. 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
    g. 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.

h. H2.7. Prescription opioid misuse behaviors, among participants receiving prescribed opioids:

i. Days of taking prescribed opioids for symptoms other than for pain, or for 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.

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

j. 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)

c. Exploratory Objective 3. Overdose death is expected to be a rare event in this population 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. 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 will be for the period beginning 12 months prior to start of the intervention, through 12 months after the last patient participant is enrolled.

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

Other outcome measures.

The following additional measures will be collected to assess exploratory outcomes, characterize domains from our conceptual model, 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).

1. Demographic characteristics and insurance status.
2. 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.

3. Social support will be assessed using the PROMIS instrumental and emotional health short forms.
4. Patient engagement in primary care (Exploratory Objective 1): Number and frequency of kept appointments and missed appointments for primary care visits.
5. 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.
6. PCP knowledge and attitudes regarding substance use, subthreshold OUD, and opioid management, assessed at baseline and at the end of the intervention period.
7. TLFB measure of substance use in the past 90 days. 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.
8. 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.

14.3 Recruitment

The study will enroll approximately 100 PCPs from a total of 5 sites. We estimate, however, that 30-40% of the enrolled PCPs will have no participating patients, (because we may not identify any eligible patients within their panel), leaving approximately 60 PCPs who will have patients that will enroll into the study.

Enrolled patients with risky opioid use fall into two groups: (1) those using prescribed opioids and (2) those in the general population. We expect that approximately 15-20% of enrolled patients will be those receiving prescribed opioids. Based on urine toxicology data collected in the TOPCARE study, we anticipate that approximately 30% of patients who are receiving prescribed opioids will have subthreshold opioid use disorder, so we expect that for a PCP with 8 long-term opioid patients, 1-2 of these will be eligible. (PCPs with more than 8 long-term opioid patients are likely to have more eligible patients in this category, but we emphasize the lower bound in order to conservatively estimate screening numbers). In addition, we expect that at least 1% of adult primary care patients in the general population will screen positive for illicit opioid use. This is a conservative estimate, as our prior studies found that between 3.9% and 6.6% of adult primary care patients screened positive for illicit opioid use.[12, 21] Therefore, screening approximately 460 patients for a PCP should yield approximately 5 patients engaged in illicit use. Therefore, each PCP will have approximately 6-7 eligible patients in total. Assuming that 75% of eligible patients are enrolled, we expect each PCP to have approximately 5 patients participating in the study.

This results in a total of 300 patients among the 60 PCPs who have patients participating in the study, although the study can achieve patient recruitment in a variety of ways, e.g., 60 PCPs may have 5 patients enrolled each; OR 50 PCPs may have 4 patients, 5 PCPs may have 6 patients, and 7 PCPs may have 10 patients.

As described in section 2.1.2, original recruitment targets were based on 5 sites recruiting for the duration of the study. In October 2021, one site stopped recruiting, leaving 4 sites to continue. The sample of approximately 300 patients is thus comprised of recruitment from 5 sites for the initial 6 months, and from 4 sites for the remainder of the study.

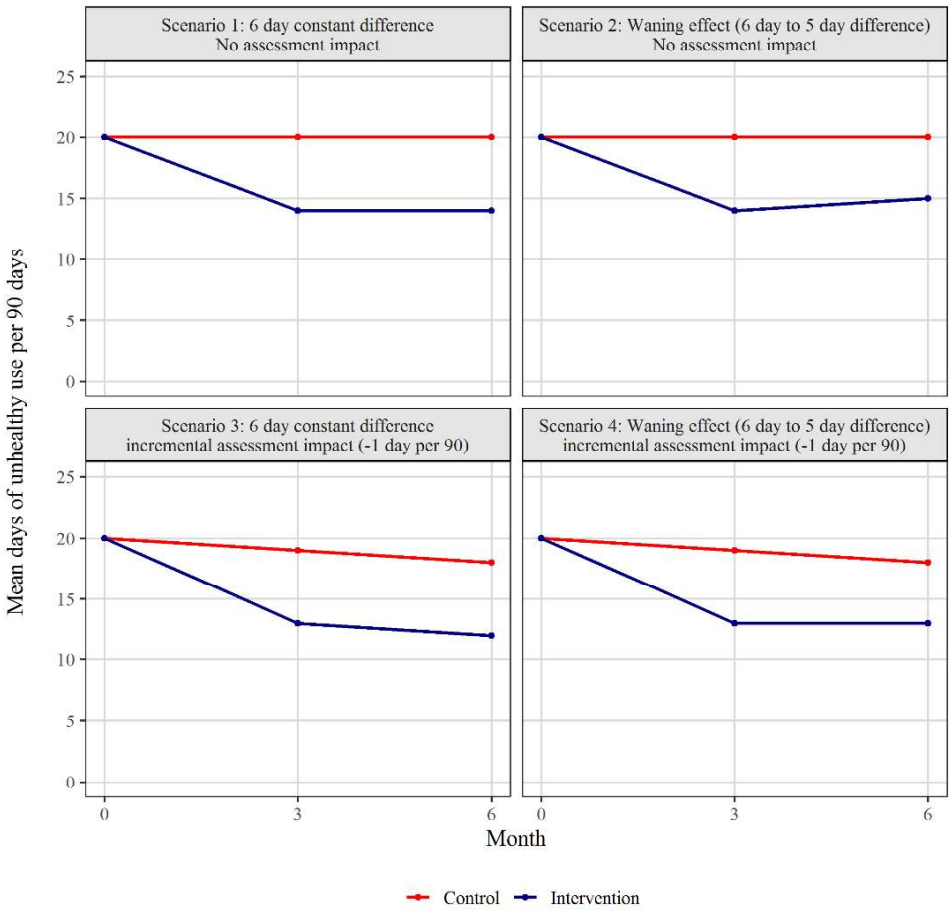
14.4 Randomization and Factors for Stratification

This is a cluster-randomized trial in which PCPs are the clusters. PCPs will be randomized, stratified by site, in a 1:1 ratio to either the intervention or control condition.

14.5 Rationale for Sample Size and Statistical 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.

14.5.1 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 9 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.

14.5.2 Table 9: 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

Condi-tion	No. of PCPs	No. of pts per PCP	Scenario	Group means (3-mo, 6-mo)		Power
				Control	Treatment	
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.

14.5.3 Projected Number of Sites

Five sites have enrolled patient participants. Starting October 2021, four sites are still actively recruiting patients.

14.5.4 Projected Number of Participants per Site

This is a cluster-randomized trial in which PCPs are the clusters. The study aims to enroll approximately 100 PCPs. We estimate, however, that 30-40% of the enrolled PCPs will have no participating patients because we will not identify any eligible patients in their panel, leaving approximately 60 PCPs who will have patients that will enroll into the study. Each of these PCPs is expected to have approximately 5 patient participants. This results in a total of approximately 300 patient participants enrolled in the study.

As of November 2021, there are 85 patient participants enrolled, requiring that another 215 patient participants need to be enrolled during the remaining 12 months of enrollment. Original recruitment targets were based on 5 sites recruiting for the duration of the study. In October 2021, one site stopped recruiting, leaving 4 sites to continue. The sample of approximately 300 patients is thus comprised of recruitment from 5 sites for the initial 6 months, and from 4 sites for the remainder of the study (12 months), with an enrollment target of on average 15-20 patients per

month across the 4 sites. For the 4 sites recruiting until the end of the study, each site is anticipated to enroll on average 4-5 patients per month.

14.6 Statistical Methods for Primary and Secondary Outcomes

The primary outcome is the number of days of risky opioid use within the first 180 days following the baseline assessment. A mixed effects negative binomial model with a log link will be fit to estimate the difference in means between treatment and control groups. The model will include random PCP intercepts to account for within-PCP correlation of participant response values, fixed site effects to account for within-site correlation of responses, a fixed treatment 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. Letting Y_{jk} denote the response variable of a participant in site j with PCP k, *treatment* denote a binary treatment indicator variable, and *baseline* denote the baseline value, the formula for the log-transformed expectation of Y_{jk} is below:

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

where α_j is the fixed effect for site *j* and γ_k is normally distributed with mean zero and standard deviation σ_γ. 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. If 2 or more PCPs are randomized as a single cluster because they share patients regularly, they will be analyzed as a single cluster.

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.

Example R code for the primary analysis is below:

```
library(lme4)

mod = glmer.nb(daysin180 ~ rx + baseline + (1|PCP) + factor(site), data = dat)
```

The primary analysis will be performed on the Intention-to-Treat (ITT) Population, analyzing participants according to their 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. See Section 14.10, Missing Data, for further details. A secondary analysis will be performed on the Per Protocol (PP) population. This population will exclude participants who had appointments with PCPs in the opposite treatment arm. A secondary analysis will adjust for individual-level covariates which may be associated with the response, such as demographic variables, baseline measures of risk behaviors, substance use, presence of alcohol or drug use disorder, pain ratings, mental health symptoms or conditions, and health-related quality of life. Details regarding selection of covariates for inclusion and potential transformations will be specified in the Statistical Analysis Plan (SAP).

A secondary analysis will fit the same model to the 180-day outcome measured at the 12-month timepoint in order to assess durability. Further secondary analyses will explore temporal patterns of number of days of risky opioid use. 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) secondary outcome measures will

assess early intervention effects. The measures at 9 and 12 months will assess the durability of intervention effects (which may be maintained, increased, or decreased) over time.

Time trends of the mean number of days of use per 90 days will be visualized over the course of the year by treatment group with 95% confidence intervals. In addition, a mixed effects negative binomial model will be fit including treatment by time interactions for each timepoint. The model will include participant random intercepts to account for correlation in responses arising from multiple observations for each participant. Further details, including specification of the distributions of the random terms and possible inclusion of participant random slopes, will be specified in the SAP.

As month-to-month variability and temporal trends in the response are not known, this time trend analysis will be repeated for monthly observations of the 30-day sum of unhealthy days in order to further understand and describe temporal patterns.

A secondary aim is to evaluate the impact of the STOP intervention on days of alcohol and drug use that increases risk of overdose. For this aim, three variables will be analyzed separately: number of days of binge alcohol use, number of days of benzodiazepine use, and number of days of stimulant use. The analyses will be executed in the same way as the above analyses for days of risky opioid use. Time trend analyses will be executed as described above. Analogous analyses will be performed for another secondary aim, which is to assess impact of STOP on the number of days of marijuana and other drug use (also analyzed separately as two distinct variables), and on the number of days of taking prescribed opioids for symptoms other than for pain and the number of days of taking pain medication belonging to someone else.

Analyses for several Aim 2 secondary outcomes are outlined below. In general, mixed effects regression models with treatment by time interactions (analogous to those described above for the primary outcome) or generalized linear models with generalized estimating equations (GEE) to account for correlation of responses, will be fit. Further details for these models, including distributional assumptions and covariance structure, will be specified in the SAP.

- The incidence of moderate to severe OUD (defined as a score of at least 4 on the CIDI) within 12 months of follow-up will be compared between treatment groups and may be compared for shorter time intervals.
- 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) will be compared between groups at 6 and 12 months.
- 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 with regression models.
- 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.

- Changes in pain-related symptoms and functioning from baseline as measured by the BPI (which calculates a numeric score) will be compared between treatment groups. 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 between the effect of STOP on the change in pain-related symptoms for participants with opioid prescriptions at baseline to the effect for those who were enrolled solely due to illicit use.
- Symptoms of depression, suicidality, anxiety, and poor sleep 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), which provide numeric measures. Mean values will be compared between treatment groups.
- Mean values for health-related quality of life scores and COMM scores will be compared between groups.

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 groups 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.

14.7 Significance Testing

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.

14.8 Interim Analysis

No interim analyses are planned.

14.9 Exploratory Analysis

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 groups. Proportions of fatal overdose deaths will be presented by treatment group 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.

14.10 Missing Data and Dropouts

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:* participants may withdraw early from the study and miss all subsequent monthly measurements.
- *Intermittent missingness:* participants may miss one or more monthly surveys while remaining enrolled in the study.

It is anticipated that up to 20% of participants may be missing data for the primary endpoint due to dropout and/or nonresponse. It is possible that participants who drop out will have higher use after their dropout date than those who remain in the study. For example, it is possible 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 participants. In this case it is possible that a complete case analysis could overestimate the treatment effect if there is a high level of missing data (and if control dropouts do not have an analogous increase). Multiple imputation will be performed for the primary analysis to account for missingness of the primary outcome variable. A repeated measures model with treatment by time interactions will be created for the imputation in order to take full advantage of information from partial reports by participants with intermittent missingness. Information on days of risky use assessed by TLFB will be included in the imputation model. Further details of the imputation models will be specified in the SAP. If multiple imputation is performed, a complete-case analysis will be performed as a secondary analysis. In either case, sensitivity analyses will be performed to assess robustness of the treatment effect estimate to different patterns of responses for the missing values.

14.11 Demographic and Baseline Characteristics

Baseline demographic variables (including sex and race/ethnicity) and all covariates included as potential confounders in the adjusted model will be summarized for participants enrolled and randomized. Descriptive summaries, such as mean, median, standard deviation, minimum, maximum, and quartiles of the distribution of continuous baseline variables will be presented. Categorical variables will be summarized in terms of frequencies and percentages. Subgroup analyses by sex and minority status will be performed.

14.12 Safety Analysis

All Safety Events will be presented as: (1) the number and proportion of participants experiencing at least one incidence of each event overall and by intervention group; and (2) a table displaying the total number of each event overall and by intervention group. Safety Events that are associated with participant death will be summarized by body system and preferred term using MedDRA codes (per The Medical Dictionary for Regulatory Activities). Listings of death events will be sorted by system organ class (SOC) and preferred term (PT). Concomitant medications of interest will be coded using the World Health Organization Drug Dictionaries (WHO DD) and presented by preferred drug name and WHO Anatomical Therapeutic Chemical (ATC) classification analogous to Safety Event reporting.

15.0 REGULATORY COMPLIANCE, REPORTING AND MONITORING

15.1 Statement of Compliance

This trial will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Protection of Human Subjects described in the International Council for Harmonisation Good Clinical Practice (GCP) Guidelines, applicable United States (U.S.) Code of Federal Regulations (CFR), the NIDA Terms and Conditions of Award, and all other applicable state, local, and federal regulatory requirements. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. An Operations Manual will be provided as a reference guide and study quality assurance tool.

15.2 Institutional Review Board Approval

The Biomedical Research Alliance of New York (BRANY) will be the IRB of record for the protocol and will provide study oversight in accordance with 45 CFR 46. Participating institutions will agree to rely on BRANY and will enter into reliance/authorization agreements for Protocol CTN-0101. BRANY will follow written procedures for reporting its findings and actions to appropriate officials at each participating institution.

Prior to initiating the study, participating site investigators will obtain written IRB approval from BRANY to conduct the study at their respective site, which will include approval of the study protocol. If changes to the study protocol become necessary, protocol amendments will be submitted in writing by the Lead Node for IRB approval prior to implementation. In addition, the IRB will approve all consent forms, recruitment materials, any materials given to the participant, and any changes made to these documents throughout study implementation. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. For changes to the consent form, a decision will be made regarding whether previously consented participants need to be re-consented. IRB continuing review will be performed annually, or at a greater frequency contingent upon the complexity and risk of the study. Each site principal investigator (PI) is responsible for maintaining copies of all current IRB approval notices, IRB-approved consent documents, and approval for all protocol modifications. These materials must be received by the Lead investigators prior to the initiation of research activities at the site and must be available at any time for audit. Unanticipated problems involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures.

15.3 Informed Consent

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. Informed consent continues throughout the individual's study participation.

The informed consent forms for the pilot participants, provider participants, and patient participants will include all of the required elements of informed consent and may contain additional relevant consent elements and NIDA CCTN specific additional elements. Each study

site must have the study informed consent forms approved by the Single IRB (sIRB). Prior to initial submission to the IRB and with each subsequent consent revision, the consent form(s) must be sent to the Clinical Coordinating Center (CCC) and the Lead Node (LN) to confirm that each consent form contains the required elements of informed consent as delineated in 45 CFR 46.116(b), as well as pertinent additional elements detailed in 45 CFR 46.116(c) and any applicable CCTN requirements. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures, except where documentation of informed consent is waived. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with all applicable IRB and institutional policies and that is accessible to the study monitors. Every study participant must be given a copy of the signed consent form.

Electronic consent (eConsent) will be obtained in accordance with IRB and institutional policies, including 21 CFR Part 11 compliance, as applicable. All signed eConsent forms will be saved as a PDF on a secure sever. Site staff will download the completed and electronically signed eConsent PDF and save it in the electronic patient participant PHI file located in the site's secure server.

During the informed consent process, research staff will explain the study to the potential participant and provide the potential participant with a copy of the consent form to read and keep for reference. All participants will receive a verbal explanation in English of the purposes, procedures, and potential risks of the study and their rights as research participants. Extensive discussion of risks and possible benefits will be provided to the participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family and close friends or think about it prior to agreeing to participate. If the participant is interested in participating in the study, a qualified staff member will review each section of the IRB-approved informed consent form in detail and answer any questions the participant may pose. The participant will consent by signing and dating the consent document. The person obtaining consent and a witness, if required by the IRB of record, will also sign and date the consent document. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Staff members delegated by the PI to obtain informed consent must be listed on the Delegation of Responsibility and Staff Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate GCP and HSP training, as mandated by NIDA standard operating procedures.

The informed consent form(s) must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect participants' participation in the trial. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participant will be informed that their participation is voluntary, and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

15.4 Quality Assurance Monitoring

In accordance with federal regulations, the study sponsor is responsible for ensuring proper monitoring of an investigation and ensuring that the investigation is conducted in accordance with the protocol. Qualified monitors will oversee aspects of site conformity to make certain the site staff is operating within the confines of the protocol, and in accordance with GCP. This includes but is not limited to protocol compliance, documentation auditing, and ensuring the informed consent process is being correctly followed and documented. Non-conformity with protocol and federal regulations will be reported as a protocol deviation and submitted to the study sponsor and IRB of record (as applicable) for further review.

15.5 Participant and Data Confidentiality

Participant confidentiality and privacy are strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency, and will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency. All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as denoted in Section 15.11, Records Retention and Requirements.

By signing the protocol signature page, the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB/Privacy Board, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

15.5.1 Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see https://humansubjects.nih.gov/coc/index). This protects participants from disclosure of sensitive

information (e.g., drug use). The CoC allows the investigator and others who have access to research records to permanently refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level, excepting certain circumstances.

By protecting researchers and institutions from being compelled to disclose information that would identify research participants, the Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

15.5.2 Health Insurance Portability Accountability Act (HIPAA)

Study sites will be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with the sIRB or Privacy Boards of record and obtaining the appropriate approvals to be in regulatory compliance. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

15.6 Investigator Assurances

Each site must file (or have previously filed) a Federalwide Assurance (FWA) with the HHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

15.6.1 Financial Disclosure/Conflict of Interest

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will confirm to the sponsor annually that they have met their institutional financial disclosure requirements.

15.7 Clinical Monitoring

Investigators will host periodic visits by NIDA contract monitors who will examine whether study procedures are conducted appropriately, and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, CRFs, informed consent forms and corresponding source documents for each participant. Monitors will have the opportunity and ability to review any study-associated document or file.

NIDA-contracted monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the sIRB. Areas of particular concern will be participant informed consent

forms, protocol adherence, reported Safety Events and corresponding assessments, and principal investigator oversight and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the lead investigator and NIDA CCTN.

Qualified node personnel (Node QA monitors) or other designated party(ies) will provide site management for each site during the trial. Node QA staff or other designated party(ies) will audit source documentation, including informed consent forms and HIPAA forms. This will take place as specified by the local protocol team, node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node QA personnel will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately. If the node personnel's review of study documentation indicates that additional training of site study personnel is needed, node QA personnel will undertake or arrange for that training. Details of the contract, node QA and data monitoring are found in the study QA monitoring plan.

15.8 Inclusion of Women and Minorities

The study sites should aim and take steps to enroll a diverse study population. Based on prior studies in primary care, we anticipate that at least one-third of participants will be female. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings.

15.9 Prisoner Certification

As per 45 CFR 46 Subpart C, there are additional protections pertaining to prisoners as study participants. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. In order to meet these additional protections, the study team will obtain certification from the Office for Human Research Protections (OHRP) to follow-up with participants who become prisoners during the course of the study, as necessary.

If a participant in the study becomes incarcerated or otherwise meets the 45 CFR 46 Part C definition of a prisoner during the course of the study, and the relevant research proposal was not reviewed and approved by the IRB in accordance with the requirements for research involving prisoners under Subpart C of 45 CFR 46, the investigator must promptly notify the IRB. All research interactions and interventions with, and obtaining identifiable private information about, the participant must be suspended immediately. The lone exception to this regulation is if the investigator asserts that it is in the best interests of the prisoner-participant to remain in the study. The investigator must promptly notify the IRB of this occurrence.

15.10 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for

regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

15.11 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, audio and video recordings, and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with sIRB, state and federal requirements, whichever is longest. The sponsor and Lead Investigator must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of research records.

15.12 Reporting to Sponsor

The site principal investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Safety reporting will occur as previously described. At the completion of the trial, the Lead Investigator will provide a final report to the Sponsor.

15.13 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to good clinical research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the National Lead Study Team; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as the Department of Health and Human Services (HHS), the Office for Human Research Protection (OHRP) and the Institutional Review Board of record may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

15.14 Study Documentation

Each participating site will maintain appropriate study documentation (including medical and research records) for this trial, in compliance with ICH E6(R2) and regulatory and institutional requirements for the protection of confidentiality of participants. Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, signed protocol and amendments, Institutional Review Board correspondence and approved consent forms, and signed participant consent forms. As part of participating in a NIDA-sponsored study, each site will permit authorized representatives from NIDA and regulatory agencies to examine (and when permitted by law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source

document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

15.15 Protocol Deviations

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Lead Node and the CCC with overall approval by the IRB of record as needed. All protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial.

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Deviation CRF. The CCC, DSC and the Lead Investigator must be contacted immediately if an unqualified or ineligible participant is randomized into the study.

Additionally, each site is responsible for reviewing the sIRB of record's definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

15.16 Safety Monitoring

Because this is a minimal risk study with no pharmacological intervention, causally related Adverse and Serious Adverse events are not anticipated for this study.

Safety reporting will be limited to reporting the following Safety Events: Emergency Department (ED) visits, hospitalizations, overdose events, suicidal ideation, and deaths. Any Safety Event that occurs will be recorded on a designated form through the Advantage eClinical data system. As there is no medication intervention, pregnancy will not be followed within the context of this study.

Each of the sites has established practices for managing medical and psychiatric emergencies including Suicidality, and the study staff will continue to utilize these procedures. Treatment providers at each site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

15.16.1 Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment). Reports will be generated and presented for Data and Safety Monitoring Board (DSMB) meetings at a frequency requested by the DSMB, but at least annually.

15.16.2 Safety Monitor/Medical Monitor

The CCC Safety Monitor/Medical Monitor is responsible for reviewing all Safety Events reported. Where further information is needed, the Safety Monitor/Medical Monitor will discuss the Safety Event with the site. Reviews of Safety Events will be conducted in the Advantage eClinical data system and will be a part of the safety database. All Safety Events are reviewed on a regular basis to observe trends or unusual events.

The CCC Safety Monitor/Medical Monitor will in turn report Safety Events to the sponsor and regulatory authorities if the event meets the definition of an expedited event. Reports will be generated and presented for Data Safety Monitoring Board (DSMB) meetings.

15.16.3 Adverse Events (AEs)

For the purposes of this protocol, the collection and reporting of Adverse Events is not required in the data system.

16.0 DATA MANAGEMENT

16.1 Design and Development

This protocol will utilize a centralized Data and Statistics Center (DSC). The DSC will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. Advantage eClinical and Qualtrics^{XM}, web-based distributed data entry systems, will be implemented. These systems will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

16.2 Site Responsibilities

The data management responsibilities of each individual site will be specified by the DSC and outlined in the Advantage eClinical User's Guide and CRF Manual.

16.3 Data Center Responsibilities

The DSC will 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide final guided Case Report Forms (CRFs) and electronic CRFs (eCRFs) for the collection of data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for use of Advantage eClinical and for completion of CRFs/eCRFs, 5) conduct ongoing data validation and cleaning activities on study data from all participating sites, 6) perform data validation and cleaning activities prior to any interim analyses and prior to the final study database lock.

16.4 Data Collection

Data will be collected at the study sites on source documents and entered by the site into eCRFs in Advantage eClinical or will be collected via direct entry into the eCRF. In the event that Advantage eClinical is not available, the DSC will provide the sites with a set of CRF paper source documents and completion instructions. Data entry into Advantage eClinical should be completed according to the instructions provided and project specific training and guidelines established by the DSC. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant. Selected eCRFs may also require the investigator's electronic signature. In some situations, data collected on source document will not be entered into Advantage eClinical, but when it is entered, it will follow the guidelines stated above.

16.5 Data Editing

Data will be entered into the DSC automated data acquisition and management system (Advantage eClinical) in accordance with the Advantage eClinical User's Guide. Only authorized individuals shall have access to eCRFs.

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in Advantage eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies

within eCRFs and between eCRFs and post data clarification requests or queries in Advantage eClinical on a scheduled basis. Sites will resolve data inconsistencies and errors and enter all corrections and changes into Advantage eClinical.

The CCC will conduct regular on-site and monitoring visits, during which audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on items such as recruitment, availability of primary outcome, treatment exposure, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site staff, the local node staff, the lead node, the coordinating centers, NIDA CCTN and NIDA to monitor study progress overall and at each individual participating site.

16.6 Data Transfer/Lock

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DSC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DSC staff will be secured and password protected.

The DSC will conduct final data cleaning activities and "lock" the study database from further modification. The final raw analysis datasets will be transferred to the Lead Investigator or designee and to NIDA, as requested, for storage and archive. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated party for storage and archiving. These datasets may be posted on the NIDA Data Share website.

16.7 Data Training

The training plan for site staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of Advantage eClinical.

16.8 Data Quality Assurance

To address the issue of data entry quality, the DSC will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

17.0 PUBLIC ACCESS AND DATA SHARING PLAN

This study will comply with the NIH Data Sharing Policy and Implementation Guidance (https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm) and (for HEAL-funded studies) the HEAL Public Access and Data Sharing Policy (https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/research/heal-public-access-data-sharing-policy). Investigators will also register and report results of the trial in ClinicalTrials.gov, consistent with the requirements of the Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration (https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm).

Primary data for this study will be available to the public in the NIDA data repository, per NIDA CTN policy. For more details on data sharing please visit https://datashare.nida.nih.gov/.

The primary outcome(s) publication will be included along with study underlying primary data in the data share repository, and it will also be deposited in PubMed Central http://www.pubmedcentral.nih.gov/ per NIH Policy (http://publicaccess.nih.gov/).

The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN.

18.0 PROTOCOL SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE (CCTN SCIENTIFIC OFFICER OR DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 8.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (DHHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

Node Affiliation _____

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20.0 APPENDIX A: DATA AND SAFETY MONITORING PLAN

1.0 BRIEF STUDY OVERVIEW

The Subthreshold Opioid Use Disorder Prevention (STOP) trial is a cluster-randomized clinical trial that examines the efficacy of a primary care intervention to reduce opioid use and overdose risk, and prevent progression to OUD, in adults with risky opioid use. STOP is a collaborative care model consisting of:

1) A practice-embedded nurse care manager 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 that may be delivered to patient participants by their PCP and/or a video doctor, and
3) Coaching of patient participants by health coaches and mental health providers to motivate and support behavior change.

The STOP trial will be conducted in 5 primary care practices, with approximately 100 PCPs and 300 adult primary care patients and will test the efficacy of STOP versus enhanced usual care (EUC). Patient participants with providers assigned to the intervention condition will receive the full STOP intervention, while those with providers assigned to EUC will receive printed educational materials on the health risks of opioid use, including overdose.

The primary objective (Aim 1) is to determine the efficacy of the STOP collaborative care intervention, in comparison to EUC, for reducing unhealthy opioid use in adult primary care patients. The primary hypothesis is that patient participants with primary care providers assigned to the STOP intervention will have fewer days of unhealthy opioid use, measured at 6 months (primary outcome), and at 3, 9, and 12 months (secondary outcome), in comparison to patient participants with primary care providers assigned to EUC.

The patient-level secondary objective (Aim 2) is to examine the impact of STOP on patient outcomes of progression to moderate-severe OUD, overdose risk behavior and overdose events, alcohol and other drug use, pain-related disability, health-related quality of life, sleep and mental health.

The provider-level secondary objective (Aim 3) is to characterize the impact of STOP on primary care provider behaviors, including prescribing practices and monitoring of patients with unhealthy opioid use.

2.0 OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. Site Principal Investigator

Each participating site's Principal Investigator (PI) is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

B. CCC Safety Monitor/Medical Monitor

The NIDA CTN Clinical Coordinating Center's (CCC) Safety Monitor/Medical Monitor or designee is responsible for reviewing all reported Safety Events. The CCC Safety Monitor/Medical Monitor is alerted via email each time a death-related Safety Event is reported in the EDC. All death-related Safety Events will be reviewed at the time they are reported in the EDC. All other Safety Events will be reported to and reviewed by the CCC Safety Monitor/Medical Monitor on a weekly basis to observe for trends or unusual events. The Safety Monitor/Medical Monitor or designee will also indicate concurrence or not with the details of Safety Event reports provided by the site PI. Where further information is needed, the Safety Monitor/Medical Monitor or designee will discuss the event with the site staff. Reviews of Safety Events by the CCC Safety Monitor/Medical Monitor or designee will be documented in study-specific safety files and will be a part of the safety database.

C. Data and Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. Reports will be generated and presented for Data and Safety Monitoring Board (DSMB) meetings. The DSMB will receive Safety Events at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of Safety Events. The DSMB will make recommendations to NIDA CCTN as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific site) should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment).

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on DSMB recommendations, in writing to the study Lead Investigator. This communication summarizing study safety information will be submitted to participating IRBs.

D. Quality Assurance (QA) Monitoring

The monitoring of the study site(s) will be conducted on a regular basis using a combination of NIDA CCTN CCC monitors and the local Node QA Monitors. Investigators will host periodic visits for the monitors. The purpose of these visits is to assess compliance with the protocol, GCP requirements, and other applicable regulatory requirements, as well as to document the integrity of the trial progress. The investigative site will provide direct access to all trial related sites (e.g., research office), source data/documentation, and reports for the purpose of monitoring and auditing by the monitors, as well as for inspection by local and regulatory authorities. Areas of particular concern will be the review of inclusion/exclusion criteria, participant Informed Consent Forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, and Principal Investigator supervision and involvement in the trial. The monitors will interact with the site staff to identify issues and re-train the site as needed to enhance research quality.

Site Visit Reports will be prepared by the NIDA CCC monitors following each site visit. These reports will be sent to the site Principal Investigator, the study Lead Investigator, NIDA CCTN, and other parties as designated.

Local Node QA site visit reports will be prepared following each site visit, as applicable. These reports are sent to those entities required of them by the Lead Investigative team, generally including the Lead Investigator, Lead Project Manager, site Principal Investigator, Node PI and a CCC representative, usually the protocol specialist for the study.

E. Management of Risks to Participants

Confidentiality

Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs, and secure storage of any documents that have participant identifiers on site, as well as secure computing procedures for entering and transferring electronic data. The documents or logs linking the study codes with the study participant on site will be kept locked/securely stored separately from the study files and the medical records. No identifying information will be disclosed in reports, publications or presentations.

Information That Meets Reporting Requirements

The consent form will specifically state the types of information that are required for reporting and that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

Participant Protection

The site's study clinician or other designated and qualified individual will evaluate all pertinent screening and baseline assessments prior to participant randomization to ensure that the participant is eligible and safe to enter the study.

Pregnancy

As there is no medication intervention, pregnancy will not be followed within the context of this study.

3.0 DATA MANAGEMENT PROCEDURES

This protocol will utilize a centralized Data and Statistics Center (DSC). Advantage eClinical, a web-based distributed data entry model will be implemented. This electronic data capture system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld.

4.0 DATA AND STATISTICS CENTER RESPONSIBILITIES

The DSC will: 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide final Case Report Forms (CRFs) and electronic Case Report Forms (eCRFs) for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for the use of Advantage eClinical and for the completion of CRFs/eCRFs, 5) conduct data validations and cleaning activities on study data collected from all participating sites, and 6) perform data cleaning activities prior to the final study database lock.

5.0 DATA COLLECTION AND ENTRY

Data will be collected at the study sites on source documents and entered by the site into eCRFs in Advantage eClinical, or will be collected via direct entry into the eCRF. In the event that Advantage eClinical is not available, the DSC will provide the sites with CRF paper source documents and completion instructions. Data entry into Advantage eClinical should be completed in accordance with the instructions provided during protocol-specific training and guidelines established by the DSC. Data entry into the eCRFs is performed by authorized individuals. Selected source documents and eCRFs may also require the investigator's signature (wet or electronic). In some situations, data collected on source documents will not be entered into Advantage eClinical, but when it is entered, it will follow the guidelines stated above.

The Principal Investigator at the site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the Principal Investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

6.0 DATA MONITORING, CLEANING AND EDITING

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and missing forms are available to sites at all times in Advantage eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post queries in Advantage eClinical on a scheduled basis. Sites will resolve data queries by entering all corrections and changes directly into Advantage eClinical or verifying the data are correct as is.

As described above, the CCC will conduct regular monitoring visits, during which audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on items such as recruitment, availability of primary outcome, treatment exposure, attendance at long term follow-up visits, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site staff, the local Node staff, the Lead Investigator, the coordinating centers, and NIDA CCTN, to monitor each site's progress on the study.

7.0 DATABASE LOCK AND TRANSFER

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DSC. Individual participants and their research data will be identified by a unique study identification number; further, some identifiable data may be collected in eClinical. The study data entry and study management systems used by clinical sites and by DSC staff will be secured and password protected.

At the conclusion of data collection for the study, the DSC will perform final data cleaning activities and will "lock" the study database from further modification. The final raw datasets will be transferred to the Lead Investigator or designee and to NIDA as requested. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated party for storage and archiving. These datasets may be posted on the NIDA Data Share website.

Reference: http://grants.nih.gov/grants/guide/notice-files/not98-084.html