Integrated Health Services to Reduce Opioid Use While Managing Chronic Pain: The INSPIRE Trial

STUDY PROTOCOL

IRB Number: 18-0703

PI: Lauren McCormack, PhD, MSPH

National Clinical Trial (NCT) Identifier Number: NCT03454555

Sponsor: RTI International

Funded by: Patient-Centered Outcomes Research Institute (PCORI)

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Version number: 16

CHANGE LOG*		
Version date	**Version Number**	**Changes**
07/27/2018	0.1	Initial version submitted to UNC Scientific Review Committee
08/01/2018	0.2	Version sent to PCORI. • Added cover page and IRB number • Wording revisions for clarity and to reduce redundancy
09/06/2018	1.0	First version submitted to UNC IRB. • Added contact information for PIs • Added CBT as an exclusion • Added active suicidal ideation as exclusion • Added screening items to protocol • Added information about qualitative data component • Revised Efficacy Evaluation section and Statistical Analysis section to respond to SRC comments • Added revised SDM materials • Added safety protocol as an appendix and added references to protocol

CHANGE LOG*		
Version date	**Version Number**	**Changes**
10/30/2018	2.0	Version re-submitted to IRB to respond to stipulations: • Added recruitment manual, recruitment script, FAQ, voicemail/message script, screening and consent script, screening informed consent form, study informed consent form, HIPAA authorization form, SDM patient handouts, MI-CBT patient handouts, MI-CBT therapist manual, T2/T3 follow-up survey, alternate contact script, and DSMB charter as appendices and added references throughout the protocol • Clarified the study phase • Clarified the roles and responsibilities of the study team • Changed consent to screen from verbal to written • Added DSMB description • Added rationale for interventions • Revised description of recruitment targets across sites • Added English language inclusion criterion • Clarified which exclusion criteria relate to past medical history • Revised description of policy regarding blanket permission to contact • Added rationale for excluding patients for other reasons at investigator's discretion • Clarified factors that are not exclusion criteria • Added information about UDTs • Clarified recruitment staff roles • Added recruitment plan information • Added measures to reduce coercion; removed language about emphasizing the importance of follow-up to patients • Added that total compensation is under $200 • Changed extraction of EHR data from opt-out to opt-in consent if patient withdraws from study • Added expectations for qualitative data collection; removed incentive amount for qualitative activities • Added satisfaction with care as an outcome measure and removed knowledge check • Removed interim analysis • Added information about MI-CBT provider training/qualifications • Added potential for risk for opioid tapering and loss of confidentiality
11/29/2018	3.0	Version re-submitted to IRB to respond to stipulations: • Added information about study rationale to study overview and to introduction • Revised cancer-related exclusion criterion • Added information about the additional costs of participating in the study • Added Withdrawal Consent Addendum to seek permission to extract EHR data if patient withdraws from study • Clarified opioid management procedures for Arm 1

CHANGE LOG*		
Version date	**Version Number**	**Changes**
12/06/2018	4.0	Version submitted to PCORI with changes to reflect contract modification • Changed opioid dose cutoff from 50 mg MED to 40 mg MED. This change will enhance enrollment and have no impact on study sample size or power. We also made administrative updates to power calculations in the protocol • Added clarifications regarding the cost of the intervention • Revised the number of contact attempts
02/21/2019	5.0	Version submitted to IRB for study amendment: • Clarified inclusion criteria that patient must be on opioids for chronic non-cancer pain (CNCP) • Added that we will confirm in the EHR that the actual dosage prescribed is at least 40 mg daily MED. • Clarified that patients taking opioids for maintenance treatment of an opioid use disorder (OUD) will be excluded from the study • Updated CONSORT diagram and Figure 5 to match the above clarifications • Clarified that lack of insurance is not an exclusion criterion • Added patient-centered communication measure to surveys • Added text messaging as a recruitment method • Changed length of MI session to 30 to 60 minutes • Removed language about sites obtaining a Certificate of Confidentiality; RTI will request the Certificate. • Removed language about participants in CBT not being asked to share full names • Removed reference to using pain contract as a proxy for cognitive status • Participating clinicians will affirm relevant training but will not be required to produce documentation • Clarified the process evaluation plan • Fixed reference to CBT-MI providers to include licensed professional counselors and other licensed clinicians. • Minor administrative revisions to data management section • Added change log, revised cover page
3/26/2019	6.0	• Removed text messaging as a recruitment method after receiving IRB guidance that text messaging is not allowable for recruitment purposes.
07/03/2019	7.0	• Added brochure as a recruitment method. • Added patient incentive receipt.
11/07/2019	8.0	• Updated the T2/T3 follow-up survey protocol • Changed the upper age limit for exclusion criteria from 75 to 85 years • Removed current CBT exclusion criterion • Clarified cancer exclusion criterion • Updated the name of Mid-South CDRN to STAR CRN • Updated the plans for data management for T2 and T3 follow-up surveys • Removed the exclusion criterion about visit scheduled within next 90 days. This criterion is not clinically meaningful. • Revised the post-CBT group session form

CHANGE LOG*		
Version date	**Version Number**	**Changes**
12/13/2019	9.0	• Changed opioid dose cutoff from 40 mg MED to 20 mg MED. This change will enhance enrollment and have no impact on study sample size or power. We also made administrative updates to power calculations in the protocol. • Removed current CBT exclusion criterion as per PCORI request
4/16/2020	10.0	• Described remote intervention delivery measures • Clarified enrollment procedures for Arm 1
07/08/2020	11	• Described remote enrollment procedures
06/30/2021	12	• Decreased the target sample size from 1,060 to 608. Updated power calculations. • Revised the study timeline and duration. • Described qualitative research activities for focus groups and individual interviews with enrolled participants, • Updated recruitment and retention procedures (removed contacting alternate contacts; added option to contact participants during telehealth appointments; added option to send text message reminders to enrolled participant about follow-up surveys; added option to mail follow-up surveys to participants). • Updated study safety reporting procedures. • Updated background information about opioid use trends. • Made minor clarifications regarding remote enrollment and remote intervention delivery.
08/09/2021	13	Revised to respond to IRB stipulations: • In section 3.6, removed collection of participant alternate information. • In section 3.9.2, replaced “Stakeholder Advisory Committee” with “SAC” which is a reference to the Study Advisory Committee as defined in the Abbreviations section. • In section 3.9.2, in reference to planned periodic newsletter, deleted “if required” which followed “newsletter content will be submitted to IRB for approval.” Corrected minor errors: • Replaced reference to “section X” with “section 3.9.3” in Table 2, reference to “Table 7” with “Table 9” in section 6.3.1; reference to “Table 8” with “Table 10” in section 7.2, and reference to “Table 9” with “Table 11” in section 8.3.1. • Updated headers and footers in Sections 4-12.
10/07/2021	14	Corrected version numbers and dates in the list of attachments.
12/23/2021	15	Revised to include publicly available data as a data source.
3/30/2022	16	Revised to describe procedures related to requesting death certificates: maintaining the confidentiality of the data, procedures for ensuring the privacy of subjects, and how these data will be used.

*Version numbers will be updated upon subsequent final versions submitted to IRB with additions, modifications, and deletions described.

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Appendix (List of Attachments)

A. Consent Forms

Document Type	File Name
Adult Consent form	• INSPIRE Study Informed Consent Form_2019-02-21.docx • INSPIRE Informed Consent for Duke 2019-11-05.docx • INSPIRE Study Consent Form for VUMC - clean.docx
Consent addendum for current subjects	• INSPIRE Withdrawal Consent Addendum.docx • INSPIRE Withdrawal Consent Addendum Duke 2019-11-05.docx • INSPIRE Withdrawal Consent Addendum-VUMC - Tracked.docx
HIPAA Authorization	• INSPIRE Study HIPAA Authorization_2021-12-23.docx • INSPIRE Study VUMC Consent Form_2018-12-21 Subject Injury and HIPAA Included - Clean_final.docx
Other Consent Materials	• INSPIRE Informed Consent for Screening_2019-02-12.docx • INSPIRE Informed Consent for Screening_Duke_2019-11-05.docx • INSPIRE VUMC Informed Consent for Screening_2019-06-12.docx • INSPIRE Informed Consent for CBT Participant Focus Group 2021-06-28.docx • INSPIRE Informed Consent for SDM Participant Interview 2021-08-09.docx

B. Other Attachments

Document Type	File Name
Master Protocol	• INSPIRE Study Protocol v16 2022-03-30
Other Study Protocol	• INSPIRE Combined MI+CBT Patient Packet_FINAL_2020-06-25.pdf • INSPIRE Combined SDM Patient Packet_2020-04-16.pdf • INSPIRE Safety Protocol v3 2020-07-08.docx • MI and CBT for Chronic Pain Manual v4 2020-06-24.docx
DSMB Charter or Stopping Rules	• INSPIRE B4 DSMB Charter V4 2020-final version_signed.pdf
DSMB/DSMC Report	• DSMB Recommendation letter_for signature_2020-11-17--signed by TK 11-29-20.pdf • INSPIREStudyDSMBReport(2019.09.17)_OPEN_Final.pdf • INSPIREStudyDSMBReport_Open_FINAL_2021-07-16.pdf • DSMB Recommendation letter_for signature_2021-08-03 signed 2021-08-06.pdf
Email or Listserv Recruitment	• INSPIRE Email Recruitment Announcement 2020-07-08.docx • INSPIRE Remote Enrollment Forms Email 2020-07-10.docx
Recruitment Listing PDF – Research for Me @ UNC	• RFM_ResearchStudy_18-0703_2020-07-16_1527_to submit with modification_Reviewed by NC TRacs_1.pdf
Recruitment Follow-Up	• INSPIRE Appointment and Survey Reminders Handout 2021-06-25.docx • INSPIRE T1 Emails 2020-07-10.docx
Script for In-Person Recruitment	• INSPIRE Participant Screening and Consent Script 2020-07-14.docx
Flyer for Recruitment	• 13343_INSPIRE Poster_DUKE_Printer.pdf • 13343_INSPIRE Poster_UNC_v2.pdf • 13343_INSPIRE Poster_v3.pdf • 13343_INSPIRE Poster_VUMC_v2.pdf • INSPIRE Study Recruitment Ad 2018-11-28.docx
Letter for Recruitment	• INSPIRE Recruitment Letter v2 2020-07-05.docx

Document Type	File Name
Other Materials for Recruitment	• INSPIRE Baseline Receipt_2019-06-25.doc • INSPIRE Brochure 2019-05-22.pdf • INSPIRE Provider Talking Points 2020-07-08.docx • INSPIRE Recruitment Manual v5 2020-07-09.docx • INSPIRE Thank You Letter with Incentive 2020-07-10.docx • Summary_Sheet_UNC.pdf
Telephone Script for Recruitment	• INSPIRE Messages Script_2019-03-26_final.docx • INSPIRE Recruitment Script_2019-05-22.docx
Electronic Questionnaire Survey	• INSPIRE T1 Baseline Survey_2019_02-21.docx
Interview Questionnaire Survey	• INSPIRE Qualitative Research CBT Focus Group Guide 2021-06-28.docx • INSPIRE Qualitative Research SDM Interview Guide 2021-08-09.docx
Other Questionnaire Survey	• INSPIRE T2 and T3 Follow-Up Survey_2019-10-21.docx
Certificate of confidentiality	• 18-0703 Chelminski CoC Assurance Page ex'd 4-1-19.pdf
Data Use Agreement	• 68331 DUA FE.pdf • Data Use Agreement for Carolina Data Warehouse (Patient Authorization or IRB Waiver) (00056536-6)_Version2.0 _06282019-FullyExecuted.pdf
Scientific Review Committee Approval Letter	• 18-SRC057_Chelminski_IRB Documents_(2018-07-30).pdf
Other	• INSPIRE FAQ script 2020-07-08.docx • Figure 1_Recruitment Process Flowchart.pdf • INSPIRE Qualitative Research Recruitment Materials 2021-06-28.docx • INSPIRE Qualitative Research Thank You Letter 2021-06-28.docx • INSPIRE participant newsletter content 2021-10-07.docx
Scientific Review Documentation	• 18-SRC057_Chelminski_SRC review_clean_compilation_(2018-07-26).pdf

Abbreviations

Abbreviation	Definition
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
CBT-CP	Cognitive Behavioral Therapy for Chronic Pain
GCC	guideline-concordant care
CATI	Computer-Assisted Telephone Interviewing
CDC	Centers for Disease Control and Prevention
CDM	common data model
CFR	Code of Federal Regulations
CI	confidence interval
CITI	Collaborative Institutional Training Initiative
CME	Continuing Medical Education
CNCP	chronic noncancer pain

Abbreviation	Definition
CONSORT	Consolidated Standards of Reporting Trials
COT	chronic opioid therapy
CRF	case report form
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
DUA	Data Use Agreement
ED	emergency department
EHR	electronic health record
ESN	Enhanced Security Network
FAQ	frequently asked question
FIPS	Federal Information Processing Standards
FISMA	Federal Information Security Management Act
FTP	File Transfer Protocol
FWA	Federal-Wide Assurance
GCC	guideline-concordant care
GUID	global unique identifier
HIPAA	Health Insurance Portability and Accountability Act
ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision
INSPIRE	Integrated Services for Pain: Interventions to Reduce pain Effectively
IOM	Institute of Medicine
IRB	Institutional Review Board
ITT	intent to treat
LTF	loss to follow-up
MAR	missing at random
MCID	minimal clinically important differences
MED	morphine-equivalent dose
MI	motivational interviewing
MID	minimally important difference
NCT	National Clinical Trials
NIH	National Institutes of Health
NPS	National Pain Strategy
OHRP	Office for Human Research Protection
OUD	Opioid Use Disorder
PCORI	Patient-Centered Outcomes Research Institute
PCORNet	National Patient-Centered Clinical Research Network
PCP	primary care provider
PDMP	Prescription Drug Monitoring Program
PHI	Protected Health Information
PI	Principal investigator
PII	Personally Identifiable Information
PROMIS	Patient-Reported Outcomes Measurement Information System
PROMIS-PF	Patient-Reported Outcomes Measurement Information System—Physical Functioning
PROMIS-PI	Patient-Reported Outcomes Measurement Information System—Pain Interference

Abbreviation	Definition
REDCap	Research Electronic Data Capture
RTI	RTI International
SAC	Study Advisory Committee
SAE	serious adverse event
SD	standard deviation
SDM	Shared Decision Making
SFTP	Secure File Transfer Protocol
STAR CRN	Stakeholders, Technology and Research Clinical Research Network
SUD	substance use disorder
UNC	University of North Carolina
UDT	urine drug testing
VUMC	Vanderbilt University Medical Center

Protocol Synopsis

PROTOCOL SYNOPSIS	
Title	**Integrated Health Services to Reduce Opioid Use While Managing Chronic Pain (Short title: Integrated Services for Pain: Interventions to Reduce pain Effectively (INSPIRE))**
Clinical Phase	The research is a pragmatic trial and does not fit within the usual framework of the clinical trial rubric of phase I-IV phases
Study Team	RTI International (RTI) was awarded funding from the Patient-Centered Outcomes Research Institute (PCORI) and is the data coordinating center. To the extent permitted under applicable law, RTI has full responsibility and liability for the conduct of the study and for the results reported. Three sites will be enrolling participants for the INSPIRE study: • Duke University • The University of North Carolina at Chapel Hill (UNC) • Vanderbilt University Medical Center (VUMC)
Study Rationale	• Up to one-third of Americans suffer from chronic noncancer pain (CNCP). • Opioids are often used to treat CNCP. Once on chronic opioid therapy (COT), individuals often continue with this class of medication for years. • Evidence for the effectiveness of COT to treat CNCP is limited, exposing individuals to known risks. • Modified or novel pharmacological and nonpharmacological strategies are needed to improve pain management and promote informed decision making regarding possible opioid dose reduction. • This project will evaluate two nonpharmacologic approaches to pain management and opioid reduction in primary care and specialty pain clinics. • The approaches are designed to educate medical care providers and patients currently being treated for CNCP, help patients address pain and pain coping skills, and enhance patient motivation to reduce or discontinue opioid use • This study will determine the feasibility, effectiveness, and potential scalability of these interventions in reducing opioid use in patients who are using at least 20 morphine equivalent doses [MED]). • The study will also assess patient acceptability of the interventions including involvement in their implementation and willingness to incur out-of-pocket costs associated with the visits.
Objective	To conduct a multisite pragmatic trial of two active interventions: shared decision making (SDM) as compared with cognitive behavioral therapy for chronic pain with motivational interviewing (MI+CBT-CP). **Primary Objective** • To assess if the interventions result in opioid dose reduction and compare their effectiveness. **Secondary Objectives** • To examine the impact of the interventions on physical function. • To examine the impact of the interventions on pain interference.

PROTOCOL SYNOPSIS	
Description of Study Intervention	**Intervention 1 (Arm 1)** • The Shared Decision-Making intervention is patient-provider communication intervention to explore and compare treatment options for chronic pain, assess a patient's values and preferences, and reach a shared decision about chronic pain treatment. • Patients randomized to Arm 1 will have their study visits and opioid use managed by an SDM-trained provider at their practice. **Intervention 2 (Arm 2)** • The Motivational Interviewing Plus Cognitive Behavioral Therapy (CBT) for Chronic Pain intervention is an empirically based behavioral pain management intervention that includes MI to enhance motivation for active participation in the CBT-CP, and the use of CBT-CP to enhance pain coping skills. • One individual MI session that will focus on patient engagement and enhancing a patient's own intrinsic motivation for CBT-CP participation. MI will also be woven into the group CBT-CP sessions. Participants in each study arm will receive guideline-concordant pharmacotherapy treatment, based on clinical guidelines for opioid therapy for CNCP.
Study Design	This study is a multisite, randomized pragmatic trial to examine the comparative effectiveness of 2 interventions: 1. A guideline-concordant pharmacotherapy approach with SDM (Arm 1) 2. A guideline-concordant pharmacotherapy approach with CBT-CP and MI (Arm 2)
Subject Population **Key Criteria for Inclusion and Exclusion**	**Inclusion Criteria** • Ages 18 to 85 years • History of CNCP • Average daily dose of at least 20 mg morphine-equivalent dose (MED) for CNCP according to most recent prescription • Receiving care at a participating clinic from a participating provider as evidenced by at least 1 in-person visit within the past 12 months **Exclusion Criteria** • Opioid use is for pain directly related to a cancer diagnosis • Opioid use is for maintenance treatment of an opioid use disorder (OUD) • Suicide attempt within the past 3 years • Active suicidal ideation • Currently receiving CBT • Non-English speaking • Other reason at the discretion of the investigator
Number of Subjects	608
Study Duration	The entire study is expected to last 72 months, from February 2018 to January 2024.

PROTOCOL SYNOPSIS	
Study Phases **Prescreening** **Screening** **Enrollment** **Randomization** **Intervention** **Follow-up**	**Prescreening:** Potentially eligible participants will be identified through electronic health records (EHRs) and invited to participate. **Screening:** The Research Coordinator will explain the study to the potential participant. Potential participants will provide written or electronic consent to complete screening. The Research Coordinator will screen the participant. **Enrollment:** Eligible participants will be asked to provide written or electronic consent to take part in the study and written or electronic HIPAA authorization. Once consented, they will take a baseline survey to complete enrollment. **Randomization/Allocation:** Once enrolled, participants will be randomized to either Arm 1 or Arm 2 of the intervention using a 1:1 ratio. **Intervention:** In Arm 1, participants and providers will engage in SDM. In Arm 2, participants will attend MI+CBT-CP sessions. Participants in both study arms will receive guideline-concordant pharmacotherapy treatment, based on Center for Disease Control and Prevention (CDC) clinical guidelines for COT for CNCP. **Follow-up:** A comprehensive, multimode data collection method will be used that includes collecting patient-reported outcomes through Web-based and telephone approaches and leveraging existing harmonized EHR data maintained by the PCORnet STAR CRN. Considering the pragmatic nature of the trial, we will track loss to follow-up (LTF) and intervention fidelity.
Efficacy Evaluations	• The primary outcome, opioid dose reduction from baseline, will be assessed using prescribing information from the EHRs. This outcome will be assessed at 6, 12, and 18 months after enrollment. • Patient self-reported outcomes, including physical function and pain interference, will be measured via patient survey at 3 timepoints: baseline, 6 months, and 12 months.
Safety Evaluations	The study team and the Data and Safety Monitoring Board (DSMB) will monitor for potential adverse events (AEs) and serious adverse events (SAEs). This DSMB consists of three individuals who are not participating investigators in this trial, who were nominated by the participating clinical institutions, and appointed by the study sponsor, RTI. The board includes a primary care clinician, a psychiatry researcher, and a biostatistician.
Statistical and Analytic Plan	Clinical and patient-reported outcomes will be evaluated using cross-sectional and longitudinal intent-to-treat analyses. These analyses will use mixed effects models to compare opioid dose between the two study arms over an 18-month period. We also will explore differences in the intervention effect according to participant characteristics, such as age, sex, baseline pain level, baseline opioid dose, and the presence of physical comorbidities, mental health comorbidities, or a history of substance misuse or abuse.
Data and Safety Monitoring Plan *(Cross-reference: UNC IRBIS application section 1.7.1)*	The study PI and the institution PIs will be responsible for data quality management and ongoing assessment of safety. They will be aided by the Data and Safety Monitoring Board (DSMB), which will review cumulative study data to evaluate intervention safety, study conduct, scientific validity, and data integrity to ensure that the study is operating in a safe and ethical manner.

1 BACKGROUND AND RATIONALE

Cross-reference: UNC IRBIS Application section A.1.1.

1.1 Introduction

Chronic noncancer pain (CNCP) is common, and the societal and clinical burden is high. A recent Institute of Medicine (IOM) report estimated that up to one-third of Americans suffer from CNCP.[1,2] With current treatment approaches, 13% of headache patients and 18% of back pain patients remain unable to work full time because of pain.[3] CNCP costs the United States up to $635 billion annually, more than the cost for cancer or diabetes or heart disease.[4] The etiology of a patient's CNCP is often poorly understood, and no physiological test can objectively identify its presence or intensity. Mental health disorders and substance use disorders (SUDs) are often comorbid with CNCP.[5-10] Complete resolution of CNCP symptoms is uncommon.

Primary care and specialty pain clinics have relied disproportionately on pharmacologic approaches, typically opioids, to treat pain. Prescribed opioid use increased threefold in the 1990s and 2000s, peaking around 2011, [11-18] and has decreased 60% since that time.[18] (However, due to data lags, this peak did not become apparent until around 2015). Whereas 50% of all the prescriptions written by pain specialists are for opioids, only 6% of the prescriptions written by primary care physicians (PCPs) are for opioids. However, PCPs write 56% of all opioid prescriptions.[19] For some patients, opioids may be the most effective, or only effective, analgesic for pain management. Most prescription opioid use is chronic opioid therapy (COT) for CNCP. Patients initiating COT remain on this treatment for years. [20,21] A large body of anecdotal evidence suggests that discontinuation has become more common in the past 5 years, but empirical studies quantifying this are lacking. Individuals on high-dose COT are the least likely to discontinue COT.

Despite the dramatic increase in use, opioids are a challenging treatment modality for CNCP. Their efficacy is incomplete, and some individuals may receive little or no pain relief from COT. A recent Agency for Healthcare Research and Quality (AHRQ) systematic review concluded that evidence for the effectiveness of COT is insufficient.[22]

No studies have evaluated the effects of discontinuing opioids on pain level, function, quality of life, or withdrawal symptoms. Despite the lack of evidence for the effectiveness of COT for chronic pain, it is commonly used in practice.

Further, COT has substantial potential for harm. Opioid overdose deaths continue to be an "epidemic,"[16,23-26] with over 46,000 deaths in 2018.[26-29] Men have almost twice the mortality rate from opioid use than women.[22] In one study, most prescription opioid overdose deaths were attributed to diversion,[23] illustrating that opioid risks are not limited to individuals receiving opioid prescriptions. Additionally, individuals on higher doses of COT are at greater risk for overdose death[24] and for the development of misuse or abuse. The annual societal cost of opioid abuse was estimated at $55.7 billion in 2007.[25] In younger persons, new marijuana use and new misuse of prescription opioids are roughly equivalent.[26,27] Other substantial unintended consequences include opioid-induced decreases in quality of life. The Centers for Disease Control and Prevention (CDC), the Federation of State Medical Boards, and individual state medical boards have issued guidelines to promote the safe and effective prescribing

of opioid analgesics. These guidelines advise that opioids only be used when other pharmacological and nonpharmacological treatment modalities are not effective. Clinical guidelines for opioid prescribing emphasize patient selection for opioid initiation, monitoring, and reducing opioid misuse and abuse. However, the guidelines and scientific literature generally provide only limited discussion of opioid reduction or discontinuation if an opioid-based approach is not working for the patient. That is, guidelines address only the technical aspects of reducing medication dosages for COT (i.e., how quickly to decrease the dosage).[28-32] Importantly, the existing literature does not discuss how to motivate individuals to discontinue or decrease their opioid dosage or to reduce the risk of opioid misuse;[33] nor how to manage pain symptoms in a patient-centered fashion during and after opioid reduction or discontinuation. This evidence gap leads to a predictable clinical practice gap. In the absence of an evidence base to guide providers and patients on how to decrease opioids, reduction in opioid dosage or discontinuation of COT is infrequent.

This study focuses on the Mid-South area of the United States, where the opioid epidemic has had a disproportionate impact. The study will include opioid users from North Carolina and Tennessee. Individuals living in the Southeastern United States (especially in rural Appalachia), younger persons, and individuals with mental health disorders are at particularly high risk of serious opioid adverse effects. Appalachian areas have very high rates of opioid use. For example, using data from IMS Health, which collects a variety of healthcare information and is the largest vendor of U.S. physician prescribing data, McDonald and colleagues reported that Tennessee was 55% over and North Carolina was 18% over the national per-capita mean milligrams of opioids.[34] Also using IMS Health data,[35] the CDC reported that both Tennessee and North Carolina are among the 13 states with the highest rates of opioid prescribing, ranging from 96 to 143 opioid prescriptions per 100 residents. In 2014, the age-adjusted rates of drug overdose deaths were 19.5 in Tennessee and 13.8 in North Carolina.[35]

1.2 Name and Description of Investigational Product or Intervention

Clinical practice for CNCP patients using COT is changing. Physicians are being asked to maintain patients on the lowest dose of opioids needed to control their pain or to use non-opioid therapies. Often, physicians are not referring patients to cognitive behavioral therapy (CBT) as a non-opioid therapy—partly because this is a challenge to do within a primary care setting and partly because patients are unaware that this is a useful modality for pain management. Shared decision-making may also be a useful modality for managing opioid therapy in those with CNCP.

This study will provide evidence on a key decisional dilemma facing prescribing opioids to CNCP patients: What is the best way to facilitate opioid reduction or discontinuation of opioids in patients who are not receiving benefits from the opioids and/or who are interested in dose reduction? The study takes a biopsychosocial approach to addressing pain, as outlined in the National Pain Strategy (NPS).[36] Combining evidence-based behavioral interventions with pharmacological pain management is consistent with the NPS developed by the Interagency Pain Research Coordinating Committee,[36] and recommendations from a recent National Institutes of Health (NIH) panel.[37] The NPS endorsed a "biopsychosocial model that is grounded in scientific evidence, integrated, multimodal, and interdisciplinary while at the patient level is tailored to individual needs."[36]

The study will examine the comparative effectiveness of two interventions for treating chronic pain patients in a multisite, pragmatic trial. In Arm 1, patients and providers will engage in Shared Decision Making (SDM) along with guideline concordant opioid pharmacotherapy. In Arm 2, patients will participate in Motivational Interviewing Plus Cognitive Behavioral Therapy for Chronic Pain (MI+CBT-CP), along with receiving guideline concordant pharmacotherapy.

1.2.1 Shared Decision Making

SDM is a process in which providers and patients work together to make decisions about tests and treatments by discussing the clinical evidence, balancing the risks and expected outcomes, and respecting patient preferences and values.[38] SDM is an essential component of patient-centered health care[39] and is critical for improving the quality of health care.

Providers and patients often need to make decisions about tests to be done or treatments to initiate, but the optimal decision for a patient can only be made if the patient is appropriately informed about the expected benefits, risks, and potential harms of all available options. This is particularly relevant when patients are at risk of negative outcomes from continued opioid use, such as hyperalgesia and addiction, but are unaware that alternative options such as CBT, exercise, or mindfulness (e.g., meditation) may be beneficial. Studies have demonstrated the benefit of SDM in improving patient-centered outcomes for chronic illnesses such as diabetes, depression, and cardiovascular disease.[40]

Unlike the traditional patient-provider interaction, the SDM intervention uses decision aids or conversational aids to educate the patient and encourage thoughtful consideration of alternative pain management strategies, with the goal of promoting more meaningful conversations between patients and providers. Decision aids have been found to improve knowledge of treatment options, help patients feel better informed, promote more accurate expectations of benefits and harms, and increase participation in decision making.[41] SDM promotes a reciprocal rather than directive approach to care.

RTI International, in collaboration with the University of North Carolina at Chapel Hill (UNC), recently completed an assessment and analysis of the “state of the science” on SDM and practice improvement in clinical encounters for AHRQ.[42] For this project, SDM was defined as “a health care provider and a patient working together to make a health care decision that is best for the patient. The optimal decision takes into account evidence-based information about available health care options, the provider's knowledge and experience, and the patient's values and preferences.”[43] This work built on prior research led by Dr. McCormack that RTI conducted for AHRQ to develop decision support tools for patients and conversational aids for providers to promote shared decision making in clinical settings.[44]

1.2.2 Motivational Interviewing Plus Cognitive Behavioral Therapy for Chronic Pain

The MI+CBT-CP behavioral approach has a broad evidence base.[45] MI is an evidence-based, focused, goal-oriented counseling technique used to enhance an individual’s own intrinsic motivation for behavioral change.[46] MI has been studied most extensively in substance abuse treatment, but is effective for a wide range of clinical issues where patient motivation is important, such as obesity[47] and type 2 diabetes.[48] The North Carolina State Medical Board guidelines refer explicitly to both MI and SDM as promising modalities for effective patient engagement:[29]

> *Motivational interviewing and shared decision making provide practical and well-described methods to accomplish patient-centered care in the context of situations where medical evidence supports specific behavior changes and the most appropriate action depends on the patient's preferences. Many clinical consultations may require elements of both approaches, however. Both motivational interviewing and shared decision making are patient-centered methods that promote the ethical imperative of respecting autonomy, and both have been associated with improved patient outcomes."*[49, p. 270]

Recently, MI also has been used to help patients engage in CBT-CP. MI involves four processes: engaging, focusing, evoking, and planning. However, MI is not a protocol, but rather a way of talking and conversing with patients. Importantly, MI can be combined with psychotherapy, such as CBT-CP. We will use MI to enhance motivation both for (1) the CBT-CP intervention in general, to work toward goals of improved functioning, and (2) for opioid reduction or cessation. We believe this approach offers the greatest likelihood of decreasing reliance on opioids.

CBT is an evidence-based psychotherapy used for an array of behavioral health and physical health conditions—including depression, for which it was initially developed, and for anxiety, insomnia, and chronic pain, such as lower back pain.[50-55] CBT-CP is a well-established intervention for chronic pain and is recommended by pain guidelines and reviews.[30,50,56-59] Group CBT-CP therapy has been shown to be as effective as individual CBT-CP therapy.[60-62]

We anticipate our behavioral approach will be useful for a broad range of CNCP patients. CBT-CP aims to identify, challenge, and change maladaptive thoughts, emotions and behaviors, and replace them with more adaptive thoughts, emotions, and behaviors.[50] By doing so, it helps patients improve their affective state, engage in more positive behaviors, and manage their pain condition to foster improved functioning. CBT-CP posits that thoughts, emotions, and behaviors are linked, and that each acts bidirectionally with the others and can influence the interpretation of pain, pain coping skills, and overall functioning. For example, a patient may have the negative thought, "nothing can be done to help my pain," a type of thought that is known as "catastrophizing" that can lead to negative emotions such as depression and anger. Depression can worsen pain perception and make pain more difficult to treat. Further, depression can affect behaviors. For example, a depressed person may be less likely to engage in activities that might decrease the pain, such as moderate exercise, or pleasurable activities that might improve mood. This, in turn, can reinforce the pain cycle.

1.3 Nonclinical and Clinical Study Findings

Cross-reference: UNC IRBIS Application section A.5.1.

While multimodal approaches for treating pain are recommended, the evidence base for such interventions is relatively small, because in general pharmacotherapy and psychotherapy approaches have been tested in isolation. Further, little is known about the effects of multimodal approaches on opioid dose, and whether individuals receiving multimodal approaches might require lower opioid doses. Perhaps for this reason, the NPS stated that "research and demonstration efforts are needed that build on current knowledge, develop new knowledge, and support further testing and diffusion of model delivery systems."[36]

To date, no evidence-based interventions have been successful in a large-scale study at reducing opioid dose long-term while adequately managing pain symptoms. Although little has been published on opioid reduction, in a small study, Veterans (n=50) selected for opioid reduction were able to decrease their opioid dose by a mean of 46% over 12 months, with 67% of these patients experiencing either no change in pain or reduced pain.[63] In a more recent study,[64] patients (N = 35) receiving COT for CNCP and interested in tapering their opioid dose were randomly assigned to a 22-week taper support intervention (psychiatric consultation, opioid dose tapering, and 18 weekly meetings with a physician assistant to explore motivation for tapering and learn pain self-management skills) or usual care. At 22 weeks, adjusted mean daily MED in the past week (primary outcome) was lower in the taper support group; however, this difference was not statistically significant (adjusted mean difference = -42.9 mg; 95% confidence interval [CI], -92.42 to 6.62; p = .09). Pain severity ratings (0 to 10 numeric rating scale) decreased in both groups at 22 weeks, with no significant difference between groups (adjusted mean difference = -0.68; 95% CI, -2.01 to .64; p = .30). The taper support group improved significantly more than the usual care group in self-reported pain interference, pain self-efficacy, and prescription opioid problems (all p-values < .05). This demonstrates that a supported opioid reduction intervention, such as we are proposing for this study, is feasible and shows promise in reducing opioid dose while not increasing pain severity or interference with activities of daily living.

This research has the potential for high public health impact because the public health burden of high-dose COT is significant, and the societal harm associated with the epidemic of opioid misuse and abuse and overdose is unlikely to diminish without opioid dose reduction and discontinuation among CNCP patients. The significance of the study lies in the interventions, which are patient-centered, designed to be easily implemented and adopted in clinical practice, and have the potential for high public health impact. The MI+CBT-CP and SDM interventions do not require extensive training and are relatively straightforward to implement within existing care models. Both interventions are economically feasible because providers will be able to bill private insurers, Medicaid, and Medicare for the treatment. The CBT-CP portion, and some of MI, of the MI+CBT-CP intervention is delivered in a group setting, making the treatment more affordable. Perhaps more important is the fact that the group design allows more CNCP patients to receive the intervention, especially in underserved areas. Additionally, the MI+CBT-CP intervention can be delivered by licensed clinicians, such as Masters- or PhD-level psychologists, licensed clinical social workers, or licensed professional counselors, and can be delivered in-person, or via telehealth.

This real world, translational study will provide important evidence for health policymakers. While the interventions are evidence-based for pain management, the evidence for using these interventions for reducing opioid dose is based on smaller and shorter-term studies and thus, adoption of the interventions is not widespread. If this study shows the interventions are effective in a large-scale study and patients are willing to incur modest costs, this provides important data for influencing future coverage decisions and policy-level change.

Opioid dose reduction is the primary outcome; however, participants will be free to choose whether they want to maintain their current opioid dose, decrease their opioid dose, or discontinue opioids completely. Moreover, we anticipate that our intervention will simultaneously improve outcomes across several domains: somatic pain, functioning, psychological well-being, and quality of life. The study will

help address decisional uncertainty facing patients and help ensure patients have a better understanding of the limitations of the science regarding opioids. Finally, this study will also provide information on each intervention's feasibility, effectiveness, and potential scalability in reducing opioid use in patients who are using high dose opioids (at least 20 morphine equivalent doses [MED]). Beyond evaluating which intervention is best for reducing opioid dosage, the study will assess patient acceptability of the interventions including involvement in their implementation and willingness to incur out-of-pocket costs associated with the visits.

2 STUDY OBJECTIVES AND DESIGN

Cross-reference: UNC IRBIS Application section A.1.2 (objectives), A.4.2 (study design), B.3.4 (setting)

This study will compare the effectiveness of two interventions on potential opioid dose reduction, functioning and pain interference. The study will be conducted in primary care and specialty pain clinics at 3 university hospitals, 2 in North Carolina—The University of North Carolina at Chapel Hill (UNC) and Duke University, and 1 in Tennessee—Vanderbilt University Medical Center (VUMC). RTI was awarded funding from PCORI and is the data coordinating center for this study.

2.1 Primary Objective

To test whether CNCP patients who receive guideline-concordant pharmacotherapy with a MI+CBT-CP intervention (Arm 2) have greater ***opioid dose reduction*** relative to their counterparts who receive guideline-concordant pharmacotherapy integrated with SDM (Arm 1).

2.2 Secondary Objectives

To test whether CNCP patients who receive guideline-concordant pharmacotherapy with an MI+CBT-CP intervention (Arm 2) have ***improved physical functioning*** relative to their counterparts who receive guideline-concordant pharmacotherapy integrated with SDM (Arm 1).

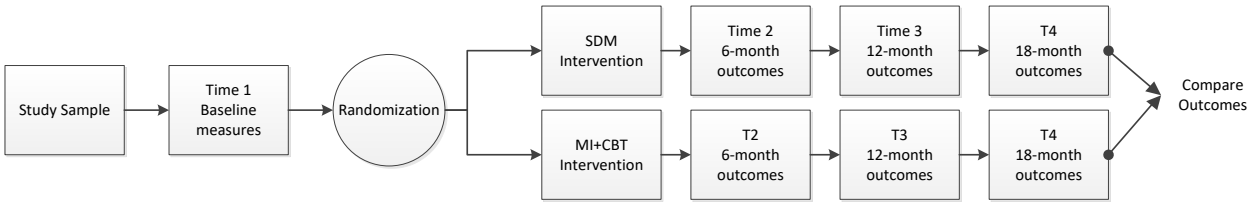
To test whether CNCP patients who receive guideline-concordant pharmacotherapy with an MI+CBT-CP intervention (Arm 2) have ***lower pain interference*** relative to their counterparts who receive guideline-concordant pharmacotherapy integrated with SDM (Arm 1).

2.3 Study Design

Cross-reference: UNC IRBIS Application Section A.4.2.

We will conduct a multisite, randomized pragmatic trial to examine the comparative effectiveness of 2 interventions: a guideline-concordant opioid pharmacotherapy approach with SDM (Arm 1) compared with a guideline-concordant opioid pharmacotherapy approach with MI and CBT-CP (Arm 2). The study design is shown in Figure 1 and a CONSORT flow diagram shell is presented in Figure 2.

Figure 1. Study Design



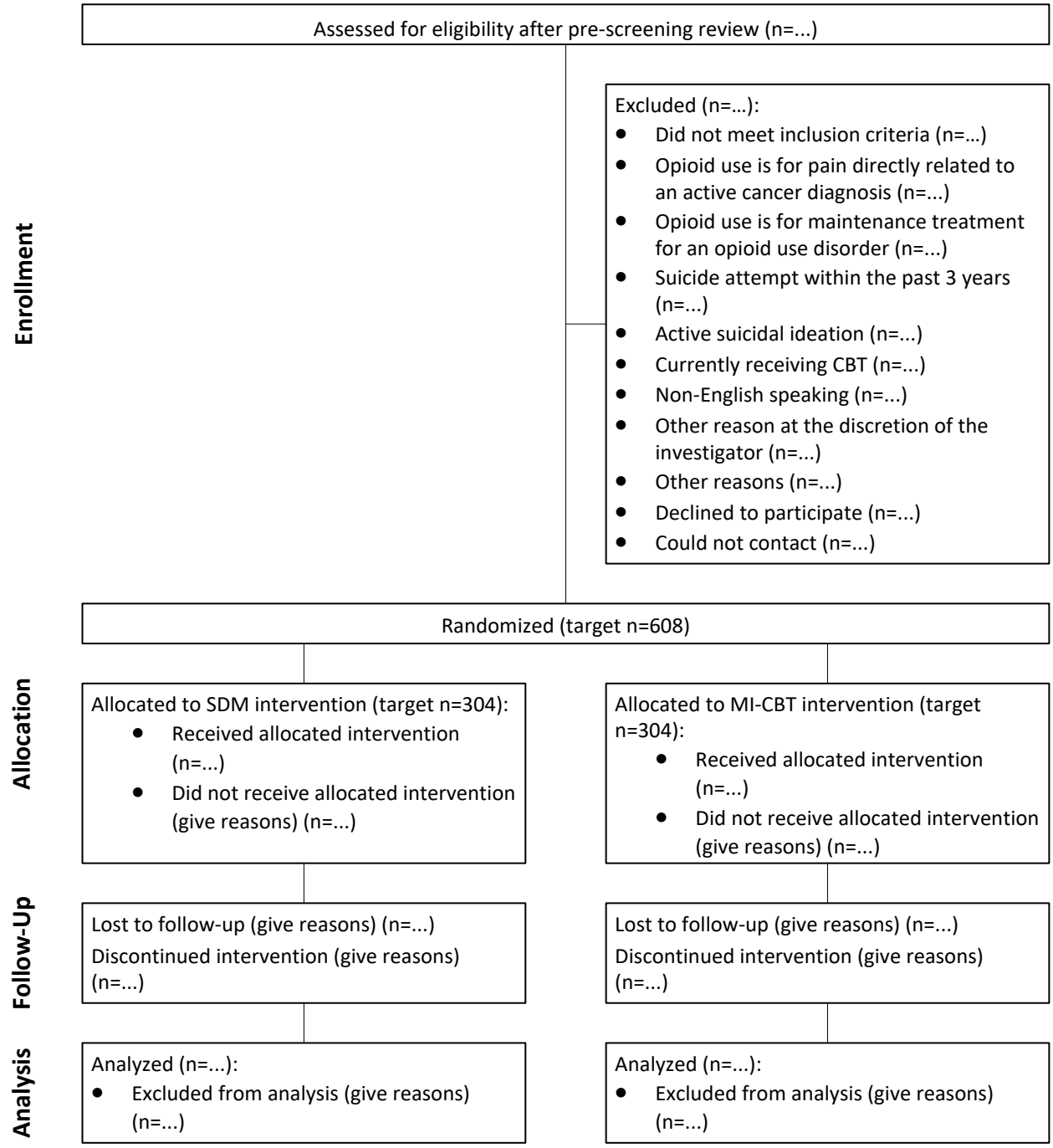
2.4 Random Allocation to Treatment Groups and Blinding

Cross-reference: UNC IRBIS Application Section A.4.3.

This study will use real-time 1:1 ratio randomization to limit participant loss prior to treatment. Eligible participants will be randomized using a stratified, permuted-block design because this constrained randomization approach ensures balance between treatment groups within each of the 3 institutions

(our only stratification factor) at the completion of each block. Consequently, throughout the trial, the intervention arms are expected to have approximately equal sample sizes both within an institution and across the study. We will not be able to blind participants or providers to intervention arm assignment because this is the nature of a real-world pragmatic trial.

Figure 2. CONSORT 2010 Flow Diagram Shell

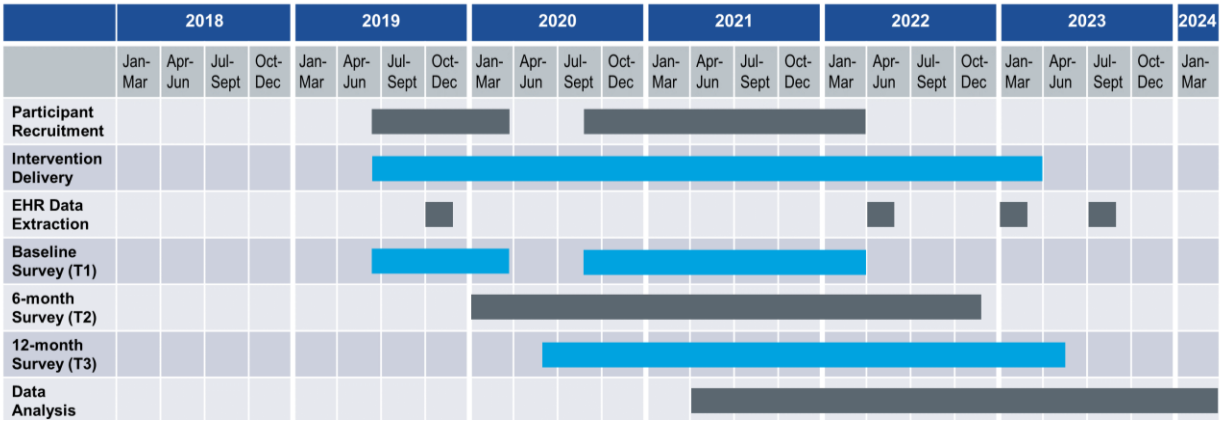


2.5 Study Duration

Cross-reference: UNC IRBIS Application sections A.4.2, A.4.5, B.3.3

We anticipate that in its entirety the study will last 72 months, from February 2018 to January 2024. Enrollment is expected to begin in April 2019 and will continue until enrollment has been completed, but no later than March 2022, as shown in Figure 3.

Figure 3. Study Timeline



2.6 Study Enrollment and Number of Subjects

Cross-reference: UNC IRBIS Application section A.4.2, A.2.1, A.2.3.

Total anticipated enrollment is 608, with about 304 participants in each arm. We expect to enroll about 203 participants per institution. However, there may be site-specific variation in recruitment to allow one or more institutions to recruit over 203 participants to achieve the overall study target of 608 participants. We will not limit each institution to a prescribed maximum number of enrolled patients because some sites may be able to enroll more patients more efficiently than other sites but will adhere to any IRB guidance on maximum number of enrollees per institution. However, we will not enroll more than 608 participants across all 3 institutions.

2.7 Study Population

Cross-reference: UNC IRBIS Application section A.4.2, B.3.5.

Participants will be from the Southeastern United States, a population disproportionately impacted by the opioid epidemic. The trial will be conducted in primary care and specialty pain clinics at 3 university health systems: UNC, Duke, and VUMC. These clinics have experience in opioid management with CNCP patients and have large populations of patients on COT. The 3 universities are part of the PCORNet Stakeholders, Technology and Research Clinical Research Network (STAR CRN), formerly known as the Mid-South CDRN.

RTI was awarded funding from the Patient-Centered Outcomes Research Institute (PCORI) and is the data coordinating center. To the extent permitted under applicable law, RTI has full responsibility and liability for the conduct of the study and for the results reported. Prescreening, recruitment, screening, consent, and enrollment for the study will occur at primary care and/or pain specialty clinics at the 3 participating clinical institutions.

2.8 Inclusion and Exclusion Criteria

Cross-reference: UNC IRBIS Application: A.2.7 (age range), A.3.1 (inclusion and exclusion criteria), A.4.2

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

- Aged 18 to 85 years
- History of CNCP
- Receiving high-dose COT for chronic non-cancer pain (CNCP) as evidenced by current or most recent prescription of an average daily morphine-equivalent dose (MED) of 20 mg or greater for CNCP. Specific opioid analgesics are noted in Section 3.
- Receiving care at a participating clinic from a participating provider, as evidenced by at least 1 in-person visit within the past 12 months

Participants must be using at least 20 mg daily MED to be eligible for the study. If MED data are not available via the institution's data warehouse, a proxy of 3 or more opioid prescriptions to treat chronic pain within the past 12 months may be used to identify these patients in the prescreening phase. However, we will confirm in the EHR that the actual dosage prescribed is at least 20 mg daily MED. Because patients will be taking various opioid medications, daily opioid dose will be standardized to daily MED using standard opioid conversion tables.

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

- Not meeting the above inclusion criteria
- Opioid use is for pain directly related to an active cancer diagnosis
- Opioid use is for maintenance treatment of an opioid use disorder (OUD)
- Suicide attempt within the past 3 years
- Active suicidal ideation
- Currently receiving CBT
- Non-English speaking
- Other reason at the discretion of the investigator

Self-report screening items that are not ascertained via medical record data are provided in the **Participant Screening and Consent Script** (see attached).

Two exclusion criteria pertain to past medical history: a) If the patient does not have a history of chronic non-cancer pain, they will be excluded; b) if the patient has a history of suicide attempt within the past 3 years, they will be excluded. There is no exclusion based on accidents or injury.

Patients may be excluded for a limited set of other reasons based on the investigator's discretion. It is difficult to anticipate the rare, often unique types of situations in which a patient may not be fit for the intervention and to develop specific exclusion criteria for each hypothetical instance.

We include this discretionary category to allow institutions to handle rare cases in which patients would clearly be inappropriate for the study such as: a) unstable behavior or b) cognitive impairment. If the patient is exhibiting *clearly* unstable behavior or if the patient is *clearly* not cognitively intact the research coordinator will note this behavior during the screening process in this category. In addition,

the research coordinator will confirm this determination with the institution PI and will document the reason a patient is excluded via a Case Report Form (CRF). While we recognize the limitations of subjective determinations, we do not want to burden respondents by having them complete a quantitative screening measure to assess the rare occurrence of unstable behavior or cognitive impairment.

If institution policy requires blanket permission from each individual provider to recruit their patients, investigators at the site will contact providers at the clinic to request permission. Clinicians at clinics participating in the INSPIRE study at each institution are told about study and that their patients may be recruited. None of these processes involve sharing any individual patient information. Patients whose providers opt-out of blanket permission to recruit patients will not be eligible and will not be contacted.

2.8.1 Clarification about Cancer-Related Pain Exclusion Criterion

If the patient has active cancer, then the patient is not eligible if <u>any</u> of the following 3 are true:

a) Opioids are being used to treat pain that is directly related to the cancer.
b) The opioids are not being used to treat cancer pain, but it is expected that opioids might be required soon to treat cancer pain.
c) The opioids are not being used to treat cancer pain, but the patient's clinician feels that bringing up the issue of tapering would be emotionally upsetting. A tapering discussion might not be good for the patient at a time when the patient is already under a lot of stress.

Otherwise, in a patient <u>with active cancer</u> receiving chronic opioids, if the opioids are <u>not</u> being used to treat cancer-related pain, then the patient <u>is</u> potentially eligible.

If the patient <u>does not have active cancer</u> (i.e., it is in remission or "cured"), then they <u>are</u> potentially eligible for the study.

If necessary, a final decision regarding eligibility will be determined by the site PI in consultation with the patient's clinician.

2.8.2 Factors that Are Not Exclusion Criteria

Current or Past Substance Use Disorders

Based on participating providers' input, we expect that substance use disorder (SUD), including the use of "street narcotics," will be uncommon in this population. Clinics are already responsible for screening patients on COT for SUD via urine drug testing (UDT), as per standard of care. As this is a pragmatic trial, clinics will continue to test patients as they would normally. We will collect data about SUD diagnoses from the PCORnet CDM to use as a covariate in the analyses. Generally, SUDs will not be an exclusion criterion; as noted above, the only exception will be when the opioid (either buprenorphine or methadone) is being used for medication assisted treatment (MAT) for an OUD.

Urine Drug Testing in Past Year

If a patient has not had a UDT in the past year, they may receive testing during the study period as part of the standard of care. That is, they will not be excluded for not having had a UDT in the past year.

Opioid Treatment Agreement

Opioid treatment agreements, sometimes known as “pain contracts” are required for patients on COT in some clinics. If a participant does not already have a treatment agreement in place, they may be asked to sign one during the intervention period. That is, they will not be excluded for not having a treatment agreement in place.

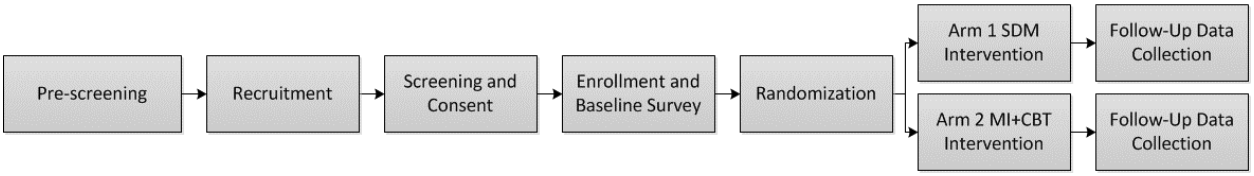
Insurance Status

Patients are not required to have insurance to be eligible for the study. However, we recognize that lack of insurance may be a barrier to participation for some patients. For this reason, we have provided additional information on the costs of participating in the study and that the uninsured may have to pay for the costs of additional visits or CBT treatment, potentially on a sliding scale. If patients cite lack of insurance as a reason for refusing to participate or withdrawing from the study, we will record this as we would any other reason for refusal or withdrawal.

3 STUDY PROCEDURES

A flow diagram of the study phases is presented in Figure 4 with an explanation of each phase below.

Figure 4. Study Phases Flow Diagram



A summary of the study phases and procedures prior to enrollment is provided in **Table 1** and **Table 2**.

Table 1. Pre-enrollment Study Phases, Procedures, and Materials

Study Phase	Procedures	Patient-facing materials
Prescreening (Identification of Potential Participants)	Extract recruitment phenotype data from local Research Data Warehouses	None
	Verify patient eligibility via EHR	None
Recruitment	Recruit participants by mail or e-mail	Recruitment Letter Recruitment Email Announcement
	Recruit participants by telephone or in-person	Screening and Consent script Message Script Respond to questions using FAQ Guide
	Advertise study	Study Advertisement Study Brochure Study Posters
Screening	Screen patients	Screening and Consent script Screening Consent Respond to questions using FAQ Guide
Informed consent	Ask for informed consent	Study Informed Consent Form HIPAA Authorization Remote Enrollment Forms Emails

Table 2. Study Phases, Procedures, and Materials for Enrolled Participants

Study Phase	Procedures	Participant-facing materials
Enrollment	Collect participant contact information	Participant Contact Form Remote Enrollment Forms Emails
	Collect baseline data via self-report survey	T1 Survey T1 Emails Baseline Incentive Receipt Form Thank you letter with incentive
Randomization	Allocate participants to intervention Arm 1 or Arm 2	None
Intervention	Deliver guideline concordant care to participants in Arm 1 and Arm 2	None
	Deliver SDM intervention to participants in Arm 1	SDM Patient Materials
	Deliver MI+CBT-CP intervention to participants in Arm 2	CBT Session Sign-In Form MI+CBT-CP Patient Materials Intervention delivery based on MI-CBT Therapist Manual Post-CBT Session Form Thank you letter with incentive
Follow-up	Collect baseline and follow-up data via clinical data extraction	None
	Collect 6-month follow-up data via self-report survey	T2 Recruitment Materials T2 Survey (web based and CATI) Thank you letter with incentive
	Collect 12-month follow-up data via self-report survey	T3 Recruitment Materials T3 Survey (web based and CATI) Thank you letter with incentive
Qualitative data collection (see section 3.9.3 below)	Recruit participants	INSPIRE Qualitative Research Recruitment Materials
	Collect qualitative data via focus groups and interviews	Informed Consent for CBT Participant Focus Group Informed Consent for SDM Participant Interview CBT Focus Group Guide SDM Interview Guide Thank You Letter

3.1 Identification of Potential Participants

Cross-reference: UNC IRBIS Application A.9.1 (identifiers), A.9.2, B.1.2, B.1.3, B.2.1 (PHI and confidentiality), C.1.1 (data sources)

Potential participants will be identified via each institution's research data warehouse and electronic health records (EHR). Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements will be followed, as applicable. Study staff will upload this file into a local database for use in pre-enrollment study phases such as screening and recruitment (hereafter referred to as the Pre-enrollment database). Personally Identifiable Information

(PII) and Protected Health Information (PHI) data in the Pre-enrollment database will stay at each institution.

The study will collect a minimal set of information on patients who are identified, including those who are determined to be ineligible, refused, or unable to be reached. This will help to ensure transparent reporting, to meet CONSORT publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demographics, eligibility criteria, and reasons for nonparticipation. This information will be stored in the Pre-enrollment database.

Information to be obtained via query of existing clinical data includes the following:

- **Date of EHR query**
  - The date on which the query was conducted
- **Patient contact information**
  - First name
  - Last name
  - Street address
  - City
  - State
  - ZIP code
  - Telephone number (cell, home, and work, if available)
  - E-mail address
- **Other participant information**
  - EHR unique identifier (medical record number)
- **Recruitment phenotype information**
  - Date of birth
  - Name of clinic patient is being seen at
  - Name of primary care or pain clinic provider
  - Date of last clinic visit
  - Date of next upcoming clinic visit
  - Daily MED for the most recent prescription
  - Number of opioid prescriptions within the past 12 months. Includes these generic drugs and their brand name equivalents:
    - buprenorphine
    - codeine and acetaminophen (not codeine alone)
    - transdermal fentanyl only
    - hydrocodone
    - hydromorphone
    - levorphanol
    - meperidine

  - methadone
  - morphine
  - oxycodone
  - tapentadol
  - tramadol

    Note that we will not include pentazocine alone (Talwin) or pentazocine/naloxone (Talwin Nx).

- **Opioid prescription information for each prescription in the past 12 months**
  - Order ID
  - Patient EHR unique identifier
  - Provider name (prescription provider)
  - Prescription ordering date
  - Prescription name (generic name)
  - Form of drug (e.g., tablet)
  - Drug strength (dispensing units) (e.g., 100 mg)
  - Drug route of administration (e.g., oral, transdermal – IV will not count)
  - Dosing instructions
  - Drug dose (e.g., 1 capsule, 2 tablets)
  - Dose frequency (e.g., daily, twice daily)
  - Total number of units prescribed (quantity)
  - Number of refills

- **Patient demographic information**
  - Gender
  - Race
  - Ethnicity

3.2 Eligibility Screening

Cross-reference: UNC IRBIS Application sections B.1.4, B.1.5

First, research coordinators at each institution will review EHR information for the list of potential participants and will identify potential participants meeting basic eligibility criteria (e.g. age, active patient status, opioid dose, and absence of exclusionary medical or psychiatric comorbidities). Research coordinators will verify whether they may be eligible for the study.

Then, potential participants will be contacted by research coordinators, who will introduce the study and invite them to complete a brief screening in-person or remotely. This is described in section 3.4 below.

3.3 Recruitment

Cross-reference: UNC IRBIS Application sections B.1.1, B.1.5, B.1.9 (contact methods), B.1.10 (roles), B.3.2 (number of contacts)

Research coordinators (RCs) at each institution will recruit potential participants. Physicians are not contacting patients to recruit or enroll them. The RC will follow a separate, detailed recruitment plan, the **Recruitment Manual** (see Appendix). This plan is briefly summarized below and shown in Figure 5. More specific details are in the Manual.

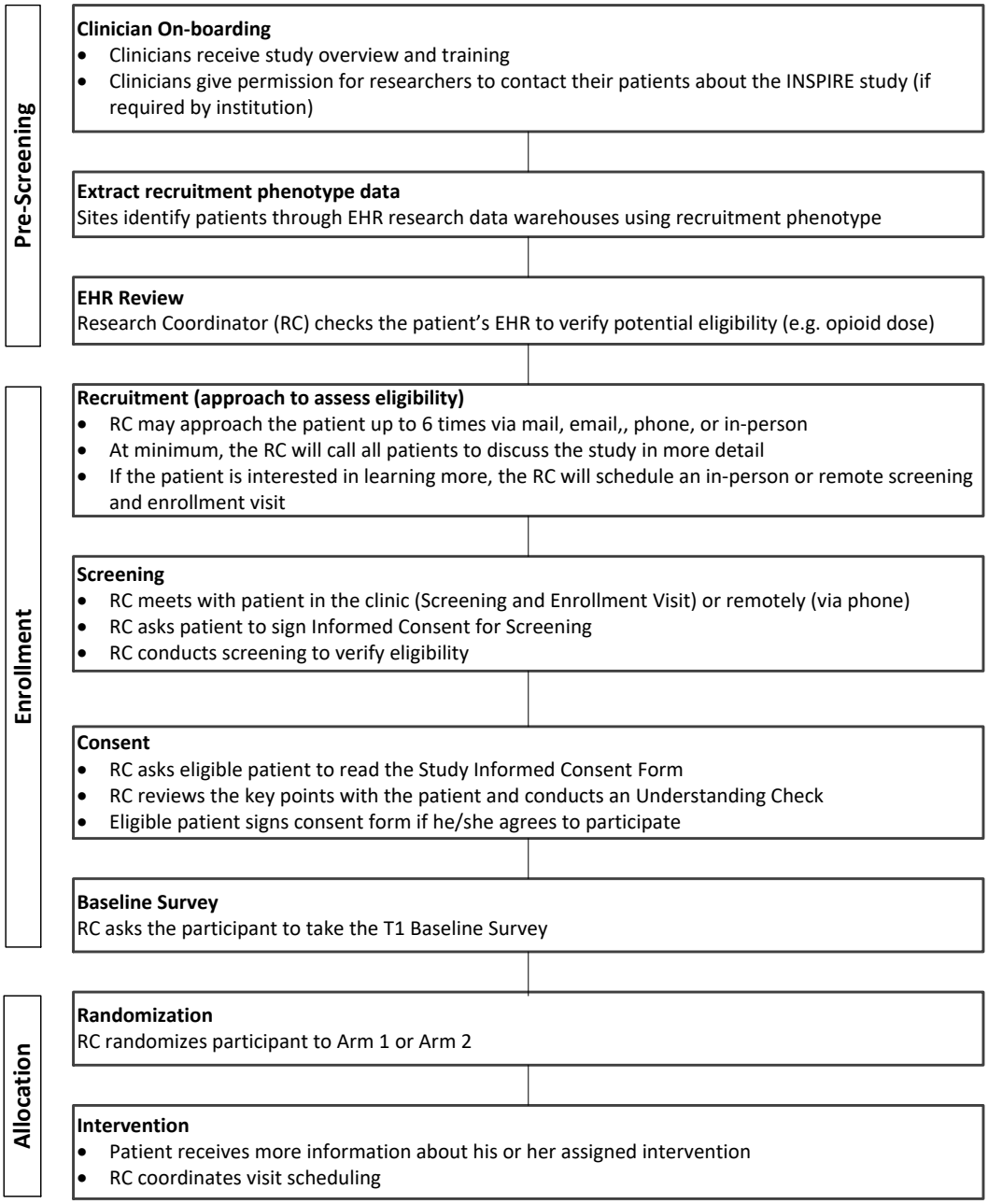
Any of the following methods that are IRB-approved may be used to approach patients about the study: mail, e-mail, telephone, study advertisements, brochures, or in-person in the clinic. During recruitment, if the potential participant indicates interest, the RC will offer to conduct screening in person or remotely. If the patient refuses, the RC will make no further contact with them about the study.

The number of contact attempts will vary by availability of participant. Because this is a challenging study for recruiting patients (i.e., eligibility criteria and potential financial burden), we will minimize intrusion by contacting the participants up to 6 times to elicit their interest in participating in the study, by any of the above methods. RCs will be instructed on how to leave a voicemail on the initial attempt if a patient is not home (see **Messages Script** in the Appendix).

A patient may refuse to participate in the INSPIRE study. If at any time, a patient indicates they do not want to be in the study (gives a hard refusal), the RC will stop contacting them. Refusals will be documented on the Recruitment Log Case Report Form maintained at the institution; this does not go to RTI. Each institution will be responsible for developing a procedure to ensure that participants are not recruited more than once, and refusals are documented so that patients who refuse are not contacted again for participation.

On a monthly basis, each institution will report aggregate consent status outcomes data using the Recruitment Summary CRF to the RTI Data Coordinating Center (DCC) via the web-based REDCap data management system. No identifiable data will be reported to the DCC. Aggregate consent status outcomes will be reported to PCORI on a monthly basis.

Figure 5. Recruitment Diagram



We will implement the following strategies to increase participant recruitment:

- Each clinic will have a "clinic champion" (a practicing clinician who has completed the necessary trainings and serves on the Study Advisory Committee [SAC]) onsite to provide clinic-specific advice on the consent and enrollment processes.
- The RC will try to establish a connection with each potential participant and communicate proactively and respectfully to ensure that participants are comfortable in their understanding of the study intervention and processes, and that participation presents no undue burdens.
- All potential participants will be given IRB-approved materials that contain a toll-free number to call to ask additional questions or to opt-out of further study recruitment efforts if they choose.
- Patient representatives from our SAC have reviewed and provided input on patient-facing materials.
- The materials are written in plain language and at an appropriate reading level for a lay audience.
- RCs will use a **Frequently Asked Questions (FAQ) Script** (see Appendix) to help answer questions that may arise in a consistent way
- This population faces significant transportation barriers to accessing health care. To make the study more accessible, we will now offer remote enrollment and remote participation in the intervention.
- RCs may recontact potential participants who previously declined in order to tell them about the remote option for taking part in the study. They will see if they are interested in participating remotely.

They will only recontact participants who were not previously offered the remote option. They will not re-contact patients who requested to not be contacted again, and they will provide potential participants with the option to no longer be contacted by the research team going forward.

Strategies such as these will increase enthusiasm for the study among patients, providers, and clinic staff, which can help promote successful recruitment.

3.3.1 Mail and E-mail Recruitment

RCs may contact potential study participants by mail, e-mail, or both to invite them to participate in the study. An IRB-approved **Recruitment Letter** (see Appendix), which is the same content whether delivered by mail or email, will tell the patient about the study, and it will ask them to contact the Research Coordinator if they are interested in participating. If the letter is returned as undeliverable, the Research Coordinator will attempt to confirm the patient's address and resend the letter. If there is no response, a follow-up letter may be sent.

3.3.2 Telephone Recruitment

The RC may use an IRB-approved **Recruitment Script** (see Appendix) to call potential participants to recruit them for the study. The RC will follow a standard script to ensure consistency. The RC will confirm they are speaking with the patient, tell them briefly about the study, assess interest, and set up an enrollment appointment. They will also offer the patient the option to enroll remotely. The remote

enrollment approach means that the RC will talk the patient through the enrollment process over the phone and email them links to electronic consent forms to complete screening and consent.

As detailed in the **Recruitment Manual** (see Appendix)**,** if the patient does not answer the telephone, the RC will leave a brief message to request a callback; this message will not contain any information about the study or the patient's health (see Appendix for the **Messages Script).**

3.3.3 Study Advertisements

The RC may post an IRB-approved **Study Recruitment Ad or Study Recruitment Poster** (see Appendix) within clinics, locally, or online (including social media) to tell potential participants about the study. These materials will follow any institutional policies regarding the posting of study ads.

3.3.4 Study Brochure

The brochure will be used during recruitment. It will be given to patients by study staff. The intent of the brochure is to provide information to patients about the study. Text for the brochure was adapted from the consent form and other IRB-approved participant-facing materials. All pictures are stock images (no actual patients are pictured).

3.3.5 In-person Recruitment

The RC may approach potential participants in-person at the clinic to tell them about the study. The RC may use an IRB-approved **Recruitment Script** (see Appendix) to approach potential participants to recruit them for the study. RCs will follow a standard script to ensure consistency. The Recruitment Script contains instructions for both in-person and phone recruitment.

3.3.6 Provider Warm Hand-off

The patient's provider may briefly introduce the study to the patient during a clinic visit. This provides a chance for the patient to learn about the study and ask questions. Providers will use a standard set of **Provider Talking Points** (see Appendix) to ensure consistency and to minimize undue influence or coercion. These talking points indicate that it is up to the patient to decide that they will support the patient for their pain management no matter what they decide. If the patient is interested in the study, the provider may make a "warm hand-off" to (i.e., introduce the patient to) an RC.

A "warm hand-off" may occur during a telehealth appointment. The recruitment coordinator may approach patients about the study during telehealth appointments, with the permission of the health care provider. Research staff will adhere to any institution or clinic policies regarding virtual patient appointments.

3.4 Screening

Cross-reference: UNC IRBIS Application section A.6.2 (steps to minimize psychol. risks)

Participant screening will occur in-person at the clinic or remotely. The RC will follow the **Participant Screening and Consent Script** (see Appendix)**.** If the screening is conducted remotely, the RC will do remote screening and enrollment over the phone with the patient, guiding them through electronic forms that are hosted securely at the clinical institution.

Written or verbal consent for screening will occur before eligibility screening is conducted.

If recruitment occurs in-person, prior to study screening, the RC will ask the patient to sign **the Informed Consent for Screening** (see Appendix)**.**

If recruitment occurs remotely, we will make an adaptation to this process. The RC will obtain consent to screen verbally by reading the screening consent form aloud and asking if the patient agrees. All of the same information will be provided to the patient, and screening will only proceed if the patient tells us they understand and agree. The study is collecting sensitive and personally identifiable information during the screening process. Depending on the responses to suicidal ideation questions, individuals need to be consented before screening activities occur. The informed consent for screening clearly outlines what information will be shared, retained, and how it will be used.

The study screening, provided in the **Participant Screening and Consent Script** (see Appendix)**,** asks about sensitive information, including: (1) whether the patient is receiving *CBT* currently, (2) *is using opioids for pain due to cancer,* and (3) *suicide risk* (2 questions, with one follow-up question if the subject indicates having thought about suicide recently). Suicide ideation includes both thoughts of being better off dead and thoughts of intentionally harming oneself.

The research coordinator (RC) will invoke the INSPIRE Study's **Safety Protocol** (see Appendix) if the patient expresses active self-harm, if the patient has a positive screen on the suicide risk assessment, or if imminent self-harm or harm to others is suspected.

The safety protocol requires that the RC contact the clinic and work with on-site or on-call personnel (such as the prescribing physician, lead clinical investigator, or other designated crisis responder, hereafter referred to as "designated responder") to arrange for further assessment. If the designated responder cannot be reached, the RC will call 911 and ask for a crisis intervention team specialist. If the research coordinator feels that 911 is the most appropriate due to suspicion of very imminent self-harm or harm to others, the RC will notify 911. The RC will report the event to the institution PI, institution project manager, RTI study PI, and RTI project manager within 48 hours for further consideration of action and follow-up. IRB, DSMB, and/or PCORI will be notified as needed.

3.5 Informed Consent

Cross-reference: UNC IRBIS Application section D.1, A.3.2 (language)

Once screened, eligible participants will be asked to provide written or electronic consent to participate in the study. For remote consent, the RC will email the patient a link to the form and walk them through it verbally on the phone (see **Remote Enrollment Forms Email Templates** in the Appendix).

A consent form describing in detail the study intervention, study procedures, and risks will be given to the participant, and written or electronic documentation of informed consent is required prior to starting the intervention. The **Study Informed Consent Form** is submitted with this protocol as an appendix. Each institution will have an approved form that is tailored to their policies and contact information. The RC will also ask the individual to read and sign (in writing or electronically) a **HIPAA Authorization Form** (see Appendix)**.** Both of these electronic forms will be hosted securely at the clinical institution.

It is outside the scope of the study to conduct the interventions in languages other than English. For that reason, we will not obtain consent in languages other than English.

3.5.1 Steps to Minimize Undue Influence during the Consent Process

Cross-reference: UNC IRBIS Application section D.1.6

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the patient will be asked to read and review the document. Study staff will explain the research study to the patient and answer any questions that may arise. A verbal explanation will be provided in terms suited to the patient's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Patients will have the opportunity to carefully review the written or electronic consent form and ask questions prior to signing. To minimize coercion or undue influence, the researchers will encourage the potential subjects to review the consent forms in private. Patients will be encouraged to discuss the study with their family, provider, or others, or think about it prior to agreeing to participate. The patient will sign the informed consent document prior to any procedures being done specifically for the study. Patients will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. All consent documentation will be written at a lay-friendly reading level. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, either in writing or electronically, before the participant undergoes any study-specific procedures. The rights and welfare of the patients 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.

Because of the nature of the interventions, we will not obtain surrogate consent for those unable to consent on their own behalf.

3.6 Enrollment and Baseline Data Collection

Cross-reference: A.4.6 (data collection methods)

Once a patient has signed the consent form, they will be considered enrolled in the study. Consented participants will be asked to provide the following contact information:

- Salutation
- First name
- Middle name
- Last name
- Preferred name
- Suffix
- Mailing address, City, State, ZIP code
- E-mail address(es)
- Phone number(s) – home, mobile, work, other
- Reminder preference (e.g., telephone, text message, e-mail, mail)
- Information preference (e.g., paper, electronic)
- Contact preferences (e.g. days and times)

Participants who enroll remotely can be asked to provide this information in an electronic form that will be hosted securely at the clinical institution (see **Remote Enrollment Forms Email Templates** in the Appendix).

Patients who have consented to participate in the study will be entered into the study's Enrolled Participant REDCap database hosted at RTI. Only information for consented participants will be stored in this database. The Enrolled Participant Database will include study status and participant data collected at and after enrollment.

This study is not FDA regulated, so 21 CFR Part 11 compliance is not applicable.

Participants will be asked to complete the baseline survey (T1) for assessment of patient-reported outcomes. The baseline survey may be self-administered electronically or verbally administered by study staff (or on paper if necessary). Participants can complete the survey in-person at the clinic or remotely. The **T1 Baseline Survey** is provided as an appendix. Participants must complete the baseline survey before being randomly assigned to the study intervention.

For remote administration, RCs will send participants an email with a private, secure survey link, asking them to complete the survey using the **T1 Emails** template for email invitations and reminders (see Appendix).

3.7 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomly assigned to the study intervention or entered in the study. For example, this could occur if a participant signs the consent form but does not complete the T1 baseline survey.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

3.8 Randomization and Intervention Delivery

After enrollment, participants will be randomly assigned to one of the two intervention arms as described in Section 2.4. Interventions will be delivered as described in Section 6.

3.9 Follow-up Assessment Procedures

Cross-reference: UNC IRBIS Application section A.4.4, A.4.6, B.3.2 (number of contacts), C.1.1 (data sources)

We will use a comprehensive, multimode data collection method that includes the collection of patient-reported outcomes through web-based and telephone approaches and leverage existing harmonized EHR data maintained by the PCORnet STAR CRN.

We will collect follow-up data in two ways:

1. EHR data extraction from the PCORI Patient-Centered Clinical Research Network (PCORNet) STAR CRN.
2. Patient surveys to collect patient-reported outcomes data.

3.9.1 Clinical Data Extraction

We will extract existing clinical data to measure the primary outcome of opioid dosage at baseline, 6, 12, and 18 months. Clinical data will be extracted from the PCORnet STAR CRN data warehouse, which will add efficiency and consistency to the project while reducing delays related to data access and management. Data extraction and transfer procedures are described in section 10.2.1 below.

3.9.2 Self-report Survey

Follow-up assessments will include the collection of patient-reported outcomes data via self-report surveys at two follow-up timepoints: 6 and 12 months after enrollment. The **T2 and T3 Follow-Up Survey** is included in the Appendix. The measures included in the surveys are described in Section 4.

Each clinical site will provide participant contact information for randomized study participants to RTI so that research staff at RTI can conduct follow-up recruitment at T2 and T3. Clinical site staff may assist in contacting hard-to-reach participants.

Access to technology and individual preferences for completing the surveys will differ across participants. To increase retention and data quality, the survey can be self-administered via the Web or on paper or administered verbally by study staff.[65]

Staff will collect survey data according to a Follow-Up Protocol in the study Manual of Procedures. Our data collection approach is based on standard best practices in the field of survey research.[66] Our phone follow-up protocol is consistent with best practices including that used by the CDC Behavioral Risk Factor Surveillance System (BRFSS).[67]

Introduction/Lead letter or email

One week prior to follow-up survey data collection at T2 and T3, RTI study staff will send a lead letter/email to enrolled participants. The purpose of the lead letter/email is to remind the participants about the follow-up surveys. The lead letter/email can be found in the Appendix (**T2 and T3 Recruitment Materials document**)

Web-based Administration

RTI study staff will send participants up to 4 emails over 4 weeks with a private, secure survey link, asking them to complete the survey. Email reminders can be found in the Appendix (**T2 and T3 Recruitment Materials document.)**

We will ask enrolled participants to complete the survey by phone or by mail if they a) do not complete the follow-up Web-based survey within 4 weeks or b) do not have a valid email address.

If a participant does not complete the web survey after 4 weeks, we will close the web survey option.

Computer-Assisted Telephone Interviewing Administration

RTI study staff will contact participants who a) do not complete the follow-up Web-based survey approximately 4 weeks after the initial invitation or b) do not have a valid email address.

For participants who do not have a valid email address, we will make up to 9 contacts over a 6-week period. For participants who have a valid email address but did not complete the web survey, we will make up to 5 phone contacts over a 2-week period. A contact is defined as when the caller reaches

someone live, by voicemail, or by text message. The calls will be made at varying days and times to increase the chance of reaching the participant.

We will ask the participant to complete the survey via telephone using standard telephone interviewing techniques for Computer-Assisted Telephone Interviewing (CATI). Phone scripts can be found in the Appendix (**T2 and T3 Recruitment Materials document).**

Mail Administration

Study staff may mail participants a paper copy of the T2/T3 survey for the participant to fill out and mail back at no cost to the participant.

Hard-To-Reach Protocol

Before a participant is deemed lost to follow-up, study staff will make every effort to regain contact with the participant.

RTI staff will use web-based location resources—such as search engines, Superpages.com, etc.—and will check with local site study staff to update contact information.

RTI will notify the local site study staff of participants who cannot be reached. The research coordinator may follow-up with the participant to remind them about the survey and to set up an appointment time for RTI to call the patient to conduct the survey.

Strategies for Retention

Because the study involves enrollment over several months, we will use procedures to enhance participant retention, including the following:

- Using multiple methods for contacting participants.
- Using study reminders.
- Providing incentives for survey completion and clinic visit attendance (described below).
- Confirming current personal contact information with the participant.
- Giving patients an **INSPIRE Appointment and Survey Reminders Handout** (see Appendix) that summarizes their steps for taking part in their assigned intervention in one clear, easy-to-read page.
- Sending a periodic newsletter to enrolled participants. The newsletters will include information such as survey and intervention reminders, background on what the study hopes to achieve, and stories from SAC members. Any pictures used will be stock images (no patients or study participants will be pictured). Newsletter content will be submitted to IRB for approval.

Additionally, institution leadership will meet regularly and obtain input from the SAC, which includes patient members, to review and assess retention.

3.9.3 Qualitative Data Collection

We will also qualitatively assess the patient-reported experience as part of this pragmatic trial by conducting virtual individual interviews with participants in Arm 1 and virtual focus groups with those in Arm 2.

Number of participants

Total anticipated recruitment in the qualitative research is up to 78 participants. For Arm 1, we will recruit up to 24 participants for individual interviews. For Arm 2, we will conduct up to six focus group sessions. We will recruit up to 9 participants for each focus group, for a total of 54 participants.

Recruitment

We will ask participants during the consent process for the main study for permission to contact them for additional research activities related to this study. RCs will contact the participants who gave permission to be re-contacted using a standard script (**See Attachments, Qualitative Recruitment Materials)**. During recruitment, the RC will confirm that the participant is willing and able to take part in a web conference call and will ask the participant upfront if they agree to be audio-recorded if they decide to participate.

Informed Consent

The RC will send the participant a confirmation email with a copy of the informed consent form (**see attachments, Informed Consent for CBT Participant Focus Group** and **Informed Consent for SDM Participant Interview).**

At the beginning of the qualitative session, the interviewer will review key points of the informed consent with the participant(s) and ask if they have any questions. The moderator will ask each participant to provide verbal consent to participate and the notetaker will document the consent.

Interview and Focus Group Administration

An interviewer and note-taker, both from RTI, will facilitate the interviews and focus groups. The moderator will use a semi-structured moderator guide **(see attachments, CBT Focus Group Guide and SDM Interview Guide)** to gather data on participant experiences with the interventions, communication with their health care providers, pain management, and opioid use. We will conduct the interviews and focus groups via a web conferencing platform. Each session will last up to 60 minutes. To facilitate engagement, we will ask participants to turn on their video/webcam if able. For privacy and security reasons, we will not video record the session. We will only record audio from the session. We will use the audio recordings to create transcripts, both of which will be stored on a password protected portion of the project share drive The RC will mail participants a $75 gift card at the conclusion of the focus group or interview as a thank you for their participation.

3.10 Incentives for Study Participation

Cross-reference: UNC IRBIS Application section A.9.3 (SSNs), B.4.1 (incentives), B.4.2 (incentives)

The following incentive will be provided for study participation:

- Participants will receive a $30 incentive payment for completing the baseline survey.
- Participants will receive a $25 incentive payment for each follow-up survey completed.
- Participants will receive a $10 incentive payment for each group CBT-CP session completed.

If the participant completes the T1 survey remotely or completes a group CBT-CP session remotely, the RC will mail them the incentive and **Thank You Letter with Incentive** (see Appendix)**.** The incentive

payments for the follow-up surveys will include the **T2/T3 Thank You Letter**, which is included in the Appendix.

The total compensation a subject could receive for either arm is under $200, therefore we are not collecting SSNs for payment. Participants receiving an incentive payment in person will be asked to sign a receipt form acknowledging receipt.

If they choose to take part in the additional qualitative research activities, participants will receive a $75 incentive payment for completing a qualitative interview or focus group.

3.11 Study Completion

The patient's participation in the intervention is complete about 12 months after the completion of the T1 baseline survey; participation in the study is complete after completion of the T3 survey.

Key tracking data pertaining to visit completion and follow-up completion will be captured. These tracking data will be used to coordinate the distribution of incentive payments to participants and to identify trends in data collection; for example, to identify patterns of loss to follow-up that can inform outreach methods.

3.12 Withdrawal from the Study

Cross-reference: UNC IRBIS Application section A.7.3.

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- Disease progression that requires discontinuation of the study intervention.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded in the Enrolled Participant Database. The study will retain participant data collected prior to withdrawal. We will not contact the participant to obtain any more self-report data, and the participant will not receive any further intervention. However, if the participant has completed any part of the intervention, we would like to continue to extract the participant's EHR data, and we will use the **Withdrawal Consent Addendum** (see Appendix) to seek permission to do so. If the participant withdraws prior to participating in the intervention, we will not collect any more of their data.

3.13 Loss to Follow-up

A participant will be considered lost to follow-up if they discontinue the intervention or are unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- As this is a pragmatic trial, the clinic will follow standard clinical operating procedures for missed appointments.

4 STUDY EVALUATIONS AND MEASUREMENTS

4.1 Efficacy Evaluation

4.1.1 Primary Outcome

Opioid dose, as measured by prescribed milligrams of daily MED, is the primary study outcome.[68] The primary outcome will be examined at baseline and months 6, 12, and 18 using opioid prescription data **(Table 3).** Prescribing data (including drug name, start and stop dates, dose, and frequency) will be derived from the EHR and provided by the PCORnet STAR CRN warehouse common data model (CDM). The field generally accepts prescribing data as documenting ingestion; other current and previously published studies also use prescribed dose as the primary endpoint.[17,20,21,68-72] However, we recognize that ingestion may not be the same as the prescribed regimen. We will analyze the absolute (primary) decrease (or increase) in opioid MED from the baseline period (average of 90 days prior to randomization) until 18 months after randomization. We also will examine percentage decrease. Total morphine equivalents for each prescription will be calculated by multiplying the quantity of each prescription by the strength of the prescription (milligrams of opioid per unit dispensed). The quantity-strength product is then multiplied by conversion factors derived from published sources to estimate the milligrams of morphine equivalent to the opioids dispensed in the prescription. The total average dose in morphine equivalents per day supplied is calculated by summing the morphine equivalents for each prescription filled during a given period and dividing by the number of days supplied.

4.1.2 Secondary Outcomes

The 2 secondary study outcomes, **physical function** and **pain interference,** are based on patient self-report **(Table 3).** These outcomes will be examined at baseline and months 6 and 12. They will be measured using validated scales that are widely recognized in the pain literature as core outcomes.[73] Both of the secondary outcomes were selected with input from patients and in consultation with pain experts,[74] and they are part of the Patient-Reported Outcomes Measurement Information System (PROMIS). PROMIS is a set of patient-centered measures that evaluates and monitors physical, mental, and social health in adults and children. The PROMIS pain interference (PROMIS-PI) is an 8-item assessment of the extent to which pain interferes with daily functioning. It is a standard outcome in pain clinical trials[73] and has excellent reliability and construct validity. The PROMIS physical functioning (PROMIS-PF) is an 8-item assessment of self-reported capability of general physical functioning over the past week rather than actual performance of physical activities.[75] It is considered by experts to be a standard for comparative effectiveness research in chronic pain.

Table 3. Primary and Secondary Outcomes

Domain	Outcome	Data Source	Title	# Items	Timepoints	Description
Primary outcome: **Clinical measure**	Opioid dose	PCORnet STAR CRN warehouse data derived from electronic health records	n/a	n/a	Baseline and months 6, 12, and 18	Average daily opioid dose in milligrams of morphine equivalent (MED).
Key secondary outcomes: **Patient Reported Outcomes (PROs)**	Pain interference	Patient survey	PROMIS Short Form v1.0 – Pain Interference 8a	8	Baseline and months 6 and 12	Assesses self-reported consequences of pain on relevant aspects of one's life. 5-point Likert scale.[74]
	Physical function	Patient survey	PROMIS Short Form v1.0-- Physical Function 8a	8	Baseline and months 6 and 12	Assesses self-reported capability rather than actual performance of physical activities. 5-point Likert scale.[75]

Note: MED = morphine equivalent dose; PROMIS = Patient-Reported Outcomes Measurement Information System

4.1.3 Other Self-Reported Outcomes

We will obtain additional self-reported outcome measures regarding pain intensity (both verbal 5-point Likert scale and numeric 10-point scale ratings) and numeric rating of physical function using the PROMIS pain intensity scale and may also use the 11 validated items of the Brief Pain Inventory (BPI) **(Table 4**).[76] Using both verbal and numeric ratings is recommended in the literature as an outcome measure for trials of chronic pain treatments. Doing so makes it possible to compare results across studies and limits the amount of missing data that results if some patients have difficulty completing one of the ratings.[73]

Chronic pain is often accompanied by emotional distress, anxiety, and depression,[73] and for this reason, we will measure anxiety and depressive symptoms at baseline, 6, and 12 months using PROMIS measures.

Intent to taper will be measured via self-report at baseline and months 6 and 12. The follow-up assessments at months 6 and 12 will also include a self-report measure of relative opioid use (no longer taking opioids, higher dose than baseline, or lower dose than baseline).

Covariates will include demographic characteristics, health insurance status, health literacy level, and patient-centered communication. Age, gender, race, and ethnicity will be included on the baseline survey. These self-report variables will be cross-referenced to EHR-derived data to confirm alignment of the two data sources.

Table 4. Additional Self-Reported Outcome Measures

Measure	Title	# Items	Timepoints	Description
Pain Intensity (verbal rating)	PROMIS Scale v1.0 Pain Intensity 3a short form	3	Baseline, months 6 and 12	Assesses how much a person hurts using a 5-point Likert scale. The first two items assess pain intensity over the past seven days. The last item for asks patients to rate their pain intensity "right now." [77]
Pain Intensity (numeric rating)	Brief Pain Inventory (BPI) – pain intensity sub-scale	4	Baseline, months 6 and 12	These items ask about level of pain and over the past week, with responses on a numeric scale of 0 to 10.[76]
Pain Interference (numeric rating)	Brief Pain Inventory (BPI) pain interference sub-scale	7	Baseline, months 6 and 12	These items ask about pain interference over the past week, with responses on a numeric scale of 0 to 10.[76]
Emotional distress (Anxiety)	PROMIS—Anxiety, 4-item Short Form	4	Baseline, months 6 and 12	Assesses generalized anxiety/distress over the past 7 days. 5-point Likert scale. [78]
Depressive symptoms	PROMIS Short Form v1.0 – Depression 4a	4	Baseline, months 6 and 12	Assesses depressive symptoms over the past 7 days. 5-point Likert scale.[78]
Demographic characteristics	n/a	8	Baseline	Age, race, ethnicity, assigned sex at birth, gender identity, education, marital status, and employment status
Health insurance status	n/a	1	Baseline, months 6 and 12	This item assesses if a patient has health coverage and what type
Health literacy	Health Literacy Skills Instrument (HLSI)	4	Baseline	Assesses the patient's understanding of health information.
Patient-centered communication	Patient-centered communication	6	Baseline, months 6 and 12	Assess the patient's experience with care and communication

4.1.4 Other EHR-Derived Outcomes

Cross-reference: UNC IRBIS Application section A.9.1 (identifiers).

Other measures collected through the PCORnet CDM include:

- Demographic information (birth date, sex, race, and ethnicity)
- Patient height and weight
- Health care provider information
- Death information (death date and source)
- Health care visit information (visit dates, primary payer, facility type, and provider ID)
- Diagnosis and condition information (condition data and type, diagnosis dates, and associated ICD/CPT codes) for:
    - Mental health disorders, defined by ICD-10 codes (e.g., depression, anxiety, schizophrenia, bipolar disorder, suicide attempt/intent)

  - Number and type of CNCP conditions per ICD-10 codes (e.g., back pain, neck pain, headache, arthritis, HIV)
  - Alcohol/substance misuse or abuse as measured by ICD-10 codes.
- Overall comorbidity using the Charlson Comorbidity Index per ICD-10 codes[79]
- Opioid prescription information including RxNorm CUI (drug prescribed), prescription dates, dose, units, frequency, route, quantity, refills, and supply days.

We will calculate time to discontinuation of opioids, where discontinuation will be measured based on our previous work,[20,21] except that the discontinuation will be defined as the first day of a minimum 90-day period with no opioid prescriptions (see Section 5.2 for additional information about the definitions and analyses).

A Schedule of Assessments indicating the timing and source of efficacy, safety, and fidelity measures is presented in **Table 6.**

4.2 Safety Evaluations

See Section 8 for information about the study's safety evaluations and procedures.

4.3 Process Evaluation

Cross-reference: UNC IRBIS Application section A.9.1 (identifiers).

The research team will develop a set of intervention fidelity measures to assess the extent to which the intervention was implemented as planned. The research team will evaluate fidelity via: EHR documentation review with a random sample of notes, clinical data extraction, and patient self-report. The measures are described in **Table 5**.

Table 5. Process Evaluation

Evaluation	Measure	Data Source
SDM intervention fidelity	Extent to which patients read or viewed SDM materials	Patient self-report (T2 and T3 surveys)
	Number of visits to an SDM-trained provider during the intervention period	Extracted from EHR using intervention-specific templates Visit status data entered into REDCap by the Research Coordinator
	Content covered during SDM intervention visits	Provider report via EHR encounter notes using intervention-specific templates
MI+CBT-CP intervention fidelity	Number of intervention sessions attended	CBT session attendance logs which will be entered as visit status data in REDCap by the Research Coordinator
	Content covered during sessions	Provider report via EHR encounter notes using intervention-specific templates
Opioid care guidelines (GCC) fidelity	Elements of GCC covered, e.g. the patient has had a UDT within the past 12 months, Prescription Drug Monitoring Program [PDMP] was checked	Provider report via EHR encounter notes

Table 6. Schedule of Assessments

Measurement	Screening (Month -12 to 0)	Enrollment/ Baseline Survey (Month 0)	Baseline Clinical Data Extraction (Month -3 to 0)	Intervention visits (Months 1-12)	Clinical Data Extraction (Months 6, 12, 18)	T2 follow-up survey (Month 6)	T3 follow-up survey (Month 12)	Qualitative research activities
Informed consent	●							●
Demographics		●	●					
Randomization		●						
Average daily opioid dose			●		●			
Charlson Comorbidity Index (ICD-9/10)			●					
Chronic noncancer pain conditions (ICD-9/10)			●					
Mental health disorders (ICD-9/10)			●					
Alcohol/substance use disorders (ICD-9/10)			●					
Body mass index (based on height and weight)			●					
Health insurance payer		●	●		●			
Opioid withdrawal or overdose medication prescriptions			●		●			
Study intervention intensity (based on number of intervention visits)					●			
PROMIS self-report scales: (Pain Interference, Physical functioning, Pain Intensity, Anxiety, Depression)		●				●	●	
Brief Pain Inventory (11 key items)		●				●	●	
Health literacy level		●						
Patient centered communication		●				●	●	●
Self-reported relative opioid use						●	●	
Intent to taper		●				●	●	●
Use of intervention content						●	●	●
Satisfaction with care		●				●	●	●
Adverse Events and death review and evaluation			●	●	●	●	●	
Fidelity review and evaluation				●		●	●	

Cross-reference: UNC IRBIS Application section A.9.1 (identifiers).

5 STATISTICAL CONSIDERATIONS

5.1 Summary of Statistical Analysis

Cross-reference: UNC IRBIS Application section A.8.1.

Statistical analyses for this study have been designed to compare (1) the effectiveness of the 2 interventions (MI+CBT-CP and SDM) in reducing opioid dosage among patients with CNCP, and (2) the effects of the 2 interventions on pain interference and physical function. The analyses will use data collected at baseline, 6, 12, and 18 months to evaluate these effects, and will formally test the primary hypothesis that the reduction in opioid dose (absolute change in MED) differs between the 2 intervention arms at 12 months and will describe differences in absolute change in opioid dose at 6 and 18 months and percent change in dose at each timepoint. The analysis also will formally test intervention arm differences for 2 key secondary outcomes: change in pain interference and physical function at 12 months. Change in outcomes at 6 months will be described. Primary and secondary analyses will use model-based approaches that take advantage of the longitudinal structure of the outcome data to address missing data caused by patient loss to follow-up or nonresponse.

The primary analyses will be based on the intention-to-treat (ITT) principle, with data from all participants analyzed according to the arm to which they were randomized irrespective of intervention received, as will key secondary analyses of pain interference and function. As in most clinical trials, some participants in this trial may not adhere to the intervention they were allocated to receive or comply with the intervention as prescribed, reducing fidelity to the intervention as designed and potentially changing the effectiveness of the intervention. The most likely form of noncompliance will be absence from group therapy sessions in the MI+CBT-CP arm or with patients on the SDM arm ceasing interaction with the assigned provider. The potential impact of this noncompliance is the dilution of the true treatment effect. In addition to the ITT analyses described above, we will conduct secondary analyses using a per protocol population that received a substantial portion of the randomized intervention, defined as at least 4 SDM sessions and at least 4 MI or CBT sessions. Details of the definition of this per protocol population will be provided in the Statistical Analysis Plan. The analysis plan will be drafted prior to the receipt of the initial PCORnet data extraction (Section 2.6) and finalized prior to REDCap study database lock and the final PCORnet data extraction.

Secondary analyses also will explore differences in the intervention effect according to participant characteristics, such as age, health literacy level, patient-centered communication, baseline pain level, baseline opioid dose, body mass index, and the presence of physical comorbidities, mental health comorbidities, or a history of substance abuse.

One single primary formal hypothesis test is planned for this study at the 0.05 level of significance, which is the comparison of the intervention arms for the primary outcome at the primary timepoint. Additionally, regardless of significance of the primary outcome, statistical significance of the 2 key secondary outcomes will be assessed, with adjustment for multiple comparisons using the Hochberg modification to the Bonferroni adjustment.[80] Primary and secondary hypothesis tests resulting in nonsignificant p-values will be interpreted as inconclusive. All other treatment group comparisons will be considered descriptive in nature with no adjustment for multiple comparisons, and all confidence intervals will be generated using 95% bounds.

5.2 Study Endpoints

5.2.1 Primary Endpoint

The primary outcome for this study is the absolute change in opioid dose (in MED) from baseline at 12 months post-randomization. Secondary timepoints for the primary outcome are at 6 and 18 months. Consistent with the pragmatic approach taken by this study, change in opioid dose will be based on data on opioid dose extracted from the medical record, as available in the PCORnet CDM. Opioid dose will be calculated as the prescribed milligrams of daily MED averaged over the 90-day period prior to randomization and 3, 6, 9, 12, 15, and 18 months post randomization. For each of the post-randomization periods, change in daily opioid dose will be computed as the difference between the dose calculated during that period and the dose from the baseline period. Although the primary outcome is the change at 12 months (with secondary timepoints at 6 and 18 months), analyses will be based on a linear mixed model using data from all 4- through 18-month time periods to account for missing data and thereby maximize information used for the primary analysis. Percentage change in MED from the baseline period also will be evaluated in a secondary analysis focusing on key clinical dosing thresholds. The distribution of opioid doses will be evaluated prior to finalizing the analysis plan, and if opioid dose change from baseline is determined to be highly skewed and substantially non-normal, then opioid doses will be transformed to the natural log scale, and the primary analysis will compare the intervention arms based on the relative dose reduction. Details of the algorithm used to calculate milligrams daily MED and for modelling the primary outcome measure will be provided in the Statistical Analysis Plan.

5.2.2 Key Secondary Endpoints

We will examine 2 key secondary effectiveness endpoints: (1) change from baseline in self-report of pain interference at 12 months, and (2) change in self-report of physical functioning at 12 months. Each outcome will also be assessed at 6 months.

Pain interference is a measure of the extent to which pain interferes with patient physical, mental, and social activities. It is an outcome that has been identified by patients in the target population as a critical patient-centered outcome for evaluating the potential effects on an opioid-reduction strategy. For this study, pain interference will be measured through patient-reported assessments at baseline, 6 and 12 months using a standardized instrument, the 8-item PROMIS-PI scale. The outcome measure is defined as the change in the total pain interference scale score from baseline to 6 and 12 months. The PROMIS-PI scale is a T-score based on PROMIS normative data such that a score of 50 represents the average score for the normative population and 10 is the standard deviation (SD) of that population.

A concern frequently expressed by patients with CNCP is a reduction in physical function that can be associated with both the chronic pain and opioid use. For this study, we will measure physical functioning using the 8-item PROMIS-PF instrument. The outcome measure is defined as the change in the total physical functioning scale score from baseline to 6 and 12 months. The PROMIS-PF scale is a T-score based on PROMIS normative data such that a score of 50 represents the average score for the normative population and 10 is the standard deviation (SD) of that population.

5.2.3 Other Endpoints

Other effectiveness endpoints include self-report of pain intensity, anxiety, depressive symptoms, and PROMIS pain intensity. Outcomes are defined as the change in T-score based on the PROMIS normative

population from baseline to 6 and 12 months. The 4 items within the Brief Pain Inventory (BPI) pain intensity subscale are analyzed individually, and a summary measure is calculated as the average of the items. The 7 items of the pain interference subscale are averaged to make a summary score for the subscale, provided that at least 4 of the 7 items are non-missing.

Time to opioid discontinuation is an exploratory effectiveness endpoint. We will examine opioid discontinuation using time-to-event models. For this study, a participant is considered to have discontinued opioids after a span of at least 90 days in duration after the run-out of the last prescription (generally 30 days) and continuing until study completion at 18 months. To distinguish clearly between opioid discontinuation and switching to an alternate health care system, participants must also have at least 1 clinic visit within 180 days after the run-out of the last prescription to be considered an opioid discontinuation event. The day of opioid discontinuation is defined as the run-out date (generally 30 days) after the last opioid prescription. Participants who have a prescription within 120 days (or prescription run-out within 90 days) prior to study completion at 18 months (or the last data extraction), or have not been seen in clinic for 180 days, have withdrawn, or otherwise been lost to follow-up without first meeting opioid discontinuation status will be right censored at the end of the dosing period for their last recorded opioid prescription (generally 30 days) and included in the time to opioid discontinuation analyses as a censored outcome using standard statistical procedures. Additional details of the computation of this outcome measure will be included in the Statistical Analysis Plan.

Safety outcomes for this pragmatic open-label intervention trial are limited to SAEs and are noted in Section 8.

5.2.4 Intervention Adherence and Fidelity Assessments

Assessments of fidelity to the planned intervention are described in Section 4.3.

5.3 Statistical Analysis Methods

The following sections briefly describe the methods that will be used for the analyses related to the primary and secondary outcome measures describe above. Additional details for these methods will be provided in the Statistical Analysis Plan.

5.3.1 Primary Analysis Methods for Opioid Usage Outcome

For reduction in opioid use, we will use a constrained linear mixed model[81-83] to generate point and interval estimates of the reduction in opioid dose MED from baseline to **4, 6, 8, 10, 12, 14, 16, and 18** months and to test the hypothesis that this reduction differs between the 2 intervention arms. While the primary and secondary time assessments are at 6, 12 and 18 months, all available opioid prescription data from baseline through 18 months will be included in the model. This approach will provide consistent estimates and valid inferences under missing at random (MAR) data assumptions while accounting for correlation among multiple measures on the same participant. This mixed model will improve the power of the study and the precision of all estimates by allowing all available measures for an individual to be incorporated in the analysis, even if other timepoints are missing. The model will include fixed effects for the treatment group, time interval (as a categorical variable), treatment-by-time interaction, baseline opioid dose, the stratification effect of institution, and random effects for participant. An intervention-arm–specific Toeplitz correlation structure will be assumed for the within-participant measures, to reflect the changing correlation of these measures over time and permit the

correlation structure to differ between study arms. The model will be used to generate point and interval estimates and to test differences in mean changes in opioid dose between the 2 intervention groups at 12 months (primary timepoint) and to generate point and interval estimates at 6 and 18 months (secondary timepoints).

This model treats missing data as ignorably missing, assuming any missing data are missing at random, after accounting for baseline opioid dose. Sensitivity analyses based on multiple imputation procedures will be performed to evaluate departures from critical distributional and missing data assumptions. Plans to address missing data are further presented below (see *Missing Data* Section) and will be described in detail in the Statistical Analysis Plan. Assessments of model assumptions and goodness-of-fit will also be specified in the Statistical Analysis Plan.

5.3.2 Secondary Analysis Methods

Opioid Usage

Secondary analyses of reduction in opioid use for the per protocol population will use models analogous to those described above for the primary analysis. Comparable models also will be used to explore the effect of potentially important covariates for both the ITT and the per protocol populations.

PROMIS Pain Interference and Physical Functioning

Secondary analyses will generate point and interval estimates of mean change in physical function as measured by the 8-item PROMIS-PF scale and mean change in pain interference as measured by the 8-item PROMIS-PI score from baseline to 6 and 12 months and point and interval estimates of the mean difference between the 2 intervention arms. These secondary analyses will use appropriate linear mixed model-based approaches analogous to those described for the primary outcome analysis.

Other secondary outcomes (PROMIS anxiety, PROMIS depression, and BPI pain intensity and pain interference will be analyzed similarly.

We will explore the percentage of participants per group who experienced an increase in pain and a decrease is in dose. Additional analyses will compare the treatment groups for the incremental impact of opioid dose -reduction per unit change in pain interference and physical functioning score.

Incidence of self-reported intent to taper opioid medication, collected at baseline, 6 and 12 months, will be compared between treatment groups using chi-square test and logistic regression with adjustment for baseline dose and intent.

Opioid Discontinuation

To evaluate the time to opioid discontinuation, a Cox proportional hazards model with adjustment for baseline opioid dose and clinical institution will be used for both the ITT and the per protocol population. The model will be used to generate point and interval estimates of the hazard ratio comparing likelihood of opioid discontinuation for the two intervention arms.

Safety Analysis for Adverse Events

Each of the safety outcomes described above can be characterized as a binary outcome. For each measure, contingency tables will be generated that summarize the risk of occurrence by intervention arm. Because AEs are expected to be relatively rare, contingency table methods will be used to generate

point and interval estimates of the risk of each AE by intervention arm, with the interval estimates based on exact binomial confidence limits. Cochran-Mantel-Haenszel tests stratified by the 3 clinical institutions will be used to generate p-values that assess potential differences in odds ratios by intervention arm.

Assessments of Intervention Adherence and Fidelity

Adherence and fidelity of the intervention arms in terms of both the average amount of planned intervention received by the participants and the quality of the intervention administered relative to the required components (as assessed by the random sample of EHR note logs) will be described overall and will be compared across the time-course of the study and between institutions with descriptive statistics. Fidelity of GCC, to be provided in each of the intervention arms, also will be compared between intervention arms. Details for these analyses will be provided in the Statistical Analysis Plan.

5.3.3 Other Analysis Considerations

Subgroup Analyses (Heterogeneity of Treatment Effect)

While multiple subgroup analyses have an inherent risk of inflating Type I error, this trial offers a unique opportunity to generate hypotheses about the profile of patients most likely to benefit from the intervention. Consequently, planned secondary analyses will assess potential differential treatment effects for two subgroups: 1) defined by participants with comorbid mental health conditions and 2) sex. Descriptive testing of the heterogeneity of treatment effect, which is meant to be hypothesis generating, will be established based on the interaction test from a mixed effects model in which the subgroup variable and an intervention arm by subgroup interaction term are added to the model used for the primary and secondary outcome analyses to test the interaction between intervention arm and the subgroup at the primary 12-month timepoint. To account for the inherent decrease in power associated with interaction tests, these tests will be conducted at a level of significance of 0.1. Because the subgroup is of interest, model-based estimates of treatment effects will be generated within the subgroups even if formal heterogeneity tests are not statistically significant. Any reporting of subgroup analyses will document the number of subgroup analyses conducted to facilitate valid interpretation of subgroup results.

The study also will include descriptive analyses to explore heterogeneity of effect according to age, baseline pain score, comorbidities (including physical comorbidities and mental health disorders, and past or current alcohol or other substance abuse and related disorders), those taking other medications, patient health literacy level, BMI, and opioid dose used at baseline in 3 categories consistent with CDC guidelines: low (20-49 MED), moderate (50-89 MED), high (90 or more MED). Testing for heterogeneity of treatment effects for these subgroups will be considered exploratory as opposed to confirmatory, and the results will be interpreted with appropriate caution. Heterogeneity of effect based on receipt of intervention by telehealth versus in-person, and based on categorized number of intervention sessions received will be similarly explored.

Missing Data

The study will implement multiple procedures to prevent and reduce the amount of missing data and use appropriate statistical procedures to evaluate whether the results are robust to missing data. The risk of missing patient-reported outcome measures has been reduced by limiting the number of visits and assessments to those essential to achieve study goals and using “short” versions of instruments to

reduce burden. It is possible, however, that there may be some nonresponse to the 6- and 12-month patient reported outcome surveys. The sample size calculation assumed as high as 25% non-response at 12 months. EHR-derived data on opioid dosage is expected to be virtually complete based on standard PCORnet data extraction procedures, yet sample size calculations allow for up to 12% missing data at 12 months from lost to follow-up within the EHR or withdrawal of consent for use of EHR data. To reduce the risk of being unable to calculate the primary outcome because of missing or uninterpretable dosing instructions, MED will be derived using only the standardized and highly accurate fields: drug name, strength, and number of pills. In the event of missing medication information for a prescription (such as strength or number of pills), we will impute medication information from the 2 closest prescriptions by date, using an algorithm developed by our clinical content experts, and conduct sensitivity analyses with and without the imputed data.

Logistic regression models will be used to compare the demographic characteristics of participants who provided 18 months of EHR data as compared with participants who were lost to follow-up within the EHR or withdrew consent for study participation to identify possible differential attrition. For primary and secondary outcomes analysis, the planned likelihood-based analysis will produce unbiased results if the data are MAR; that is, not related to the unobserved value of the outcome, but can be related to observed values of the outcome or model covariates.

Although the MAR assumption is often reasonable, in this study it will be possible that even after controlling for other correlates of missingness and outcome data observed before participants are lost, likelihood of attrition may be associated with key outcomes of interest, including opioid use, physical function, and pain interference. Consequently, sensitivity analyses to the MAR assumption based on multiple imputation strategies to include control-based imputation as well as tipping-point analysis will be described in the Statistical Analysis Plan.

5.4 Sample Size and Power

Cross-reference: UNC IRBIS Application Section A.8.3.

Sample size estimates were generated to provide robust power to detect minimal clinically important differences (MCID) in reduction of opioid use between the 2 study arms.

Based on anecdotal information from the clinics participating in the study and data available from the Liebschutz[84] and Sullivan et al.[64] studies, a reasonable estimate of mean baseline opioid use across the planned study is 55 mg/day. Based on doses of this magnitude, providers involved with the study indicated that differences in dose reduction of 10 MED or greater were likely to be viewed as clinically meaningful. Consequently, sample size estimates were generated based on an effect size of a difference of 10 MED between the 2 intervention arms. The data available from the Liebschutz[84] and Sullivan et al.[64] studies indicate that a reasonable estimate of the coefficient of variation (ratio of standard deviation to the mean) for opioid dose levels is 1.45 (range of 1.19 to 1.54), suggesting that a reasonable estimate for the standard deviation of the dose level for this study is 80 MED. Finally, data from Liebschutz[84] and Sullivan et al.[64] suggest that correlation between the baseline and follow-up opioid use levels will result in a standard deviation of the change in opioid use of the same magnitude of the baseline standard deviation, and that controlling for baseline opioid use in an Analysis of Covariance model will reduce the residual mean square error for the test of treatment differences in the change in opioid use to no more

than 50% of the baseline level, or 40 mg/day. Based on these assumptions and an assumed minimally important difference of 10 mg/day, the number of evaluable independent participants required to achieve 80% power to detect a difference of this size is approximately 253 per study arm (total of 506), assuming no attrition.

The data available from Liebschutz[84] and Sullivan et al. [64] indicate opioid doses are approximately normally distributed on the natural log (ln) scale. If the change from baseline in opioid dose is also lognormally distributed, then based on the assumptions above the standard deviation of the change from baseline ln-dose, after adjusting for baseline dose would be approximately 0.650. Correspondingly, 253 participants per study arm provides 80% power to identify a 15% relative dose reduction.

To account for potential variance inflation associated with CBT group delivery (based on a group size of 8 and an interclass correlation coefficient of 0.01) and a potential loss of follow-up information on as many as 10% to 12% of participants because of attrition, the sample size was inflated by 20% to yield a total randomized size of 304 per study arm needed for the primary outcome at 12 months. Therefore, the total study sample size will be 608 randomized participants (**Table 7).**

Additional estimates of sample size requirements were generated based on the known psychometric properties of the secondary outcomes, PROMIS physical functioning and pain interference, under the assumption that at least 80% power is desired for the PROMIS Pain Interference scales. The scoring algorithm for the PROMIS scales is designed to construct a 100-point scale with a mean of 50 and standard deviation of 10. Furthermore, studies of the properties of the instruments indicate that the minimally important difference (MID) for the physical function scale is 2 units, whereas the MID for the pain interference scale is 3.5 units. Under an assumption of independent observations, a sample size of 786 evaluable participants would be required to achieve 80% power to detect the MID of 2.0 units for the physical function scale, and a sample size of 260 evaluable participants would be required to achieve 80% power to detect the MID of 3.5 units for the pain interference scale. With the planned total of 608 randomized participants, the power for the PROMIS Pain Interference score is 96%, while the power for the PROMIS Physical Functioning scale is 57%, with a 25% increase to account for attrition or missing PROMIS scale responses. No power calculations have been specified for subgroup assessments (**Table 8**).

A review of the opioid MED change from baseline will evaluate if the data is normally distributed or skewed and thus requires log transformation prior to analysis. If the change in MED is highly skewed, analyses will compare intervention arms for relative rather than absolute dose reduction. The study has comparable power to identify a 15% relative dose reduction between intervention arms.

Table 7. Sample Size Required to Obtain 80% Power for Primary and Key Secondary Outcomes

Parameter	Mean difference between groups for change from baseline	SD	Power	N (total)	Percentage increase to account for 1-year attrition and within-cohort correlation	N with increase for attrition*
Average Daily MED	10	40	80%	506	20%	608
PROMIS Pain Interference Scale	3.5	10	80%	260	25%	350
PROMIS Physical Functioning Scale	2	10	80%	786	25%	1060
*The n is increased by 20% in the calculation to account for expected within-cohort correlation and attrition from the study before the primary 12-month timepoint. A further 5% attrition was assumed for the PROMIS scales collected via web or phone.						

Table 8. Power for Primary and Key Secondary Outcomes with N=608 Randomized Participants

Total sample size	Primary aim: Power for opioid MED*	Secondary aim: power for PROMIS Pain Interference*	Secondary aim: Power for PROMIS Physical Functioning*
608	80%	96%	57%
*MID, SD, and loss to follow-up rates are the same as noted in Table **7**.			

5.5 Interim Analysis

The Data and Safety Monitoring Board (DSMB) will routinely monitor the study for safety, conduct, and fidelity assessments of GCC, SDM, and CBP-MI with details of the monitoring approach specified in the **DSMB Charter** (see Appendix), the Data and Safety Monitoring Plan (DSMP), and the Statistical Analysis Plan. The DSMB will not formally monitor efficacy or effectiveness outcomes for purposes of stopping the study early (either due to demonstrated efficacy or futility).

6 STUDY INTERVENTION

Cross-reference: UNC IRBIS Application Section B.3.5.

This section describes the 2 interventions we will compare for managing CNCP patients on COT: a guideline-concordant pharmacotherapy approach with SDM (Arm 1) compared with a guideline-concordant pharmacotherapy approach with MI and CBT for chronic pain (Arm 2). Both arms of the intervention will be integrated into the usual workflow of the clinics. The first three months of the SDM intervention are the most intensive, similar to how the first three months of the CBT arm are the most intensive.

Participants in each of the study arms will receive guideline-concordant care (GCC), based on CDC clinical guidelines for COT for CNCP at their opioid management visits for the 12-month intervention period.

In light of the COVID-19 outbreak, the study will take measures to protect research participants, researchers, and the larger community from risk of infection.

Participant research visits will be performed remotely when appropriate and possible, via phone or telehealth/telemedicine. Telehealth services used will meet the study's security level clearance. The content of the interventions in the study will remain unchanged. Each institution will work with their IT departments to ensure they are using the telehealth services according to the institution's policy.

Participants who are currently enrolled in the trial will be given information about the change, the reasons for the change, and how the changes may impact their research activities. We will notify participants of the changes via phone call, letter, email, etc. and we will document how we notified them (see attached, Information for Participants on the INSPIRE study and COVID-19).

6.1 Guideline Concordant Care Intervention

CDC guidelines for treating adult patients for chronic pain in outpatient settings were developed to "improve communication between clinicians and patients about the benefits and risks of using prescription opioids to treat chronic pain; provider safer, more effective care for patients with chronic pain; and help reduce opioid use disorder and overdose." As a guideline for providers, the intervention content is primarily directed toward the providers participating in the study. The guidelines give guidance about medication selection, dose and duration, when and how to assess progress, and discontinue medication if needed. They support the patient-provider team to jointly assess the benefits and risks of prescription opioid use. Participants in each study arm will receive guideline-concordant pharmacotherapy treatment, based on clinical guidelines for opioid therapy for CNCP.

GCC specifies current best practices for primary care providers who are treating COT. The best practices include the following:

- *Determining when to initiate or continue opioids for chronic pain*
  - Not using opioids as first-line therapy (not applicable in this study, as participants will already be taking opioids)
  - Establishing goals with the patient for pain and function
  - Discussing risks and benefits with the patients

- *Determining opioid selection, dosage, duration, follow-up, and discontinuation*
  - Using immediate-release opioids when starting (not applicable if participants are already taking opioids)
  - Using the lowest effective dose
  - Prescribing short durations for acute pain
  - Evaluating benefits and harms frequently

- *Assessing risk and addressing harms*
  - Using strategies to mitigate risk—including patient risk assessment for prior SUDs and offering naloxone if increased risk or concurrent benzodiazepine use are present
  - Periodically reviewing state PDMPs to determine if patient is filling prescriptions or receiving opioid dosages elsewhere
  - Using UDT at least annually: UDTs are part of the opioid prescribing guidelines, which are now the standard of care for providers who prescribe opioids. They are not part of the intervention. Some clinics may use point of care UDTs, others may choose clinical laboratory tests in which the results will not be available during the clinic visit in which the urine was obtained. This will be up to each clinic on how they choose to handle the UDTs.
  - Avoiding concurrent opioid and benzodiazepine prescribing
  - Offering treatment for opioid use disorder

6.2 SDM Intervention

SDM seeks to explore and compare treatment options, assess a patient's values and preferences, and reach a shared decision between a patient and provider regarding current pain management options. SDM occurs when an SDM-trained provider and patient work together to make a health care decision that is best for the patient, which for this study is how to best manage pain with or without opioids. The optimal decision considers evidence-based information about available health care options, the provider's knowledge and experience, and the patient's values and preferences. The best way to ensure that patients can make an informed decision about their care is for them to have sufficient information about the benefits and risks of their current opioid treatment, other available treatment options, and appropriate use of opioids. With SDM, patients are typically given information in the form of decision aids that have been found to improve knowledge of treatment options, help patients feel better informed, are likely to promote more accurate expectations of benefits and harms, and most importantly to increase participation in decision making.

The SDM intervention will have both provider and patient educational components. The content of the provider component will be based on the AHRQ SHARE Approach, which is a 5-step SDM process that includes exploring and comparing the benefits, harms, and risks of each option through meaningful dialogue about what matters most to the patient. The patient materials are based on materials from AHRQ SHARE and the American Chronic Pain Association. The **SDM Combined Patient Packet** used across the course of the 12-month intervention period is provided in the Appendix. Patient-specific benefits and harms of continued opioid use are pertinent. Remote (e.g. phone and telehealth) visits are also documented in the EHR.

6.2.1 Enrollment Procedures for Arm 1

Cross-reference: UNC IRBIS Application Section B.3.2.

Arm 1 participants will receive **GCC plus the SDM intervention** during their opioid management visits. A provider trained in both GCC and SDM at their practice will conduct these visits. Patient visits may occur either in-person at the clinic or remotely using the clinic's telehealth platform.

The participant and provider will meet as often as needed for pain management. If the patient and physician decide that an opioid dose change is warranted, the patient may have more frequent visits with the SDM provider. A change in the frequency of visits due to medication changes is part of standard practice for opioid management and will be covered by health insurance. The patient may have a total of 4 to 12 visits over an approximately 12-month period. (We expect about one or more visits every 3 months to assess benefits and harms of opioid therapy. This would be for a patient on a stable dose of opioid medication who will not be adjusting the opioid dose during study follow-up. Patients who undergo opioid tapering may have more frequent follow-up visits to reinforce the provider-patient partnership, discuss potential withdrawal symptoms, such as temporary increase in pain, and assess pain and opioid management based on clinical judgement.)

If participants are assigned to Arm 1 and their provider is trained in SDM, the participant will continue seeing this provider for the 12-month intervention period. If the provider is not trained in SDM, participants will be asked to switch providers for opioid management care, and an SDM-trained provider will be assigned to the participant based on availability. In the study's consent form, participants are told about the potential need to change providers in order to receive opioid treatment from a trained provider. Participants will continue with their current PCP or another provider not trained in SDM for their non-opioid care—such as for acute or chronic conditions—with an understanding that only a provider trained in SDM can manage participants' opioid care.

Distribution of Patient Materials for Arm 1

SDM patient materials will only be provided to participants who have been randomized to Arm 1 of the study. The Research Coordinator will provide the **SDM Combined Patient Packet** (see Appendix) to the participant at the enrollment visit, electronically, or by mail. The SDM Patient Packet will include all the educational handouts (e.g., decision aids) so that participants who do not have Web access will have these documents. The packet will also contain links to Web-based versions of the materials for those who prefer to view the materials electronically. Participants will be strongly encouraged to review the suggested materials before each visit with the SDM provider.

To provide some structure to the SDM intervention, we have asked clinicians to review one or more study aids at each SDM visit as appropriate. The structure is intended to have some flexibility based on needs of the individual patient while providing guidance about content and order.

6.2.2 Coordination of Care

The SDM providers will document their opioid SDM discussion and management in an EHR note template, which will facilitate communication between the participant's SDM-trained and non-SDM–trained providers.

6.3 MI+CBT-CP Intervention

Participants in Arm 2 will receive guideline-concordant pharmacotherapy, plus an empirically-based behavioral pain management behavioral therapy intervention, including MI to enhance motivation for active participation in CBT-CP and for opioid dose reduction or cessation, and CBT-CP for pain--coping skills enhancement. The MI+CBT-CP intervention is an empirically based behavioral pain management therapy intervention. MI and CBT-CP have both been used effectively with chronic pain.

6.3.1 Enrollment Procedures for Arm 2

For Arm 2 participants, the GCC portion of the intervention will be delivered by the participant's primary care provider or pain specialist who is participating in the study and has been trained. The participant will continue to see the same provider for opioid management regardless of whether their provider is trained in SDM or not. Because Arm 2 participants will not receive SDM decision aids, the providers will be trained not to use SDM with these patients (even if they have been trained in SDM).

Licensed clinicians, including masters- or PhD-level psychologists, licensed clinical social workers, or licensed professional counselors, will deliver the MI+CBT-CP intervention**.** To verify the training of MI+CBT-CP providers, RTI will request proof/documentation of fulfilling the study's MI+CBT-CP training from each MI+CBT-CP provider. However, the MI/CBT-CP providers are clinical staff at their respective institutions and have experience with MI and CBT-CP. Thus, training will focus on the study MI/CBT-CP protocol, and not MI or CBT per se.

The intervention will include 1 individual MI session as soon as this session can be scheduled after enrollment and up to 8 CBT-CP group therapy sessions. We anticipate the MI+CBT-CP component of the intervention may occur within 3 months of enrollment but could extend longer. The process for scheduling the participant may vary slightly based on the institution or clinic. Study or clinic staff will continue to follow up with the participant until the individual MI visit and the group CBT sessions are scheduled. The goal will be to arrange for CBT to begin as soon as possible after the baseline interview.

The participant will be asked to attend one individual MI session that will last about 30 to 60 minutes, either in-person or via the clinic's telehealth platform.

MI is a style of interviewing, or a process, and because of this it is difficult to formally "manualize." (Indeed, it has generally been found to be less effective when manualized [personal communication, Stephen Rollnick, PhD].) Nevertheless, MI does have 4 processes: engagement, focusing, evoking, and planning, as described in **Table 9** and in the **MI-CBT-CP Therapist Manual** (see Appendix)**.** The MI session can be conducted anytime between the baseline interview and Session 6 of CBT. Further, additional MI will be woven into the CBT-CP sessions, as described in the CBT-CP session outline below.

If the participant is a no-show for the visit, standard clinic procedures will be used for any follow-up. This is consistent with a pragmatic trial and an ITT analysis.

Table 9. Motivational Interviewing Processes

1. Engaging a. Make patient feel comfortable, listen to their concerns b. Establish trust and mutually respectful working relationship c. Traps to avoid in the engagement phase: 1. Assessment trap 2. Expert trap 3. Premature focus trap—i.e., don't focus before engagement 4. Labeling 5. Blaming trap 6. Labeling trap
2. Focusing The focus is largely dictated by the setting and scope of the service provided (REF: M and R). Participants will enter the current study knowing that the purpose is to improve their functioning with chronic pain. A part of the effort to improve functioning is a discussion on how opioids fit with their pain management, their functioning, and other life goals—and the possibility of decreasing opioids. Consequently, the initial focus will be on the patient's chronic pain, well-being, their goals, barriers, and obstacles to their goals. One aspect of this will be a discussion on the role of opioids and possibly decreasing the dose.
3. Evoking The purpose is to strengthen motivation for change. Self-talk helps the patient express and resolve ambivalence. The patient expresses the pros and cons of available alternative strategies. In the case of opioids, the client would express what he or she sees as the advantages and disadvantages of decreasing opioids.
4. Planning MI addresses people according to their "level of change" (whether "precontemplative," "contemplative," or further along, such as in the "action" stage). While some patients may enter the study with a desire to reduce opioid dose, we anticipate that many will enter the study ambivalent about this. Regarding opioid dose, we anticipate that the patient could express a desire to (1) maintain the current opioid dose, (2) decrease opioid dose by taper, but continue to take opioids at a lower dose, (3) taper off opioids completely, or (4) increase opioids. While some plans may be developed at the initial MI session, planning will generally evolve during the CBT-CP sessions, which will also involve elements of MI.

Eight sessions of CBT-CP will be delivered in a group setting, in the clinic or over the clinic's telehealth platform. These sessions will focus on

- education about chronic pain,
- pacing and exercise,
- relaxation techniques, including deep breathing and progressive muscle relaxation,
- behavioral activation, including identification and scheduling of pleasurable activities,
- cognitive restructuring, including the identification and challenging of maladaptive thoughts, and
- behavioral sleep management training.

The topic of each CBT-CP session, aim, agenda, and patient handouts is outlined in the **MI-CBT-CP Therapist Manual**, which is included in the Appendix. The **MI-CBT-CP Session Guide and Handouts** for patients are also in the Appendix. These will be provided in-person, electronically, or by mail.

While the primary focus of CBT-CP will be to improve physical functioning, education on opioids also will be introduced. For example, we will include education on opioid effectiveness for CNCP (e.g., that opioids are not effective for many people) and opioid side effects. In the cognitive restructuring component, we will discuss common catastrophizing thoughts about medication (e.g., "I don't know what else to do for this pain other than take opioids").

The provider will document the intervention delivery in the EHR.

6.3.2 Coordination of Care

If during the MI or CBT-CP sessions, the participant expresses a desire to reduce their opioid dose or discontinue opioids, the therapist will inform the primary provider, with the participant's permission. The communication linkage between the therapist and the primary physician is crucial for the success of the trial.

To facilitate this linkage, following MI+CBT-CP group sessions, we will ask Arm 2 participants to self-report their perceptions of: the helpfulness of the CBT group sessions; the quality of their current approach to pain management; their ability to manage pain; and their goal with their opioid dose. The purpose of the form is to facilitate coordination of care. The information will only be used for clinical purposes and will not be used for data analysis.

This will be done via a form, the **Post-CBT Group Session Form** (see Appendix). The form is voluntary, and patients may skip any question they do not wish to answer. This form was developed with the input of patient representatives, primary care physicians, therapists, and the research team.

The form will ask the participant if their responses can be shared with their health care provider. If the patient says yes, the therapist will communicate the responses to the provider.

The form will be administered on paper if the CBT session is conducted in-person, and by mail or electronically if the CBT session is conducted remotely.

The inter-provider messaging system within the Epic EHR system will be the primary means of communicating the participant's motivation to decrease opioids.

We have worked with our clinical sites to solicit provider input to determine what is customary and feasible for this pragmatic trial. Means of communication may include copying the primary provider on the therapy note, sending information via secure email, requesting read receipts, requiring a response from the provider acknowledging they have read the note, and/or including the provider's nurse on the messages.

7 STUDY INTERVENTION TRAINING AND DOCUMENTATION

Cross-reference: UNC IRBIS Application section A.4.7.

7.1 CDC Guidelines Training Material Content for Providers

All primary care and pain care providers who provide opioid management to study participants will provide CDC GCC. Only providers who have the requisite GCC training will be able to see enrolled study participants.

7.1.1 CME Training for Opioid Therapy in Chronic Pain Patients

Many providers have already taken commensurate training as a requirement for maintaining their licenses or board certification, and they would be exempt from the study training. Training should have been completed within the past 12 months and administered by the state of North Carolina or Tennessee or an authoritative medical board. To document providers' qualifications to provide GCC, the study team will ask each study provider to (1) affirm documentation of state-level Continuing Medical Education (CME) training for opioid therapy in chronic pain patients or (2) complete study-specific training with the CDC guideline training modules.

7.2 SDM Provider Training

All primary care and pain care providers at clinical institutions will be asked to complete the SDM training. Only providers who have completed the study specific SDM training will be able to deliver the SDM intervention.

The content of the provider training will be based on the AHRQ SHARE Approach, which is a 5-step process for SDM that includes exploring and comparing the benefits, harms, and risks of each option through meaningful dialogue about what matters most to the patient, as shown in **Table 10.**

Table 10. SHARE Approach to Shared Decision Making

Review essential steps of shared decision making:
Step 1: Seek your patient's participation.
Step 2: Help your patient explore and compare treatment options.
Step 3: Assess your patient's values and preferences.
Step 4: Reach a decision with your patient.
Step 5: Evaluate your patient's decision.

7.3 MI+CBT-CP Provider Training

The study team will identify one to four providers to provide the MI+CBT-CP intervention. Only providers who have completed the study-specific MI+CBT-CP training will be able to deliver the MI+CBT-CP intervention. The training process will be based on *Motivational Interviewing* by Miller and Rollnick and *Managing Chronic Pain: A Cognitive Behavioral Therapy Approach Therapist Guide.*'[85]

7.4 Research Coordinator Training

All Research Coordinators will complete a study training prior to beginning of recruitment to review all elements of the protocol and their specific responsibilities.

8 SAFETY MANAGEMENT

8.1 Potential for Risk

8.1.1 Potential Psychological Risks

Cross-reference: UNC IRBIS Application section A.6.1, A.6.2.

There is a risk that some of the survey questions or intervention content could result in a participant feeling some emotional distress or embarrassment. The participant may refuse to answer the questions and may stop participation in this study at any time. A safety protocol (suicide prevention plan) will be activated in very rare instances in which a participant is feeling severe or life-threatening distress. Protocol Section 3.3, Screening, describes the procedures we will use to minimize these risks.

The chance of a breach of confidentiality is rare. There is a very small risk that someone could get access to study information we have stored about participants and may misuse it. Confidentiality is very important to us. We will take several steps to protect it, such as training staff, using secure databases, de-identifying data, collecting only the minimum amount of information necessary, and limiting access to the information. RTI will apply for a Certificate of Confidentiality from NIH. Research staff who have direct contact with participants are under the purview of HIPAA at their respective agencies. Other measures we are taking to mitigate risks to subjects' privacy and confidentiality are described in section 9.3, Protecting Confidentiality.

8.1.2 Potential Social Risks

Cross-reference: UNC IRBIS Application section A.6.3, A.6.4.

No potential social risks have been identified.

8.1.3 Potential Economic Risks

Cross-reference: UNC IRBIS Application sections A.6.5, A.6.6 (risks), B.5.1 (costs).

If the participant is randomized to the CBT arm, a co-pay may be required for each CBT session attended.

If the participant is randomized to the SDM arm, and if the participant changes opioid dose, there may be additional visits. These visits are part of the standard of care for opioid management. Clinical sites (Duke, UNC, VUMC) will work with clinic management to tailor delivery of the SDM intervention based on needs of their clinic. For example, one site may choose to enroll only the patients seen by SDM-trained providers whereas another site may have the patient switch all care to an SDM-trained clinician.

Thus, clinics can do one or more of the following if they deliver the intervention as outlined in the protocol:

- Enroll patients from only SDM-trained providers
- Adhere to clinic guidelines that use dual management of pain patients (which is currently in place in some of the clinics)
- Have SDM providers provide primary care as well

We will be fully transparent with the potential respondents when we explain the study to them, that they will be responsible for additional co-pays that may be incurred as part of the research.

8.1.4 Potential Legal Risks

Cross-reference: UNC IRBIS Application section A.6.7, A.6.8.

The study will collect information about alcohol/substance abuse and misuse via the subject's electronic medical record data, as measured by ICD-9/10 codes. The subject will not be asked about these topics via self-report surveys.

The major legal risk to subjects would come from a breach of privacy & confidentiality. To mitigate this risk, the EHR data will be de-identified and will use a study identifier instead of patient identifiers. We will have data use agreements in place to share the data across institutions. Other measures we are taking to mitigate risks to subjects' privacy and confidentiality are described in section 9.3, Protecting Confidentiality.

8.1.5 Potential Physical Risks

Cross-reference: UNC IRBIS Application section A.6.9, A.6.10.

There is some potential risk that participants may experience increased pain if they reduce or discontinue their opioid medication.

We expect any side effects to be rare or infrequent and mild-to-moderate.

This study is comparing two different behavioral interventions for patients with chronic pain who are already on chronic opioid therapy. Some of the intervention content is about tapering or discontinuing opioids. The participant may choose to request to taper or discontinue opioids. Lowering the dose of opioids has the potential for side effects from withdrawal. But, there are no extra risks from this study compared to discontinuation as part of usual care.

The approach of this trial is to promote a controlled opioid reduction, which in some cases might lead to complete discontinuation, with a patient's consent. The protocol does not specify or foresee abrupt tapering.

If patients do choose to taper, the physicians will be doing a very gradual taper of their opioids (as per CDC guidelines, 10% per week), which has rare to infrequent risk of withdrawal. If withdrawal is experienced, mild to moderate symptoms are expected. These symptoms may include low energy; irritability; anxiety; agitation; insomnia; sweats; muscle aches and pain; as well as abdominal cramping, nausea, and vomiting. Patients will be advised to call their provider if they experience symptoms of withdrawal.

To reduce physiological risk, certain safeguards will be implemented at RTI and at all clinical institutions. Procedures to reduce clinical risk include intensive medical monitoring of AEs and medical management common for this study population.

8.2 Risk Monitoring

8.2.1 Human Subjects Protection

We have developed a plan for protecting human subjects, beginning with obtaining IRB approval. The 3 clinical institutions that are part of the PCORnet STAR CRN—UNC, Duke, and VUMC—have taken steps to enter into a reliance agreement to utilize a single IRB at UNC to review this project.

Assurances that the benefits of study participation outweigh the risk are made through informed consent procedures, maintenance of participant confidentiality, adherence to HIPAA regulations, and close monitoring and reporting of AEs. All research staff who will assist with this pragmatic trial (i.e., those who contribute to the scientific development or execution of the study in a substantive, measurable way) will complete the appropriate Collaborative Institutional Training Initiative (CITI) modules, so that they are aware of requirements for protection of human subjects. Each of the participating institutions and RTI holds a Federal-Wide Assurance (FWA) for the Protection of Human Subjects, which ensures that the institution's human research activities comply with the requirements set forth in 45 CFR 46. In addition to the federal regulations, RTI will take into consideration any state or local laws regarding human subjects that may be more protective than the federal statutes.

All the institutional IRBs will monitor the research process at their respective practice under the SMART /single IRB arrangement noted above to ensure that the procedures for protecting human subject rights are followed by their staff. RTI and the participating institutions will maintain all records of initial and annual approvals.

8.2.2 Data and Safety Monitoring Board

Cross-reference: UNC IRBIS Application A.7.2.

The study has a DSMB that consists of individuals who are not participating investigators in this trial. The primary responsibility of the DSMB is to review cumulative study data to evaluate safety, study conduct, scientific validity, and data integrity to ensure that the study is operating in a safe and ethical manner. The DSMB will meet 2 times per year to review the accumulating data and recommend necessary changes to the conduct of the trial. The RTI Coordinating Center will prepare and submit reports to the DSMB. The report will include all AE data reported in REDCap (available from the PCORnet CDM data extraction or provided by self-report during participant surveys) and will be summarized by the RTI Data Coordinating Center and sent to the DSMB biannually for review.

8.2.3 Data and Safety Monitoring Plan

Cross-reference: UNC IRBIS Application A.7.2, C.1.1.

The study team has developed and finalized a DSMP. This plan will adhere to the PCORI guidelines on DSMPs.

8.3 Adverse Event/Serious Adverse Event monitoring and reporting procedures

An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the

subject's participation in the research (modified from the definition of AEs in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

An SAE is an AE that meets any one of the following criteria: results in death, is life threatening, or requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, birth defects or based on medical judgement may jeopardize the participants health or may require medical or surgical intervention. This study does not involve an investigational product, device intervention, or highly invasive data collection procedure. However, recognizing that unanticipated events (see below) can occur during any study, the following reporting protocols will apply.

Study participation and exposure to the interventions are expected to have a moderately low risk of AEs for participants, in the form of adverse effects associated with reduction of opioid dosage. At the same time, the underlying chronic conditions of the participants may naturally lead to deleterious health outcomes. To efficiently collect safety information that is relevant to study participation and the interventions, detailed information concerning a prespecified set of AEs and SAEs will be collected and evaluated throughout the conduct of the trial.

8.3.1 Reportable Adverse Events and Serious Adverse Events

For the purposes of this study, an event will be considered *reportable (collected for data entry)* if it meets at least one of the criteria below. The AEs and SAEs shown in **Table 11** will be recorded and reported. SAEs not on this list will not be recorded or reported.

Table 11. Reportable Events and Assessment Methods

Reportable Event	Assessment Method
Suicide risk (active suicidal ideation or attempted suicide) (see section 8.3.5 below)	Adverse Event Case Report Form
All Deaths (including opioid-related, suicide, and all other deaths)	Adverse Event Case Report Form, PCORnet EHR-based data, National Death Index (available after study completion), publicly available data
Hospitalizations or Emergency Department (ED) visits related to opioid use (overdose or withdrawal) or related to suicide attempt	Adverse Event Case Report Form, PCORnet EHR-based data, patient self-report via 6- and 12-month follow-up surveys

When one of these AEs is identified, the institution PI or designee will assess the event to evaluate whether it is one of the following:

- Unanticipated (i.e., unexpected). These events are AEs that are new or greater than previously known, in terms of nature, severity, frequency or occurrence, as documented in the protocol, consent, or other study documents approved by the IRB (OHRP-https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html).
- Related (possibly related, probably related, or definitely related) to study participation.

Institutions will record all reportable events in REDCap in the Adverse Event Case Report Form.

Reporting will either follow an expedited or periodic timeline.

8.3.2 Expedited Reporting

Expedited reporting procedures must be followed when an SAE meets both of these conditions:

- SAE is considered **unanticipated/unexpected,** AND
- at a minimum, **possibly related** to study participation.

Institutions must report expedited SAEs within 2 business days of the Institution's awareness to the single UNC IRB and to RTI. RTI must notify DSMB of the event within 24 hours. RTI must provide a summary report of the event to DSMB within 7 days.

8.3.3 Periodic (Non-Expedited) Reporting

Periodic (Non-Expedited) reporting procedures must be followed when the SAE meets both of these conditions:

- SAE is considered unanticipated/unexpected OR expected AND
- SAE is NOT related to study participation.

RTI must provide a summary report of the event to DSMB at the next DSMB meeting as part of the regular DSMB meeting report.

8.3.4 Unanticipated Problems

The study will collect and report unanticipated (i.e., unexpected) problems that may involve risk to the participant or study staff, but do not necessarily result in an AE (i.e., harm). An example of an unanticipated problem that may not result in an AE is misplacement of a participant's research record containing PII such that the risk of loss of confidentiality is introduced. This event is reportable regardless of whether the confidentiality is breached or not breached.

Institutions must report other unanticipated problems that are not SAEs but involve substantial harm (or genuine risk of substantive harm) to the safety, rights, or welfare of the institution's research participants, research staff, or others to the single UNC IRB and RTI within 5 business days.

Otherwise, the institution will report unanticipated problems to the single IRB and RTI on an annual basis at the time of continuing review.

8.3.5 Suicidality

We will capture suicide risk (active suicidal ideation or attempted suicide) during the intervention period during clinical encounters. As this is a pragmatic unmasked behavioral intervention trial, suicide risk will only be captured if the participant indicates intent to self-harm during the clinical intervention visit; the provider will not conduct a study-specific suicide risk assessment. If the clinic becomes aware of suicide ideation, the provider will follow the institution's or clinic's protocols, as described in our **Safety Protocol** (see Appendix). Similarly, if active suicide ideation is self-reported to the research coordinator during the screening visit review of exclusion criteria, the provider will be notified and will follow the institution's or clinic's protocols.

The therapists delivering the MI +CBT-CP intervention will all be masters- or PhD-level mental health providers with training and experience handling suicidal patients. If a participant does express suicidal ideation, the therapist will handle it in the manner that they would in their clinical practice. Similarly, if a participant being seen in the SDM intervention (Arm 1) expresses suicidal ideation, the clinic will handle it in the manner that they would in their clinical practice.

The provider will report the event to the institution's Research Coordinator, and the Research Coordinator will complete an Adverse Event Case Report Form.

We will capture whether the participant has been to the ED or had an inpatient hospitalization because of self-harm via self-report and PCORNet CDM data extraction. We will capture information on when and where this occurred.

8.3.6 Deaths

If site study staff become aware of the death of a participant, the site will report the event via the adverse event case report form. We will include the cause of death in the report. If the cause of death is unknown and not available in the EHR, the study's DSMB has requested that the study try to obtain cause of death information from the participant's death certificate. The DSMB will use the information to make an objective decision about whether the death was possibly related to the study.

Study staff at the enrolling site will request a copy of the death certificate from the appropriate state agency, if such information is publicly available. Whether death certificates are available publicly depends on the state. The NC Department of Health and Human Services makes available uncertified copies of death certificates for informational purposes to anyone who requests them, unless legal restrictions apply. Study staff will abide by the applicable state and local laws in making any such request. When requesting death certificates, study staff will not disclose any information linking the decedent to their participation in the INSPIRE study.

Once the death certificate is obtained, the site will provide the cause of death information to RTI via the adverse event case report form. RTI will then use this information to update Serious Adverse Event (SAE) reports that are provided to the DSMB.

9 DATA MANAGEMENT

Cross-reference: UNC IRBIS Application Section A.8.4.

9.1 Pre-Enrollment Data Management

Most eligibility inclusion and exclusion criteria will be determined from data recorded in the institution's EHR. Institution informatics staff will use specified criteria to develop an EHR recruitment phenotype report, in the form of a file that lists patients names, demographics, provider names, and key selected criteria for patients who meet this initial screening criteria. This file will be produced by each institution at regular intervals and be stored in a secure study folder on a HIPAA-compliant server, with access restricted to study staff. Prior to study startup, the study team will validate the phenotype and make any adjustments as needed.

All details of participant screening and recruitment will be tracked by the clinical institutions in a Pre-Screening Database stored in a secured electronic environment within each clinical institution.

To facilitate remote enrollment, we will use electronic versions of the enrollment forms (Consent to Screen, the Study Consent, the HIPAA Authorization, and the Participant Contact Information) in a REDCap database stored securely at each clinical institution. These REDCap databases will be separate from the central REDCap study database stored at RTI because they will contain PII. Electronic signatures will be captured using REDCap's Consent module. REDCap will generate and store a signed version of the consent form as a PDF. The participant will have the option to download a copy of their signed consent form.

Summary/aggregate screening data (such as counts) will be reported by the institutions to the RTI Data Coordinating Center via a central REDCap study database accessible by RTI to facilitate accurate reporting according to CONSORT standards.

9.2 Enrolled Participant Data Management

We will use REDCap[86] as our core data capture system and repository for the aggregation of participant screening, recruitment, enrollment, tracking, and baseline self-reported outcome data.

REDCap is a secure (Health Insurance Portability and Accountability Act of 1996 [HIPAA], 21 Code of Federal Regulations [CFR] Part 11), and Federal Information Security Management Act (FISMA)-compliant web application designed to facilitate participant enrollment, randomization, tracking, and multiple modes of data entry.

For consented participants, baseline monitoring and screening information will be entered into the central REDCap study database stored at RTI, and eligible participants will be randomized directly in REDCap. Collection of patient-reported outcomes at baseline will be performed using REDCap's web-based survey tools. Should some participants find the tablet challenging, paper forms will be available. Subject status and adverse events will also be recorded in the REDCap Study database.

9.3 Follow-Up Survey Data Management

RTI staff will collect the 6- (T2) and 12-month (T3) follow-up surveys using a combination of Voxco for survey data collection (via web and CATI) and the RTI's in-house survey management system (Nirvana) system for case management. Follow-up data collection will be scheduled automatically at the appropriate assessment time from the participant's randomization date.

Voxco is an integrated interviewing and case management system that provides state-of-the-art tools for conducting telephone survey research. The Voxco system runs in RTI's Federal Information Processing Standards (FIPS) moderate network, providing a secure data collection environment for data collection projects.

RTI's in-house survey management system, **Nirvana**, is a control and case management system for multimodal survey projects and runs in RTI's FIPS moderate network.

9.4 Qualitative Data Management

RTI staff will collect qualitative data using a web conferencing platform (for example, Zoom or BlueJeans). We will take security measures including:

- Using a unique, automatically generated meeting ID
- Requiring a password for the meeting
- Using the "virtual waiting room" to approve meeting participants before entering
- Locking the meeting after it has started
- Preventing participants from screen sharing

RTI staff will consult with the RTI Privacy Officer to make sure that the platform used adheres to institution requirements.

9.5 Quality Assurance

All staff involved with data collection will be required to have training on use of the study data management systems. Staff may contact the RTI Data Coordinating Center by telephone or e-mail with questions about recording study data or conducting randomizations in REDCap. The REDCap, Nirvana, and Voxco data collection screens will have embedded quality control measures such as reports on missing data fields and range-checks on data fields where applicable. Additional reports may be developed to check cross-form and cross-data source consistencies. These reports facilitate timely identification and resolution of problems in data collection and processing.

10 CONFIDENTIALITY OF THE DATA

10.1 Procedures for Maintaining Confidentiality

Cross-reference: UNC IRBIS Application A.10.1, A.11.2, B.1.8, B.3.6 (privacy procedures)

As with any research, the potential exists for a breach in confidentiality; however, this is very unlikely.

Study sites will establish and maintain the appropriate administrative, technical, and physical safeguards to protect the confidentiality of the data and to prevent unauthorized use or access to the data. The study will not disclose data nor permit others to use the data except as described in this protocol. Access to hard copy or electronic data is restricted to authorized staff members.

To maintain confidentiality during enrollment:

- During in-person enrollment, survey data will be collected in a private location, which reduces the risk that answers to interview questions will be overheard by others not directly involved in the research and which promotes comfort in discussing sensitive issues.
- Similarly, during remote enrollment, the RC will ask the patient to complete screening and enrollment in a private location.
- Information obtained through these processes will not be disclosed to anyone who is not directly involved in the study, except in cases where potentially life-threatening conditions are revealed.

To maintain confidentiality during group intervention sessions:

- Participants will be told that all information shared during the session is private and should not be shared with anyone outside the group session.
- The therapist will record information about these sessions in the form of a Patient Encounter note within the EHR to be used as an indicator of adherence with the study intervention.
- Because the post-CBT group session form is only used for clinical purposes, it is not linked to the participant ID. Participants will be asked to complete the form in a private location and return it at their next session in an envelope, in order to reduce the risk that their responses will be seen by others. After the therapist confidentially reviews the form, he/she will destroy the hard copy form as per institution policy.

To maintain confidentiality of the data:

- To ensure consistent data linking across all clinical institutions, the PCORnet data warehouse uses a global unique identifier (GUID) to uniquely identify a patient's EHR data. A GUID is a long, unique, alphanumeric identifier generated by key identifiable information that is typically collected as part of the patient's medical record. Use of a GUID facilitates the unique identification of each patient, without the need to transmit PHI or PII.

- Identifiers will be stored separately from the research data. Research data will be coded with a study-specific participant identifier. The linkage file between the participant ID and PII will be stored in a different file location maintained by study recruitment staff.
- The participant ID will be used to link research data across data collection sources and the study's REDCap, Voxco, and Nirvana data capture systems.
- All transfers of EHR data from each clinical institution's PCORnet data warehouse to the RTI Data Coordinating Center will be limited to protocol-specified data elements for randomized study subjects and will be identified only by the participant ID and not the GUID.

To maintain confidentiality during qualitative research activities:

- Participants will be told that all information shared during the session is private and should not be shared with anyone outside the group session.
- We will use a secure web conferencing platform and adhere to RTI requirements for use of web conferencing with research studies.
- We will only record audio and not video. We will also tell participants not to record the session or take screenshots.
- Audio recordings will be stored on secure, encrypted computers. They will only be used to create transcripts.
- Qualitative data will not be connected with the participant's main study participant ID.
- Participant responses will be coded with a separate identifier for the qualitative research component. The linkage file between the qualitative ID and PII will be stored in a different, secure file location maintained by RTI staff.
- Transcripts will not contain PII.
- Qualitative data will not be shared with site research staff or health care providers.

10.1.1 Certificate of Confidentiality

Cross-reference: UNC IRBIS Application A.10.4, B.3.6

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to 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. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.2 Procedures for Data Transmission

Cross-reference: UNC IRBIS Application section A.10.2, A.11.1, A.11.2, C.1.2, C.1.3, C.2.1 (DUAs)

Data Use Agreements (DUAs) will be completed between RTI and each study site prior to the transfer of any data if required by the institution.

10.2.1 PCORnet DataMart Extractions and Data Transfer

RTI and clinical and data warehousing staff will collaborate to identify a specification of data elements within the PCORnet common data model required for the study. The STAR CRN uses the PCORnet CDM to map EHR data to the same format across all participating institutions. PCORnet data warehousing staff will develop and implement software to extract the specified data elements into a study-specific DataMart extraction, which after validation at the institutions, will be transferred to the RTI Data Coordinating Center at prespecified times during the study.

The EHR data extracted from each study site's CDM will be uploaded to the RTI Data Coordinating Center via a HTTP Secure File Transfer Protocol (SFTP) setup by RTI. SFTP provides a high level of security (SSL Encryption) and allows sites to transfer files via a web browser. Each site will only have connection to their own sites' SFTP folder, which is accessed via a username and password. These credentials will only be provided to each site's Project Manager and CDM programmer. The EHR data will be housed on the FIPS Low server at RTI because they will not contain PHI/PII.

10.2.2 Transfer of Participant Contact Information for Follow-Up Surveys

Each clinical site will provide participant contact information (as described on page 37) to RTI International so that RTI can conduct the T2 and T3 follow-up surveys. Only contact information for randomized study participants will be shared.

A separate SFTP will be setup to transfer the participant contact information to the Data Coordinating Center in order to conduct the follow-up surveys. Because these data contain PHI/PII, they will be housed on a FIPS Moderate server at RTI that meets FIPS-199 requirements for PII, including Risk/Impact Levels of confidentiality (moderate), integrity (moderate), and availability (low).

10.3 Collection of Sensitive Information

Cross-reference: UNC IRBIS application A.10.3.

The research data collected from the EHR will include the following information that some individuals may consider sensitive:

- Mental health disorders, defined by ICD-10 codes (e.g., depression, anxiety, schizophrenia, bipolar disorder, suicide attempt/intent)
- Alcohol/substance misuse or abuse as measured by ICD-10 codes

These data will not contain any identifiers and will be labeled only with the study-specific participant ID.

10.4 Post-study disposition of identifiable data

Cross-reference: UNC IRBIS application A.12.1

At the end of the study, a de-identified public-use study database will be delivered to PCORI. The de-identified database will be limited to the items specified in Section 4 (Study Evaluations and Measurements) and will not include any participant identifying information, such as dates, text fields, extremely rare and potentially identifying events, or other potentially identifying data.

11 PLANS FOR PUBLICATION

We plan to disseminate the study findings via conference presentations and peer-reviewed publications in professional journals. Any study findings that are reported in professional journals or at meetings will not contain any PII or PHI. The study leadership team will develop a publication policy for the study. No patient identifying information will be included in any disseminated products.

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