NIH Collaboratory Ethics and Regulatory Core: UG3 Planning Phase Consultation Call
Adapting and Implementing a Nurse Care Management Model to Care for Rural Patients With Chronic Pain (AIM-CP)
November 15, 2023; 12:30-1:30 pm ET (via Zoom)

Attendees:

- Core, Coordinating Center, and NIH: Joe Ali (Johns Hopkins University), Beda Jean-Francois (NCCIH), David Magnus (Stanford University), Kevin McBryde (NCCIH), Kayla Mehl (Johns Hopkins University), Stephanie Morain (Johns Hopkins University), Pearl O'Rourke (retired), Caleigh Propes (Johns Hopkins University), Tammy Reece (Duke University), Kevin Weinfurt (Duke University), Dave Wendler (NIH)
- Demonstration Project team: Kushang Patel (University of Washington)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS	OWNER
Brief review of the trial	Meeting attendees received the Research Strategy, Resources and Data Sharing Plan, and Protection of Human Subjects Plan for AIM-CP with the meeting agenda (see supplementary material attached). Stephanie Morain facilitated introductions and the discussion. The AIM-CP team member present was co–principal investigator Kushang Patel. **Project overview**: Kushang Patel gave an overview of the project, which has a 2-year UG3 planning phase and a 3-year UH3 implementation phase. The goal of AIM-CP is to address inequities in access to nonpharmacological treatment for chronic pain in rural populations. The study will test a care management program vs usual care. **Healthcare system partners**: Providence Northeast (Washington) and Atrium Health Wake Forest Baptist (North Carolina) for the UG3 planning phase **NIH Institute Providing Oversight**: National Institute of Nursing Research (NINR) **Study design**: The study is proposed to be a 2-arm pragmatic trial of adults with chronic pain. Participants will be assigned by individual randomization to either usual care or the care management program. The care management program will consist of care coordination by a nurse or other licensed health professional; 8 to 10		

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	sessions of remotely delivered, one-on-one sessions of cognitive behavioral therapy provided by the care manager; and referral to EnhanceFitness, a widely available group-based tele-exercise program. **Outcomes**: The primary outcome is the Pain, Enjoyment of Life, and General Activity (PEG) scale at baseline, at 4 months after treatment, and at 6-month follow-up. Participants will be recruited to the study either through their primary care physicians' offices or through advertisements. For patients in the intervention arm, the study team will share summary notes with the primary care physician to inform them of the patient's enrollment in the study and the patient's self-identified goals of care. The study team will follow up during the trial and at the end of the program to provide information about the patient's progress. (Physicians of patients in the usual care arm will not be contacted.) The study team anticipates that most of the participating healthcare systems will recruit participants by searching the electronic health record for patients with relevant pain-related diagnosis codes, contacting the patients via email to notify them that they may be contacted by the study team, and offering the patients an opportunity to opt out. Services delivered by the healthcare system will be billed through the patient's health insurance. The study team will cover the costs of the care coordination, cognitive behavioral therapy, and the exercise program.		
Status of IRB approval	The study team received a determination that developmental work to adapt the interventions and trainings is not human subjects research. The study team plans to use the University of Washington IRB as the single IRB of record for the trial. For the 2-site pilot study, a reliance agreement is in place for the North Carolina site, and discussions are underway with the site in Eastern Washington. The group discussed whether the care managers might also be considered human subjects, since they will be interviewed about their experiences.		
Risk (Does the project meet regulatory criteria for being	The study team anticipates that the project will meet the regulatory criteria to be considered minimal risk. The remotely delivered cognitive behavioral therapy is		

AGENDA ITEMS	DISCUSSION	ACTION ITEMS	OWNER
considered minimal risk?); and consent (planned processes for relevant subjects)	minimal risk, and the exercise program is being used in another study and was designated by the University of Washington IRB as minimal risk.		
Privacy (including HIPAA)	Data collection will be managed through a REDCap platform, reducing confidentiality concerns. The exercise program is group-based but also includes people in the community who are not enrolled in the study. So there no expectation of a privacy concern related to the research.		
Monitoring and oversight	NINR will assemble a data and safety monitoring board and has asked the study team to provide names of potential members. The study team is proposing to include a physician pain specialist, a biostatistician, an exercise specialist, and possibly a psychologist. Stephanie recommended that the study team encourage NINR to include someone with experience in pragmatic clinical trials. David Magnus referred the study team to the Data and Safety Monitoring chapter of the Living Textbook: https://rethinkingclinicaltrials.org/chapters/ethics-and-regulatory/data-and-safety-monitoring/introduction-data-and-safety-monitoring/.		
Issues beyond this project (regulatory and ethics concerns raised by the project, if any)	None.		
Other matters	Joe Ali asked whether patients will have access to the intervention after the trial, if it is shown to be effective. Kushang clarified that the intent is for patients to complete the program and acquire the pain self-management skills as part of the study. The study team hopes, if the intervention is effective or seen as otherwise beneficial by the healthcare systems, that the healthcare systems will adopt the care coordination and exercise program, and perhaps even the cognitive behavioral therapy component. The EnhanceFitness exercise program is broadly available at relatively low cost. So it is conceivable that some patients will continue with this component of the intervention. Exit interviews will ask about this. In addition, it is possible that the		

AGENDA ITEMS	DISCUSSION	ACTION ITEMS	OWNER
	participating healthcare systems will adopt the exercise program and offer it at a subsidized rate for patients in their rural catchment areas. Stephanie asked about the possibility of communicating aggregate study results back to the participants at end of the trial. Kushang expressed interest in learning more about this.		

Adapting and Implementing a Nurse Care Management Model to Care for Rural Patients with Chronic Pain (AIM-CP)

PROJECT SUMMARY

Chronic pain affects over 20% of the U.S. adult population and frequently has debilitating effects on quality of life and physical and mental functioning. Individuals living in rural communities experience higher rates of chronic pain as well as poorer health outcomes because of pain. The 46 million Americans who live in rural areas frequently lack access to evidence-based, non-pharmacologic treatments for chronic pain. As such, a critical need exists to implement effective, comprehensive programs for pain management that include non-pharmacologic treatment options. Nurse care management (NCM) has been successfully used to enhance care for individuals with other chronic conditions or at high risk of complications.

Using a type 2 hybrid effectiveness-implementation design, we propose to adapt, pilot, and implement a NCM model that includes care coordination, cognitive behavioral therapy (CBT), and referrals to a remotely delivered exercise program for rural patients with chronic pain. Each health system will identify appropriate health care professionals to be trained as care managers. For the CBT component, care managers will be trained to engage patients in a remotely delivered CBT program. For exercise, we will offer remotely delivered Enhance Fitness, which is an evidence-based, 16-week program that includes aerobic and strength training exercise. In the UG3 phase, we will engage patients, clinicians, and care managers from 2 health systems serving rural patients in a learning collaborative to pilot the NCM model. In addition, we will adapt infrastructure and workflows to implement the intervention program and engage the partnering health systems in developing relationships with community partners and identifying care managers. In the UH3 phase, we will conduct a randomized controlled trial of the adapted NCM model versus usual care in rural dwelling patients with chronic pain. We have recruited 6 health systems from 2 practice-based research networks, the WWAMI (Washington, Wyoming, Alaska, Montana, and Idaho) region Practice and Research Network and the Mecklenburg Area Partnership for Primary Care Research in rural North Carolina. Our primary outcome is pain interference as measured by the Pain, Enjoyment of Life and General Activity (PEG) scale. Our secondary outcomes include physical function, sleep, pain catastrophizing, depression, anxiety, treatment satisfaction, substance use disorder, pain medication use/dosage including opioids, and health care utilization. We will explore if disparities exist by examining heterogeneity in treatment effects via subgroup analyses by age, gender, race/ethnicity, and health insurance. We will use the RE-AIM framework to assess implementation outcomes and qualitative interviews conducted with a subset of patients to evaluate experiences with the intervention. If successful, this study will have a transformative effect on chronic pain management in rural areas by expanding access to evidence-based, non-pharmacologic treatments through an innovative NCM model.

PROJECT NARRATIVE

Over 1 in 5 individuals in the United States suffer from chronic pain, which has negative effects on quality of life, mental health, and physical function. Those living in rural areas not only have higher rates of chronic pain and poorer health outcomes but also are less likely to receive evidence-based non-pharmacological treatments for chronic pain. We propose to adapt and implement a nurse care management model in health systems serving rural patients with chronic pain to provide care coordination, cognitive behavioral therapy, and referrals to a remotely delivered exercise program.

SPECIFIC AIMS

More than 20% of the U.S. adult population reports chronic pain, which is strongly associated with reduced quality of life and physical, mental, and social functioning. Many non-pharmacologic treatments for chronic pain are effective in improving pain and functioning, but relatively few adults with chronic pain have access to these treatments. Access is especially limited in rural communities where 46 million Americans (14% of the U.S. population) live. Those living in rural areas have poorer health outcomes including significantly higher rates of disability and opioid overdose; one of the leading causes of such poorer outcomes is the lack of access to appropriate health care services. As such, a critical need exists to implement programs offering non-pharmacologic treatments to care for those living in rural communities with chronic pain.

Nurse care management (NCM) has been implemented successfully to manage patients with other chronic conditions but not widely for patients with chronic pain. Care managers can provide a variety of functions including care coordination, linkages to community resources, and some counseling services. For our study, "**A**dapting and **I**mplementing a Nurse Care **M**anagement Model to Care for Rural Patients with **C**hronic **P**ain" (AIM-CP), the objective is to adapt and test the NCM model to provide comprehensive coordinated care for patients with chronic pain in rural communities. In AIM-CP, *care managers will not only provide care coordination but also (a) be trained to deliver cognitive behavioral therapy (CBT) to address maladaptive thought patterns and behaviors around chronic pain and (b) facilitate participation in remotely delivered Enhance Fitness® (tele-EF), an evidence-based exercise program*. Our rationale is that both tele-EF and CBT have been independently shown to improve pain, functioning, and quality of life and that care managers could facilitate patients in receiving and maintaining participation in such evidence-based services. Our long-term goal is to reduce geographic (rural vs non-rural) disparities in pain-related outcomes through the dissemination of this comprehensive, non-pharmacologic approach to chronic pain management.

We propose a randomized controlled trial to test our adapted NCM model with rural patients who have chronic pain. We plan to test our intervention in rural serving health care systems using two ethnically and geographically diverse practice-based research networks with substantial rural presence, the WWAMI (Washington, Wyoming, Alaska, Montana, and Idaho) region Practice and Research Network and Mecklenburg Area Partnership for Primary Care Research in North Carolina.

In the **UG3** phase of this study, our aims are:

Aim 1: To finalize outcome measures and data extraction processes through our learning collaborative and participation in NIH Collaboratory workgroups.

Aim 2: To refine trainings, identify community-based partners and streamline workflows to adapt the NCM model to serve rural patients with chronic pain.

Aim 3: To pilot test the adapted NCM model that includes care coordination, remotely delivered CBT and tele-EF for rural patients with chronic pain.

To accomplish these aims, we will engage a learning collaborative consisting of clinicians, patients and care managers in two rural-serving health systems to adapt and pilot the NCM model.

In the **UH3** phase of this study, our aims are:

Aim 1: To determine the effectiveness of the adapted NCM model vs. usual care for improving pain interference with daily functioning.

Six health systems will participate in this trial and recruit 416 rural patients with chronic pain. The primary outcome is pain interference (PEG scale), while secondary outcomes include physical functioning, pain intensity, sleep disturbance, pain catastrophizing, depression, anxiety, global satisfaction with treatment, substance use disorder, pain medication use and dosage (e.g., opioids), and health care utilization. Outcomes will be assessed at baseline, immediately after the 6-month intervention, and 6 months post intervention.

Aim 2: To evaluate the implementation of the adapted NCM intervention.

We will use the RE-AIM framework to assess implementation outcomes and conduct qualitative interviews with patients to assess experiences with the intervention.

Aim 3: To explore if there are disparities in response to the NCM intervention by examining heterogeneity in treatment effect in the primary (pain interference) and secondary outcomes.

We will explore variation in outcomes by age, race/ethnicity, gender, household income, education, comorbidities, degree of rurality, and insurance status.

This project is innovative in that it expands access to effective non-pharmacologic treatments for chronic pain using an evidence-based delivery mechanism (nurse case management) adapted for rural communities. The proposed biopsychosocial intervention is expected to have a positive impact in transforming chronic pain management and improving pain-related outcomes for millions of rural dwelling patients.

RESEARCH STRATEGY

I. Significance

Need for increasing access to non-pharmacologic treatment in rural areas: Effectively treating chronic pain often requires a comprehensive approach including the use of non-pharmacologic treatment modalities; however, patients in rural communities rarely receive these evidence-based treatments.[1, 2] Approximately 20% of the U.S. adult population has chronic pain with 8% experiencing frequent limits on daily function and work life.[3] Chronic pain reduces quality of life, functioning and productivity and is often associated with higher rates of disturbed sleep, anxiety, depression and substance use disorder.[4, 5] According to one estimate, chronic pain in the United States costs up to $635 billion annually in health care spending and lost productivity.[6]

The causes of and contributors to chronic pain are multifactorial and include biological, psychological, and social factors.[7, 8] Despite this, treatment of chronic pain is often focused on pharmacologic interventions and chronic opioid prescribing has long been a mainstay of chronic pain management.[9] Opioids have not only been shown to be ineffective for improving chronic pain but also carry significant side effects including opioid misuse, opioid use disorder, overdose and death.[10] Other medications commonly used for treatment of pain also carry substantial side effects and frequently cannot be tolerated by many adults.[11] Meanwhile, multiple nonpharmacologic treatment modalities for chronic pain have been shown to be effective but access to these services remains limited.[11, 12] Barriers to accessing non-pharmacologic treatments include lack of insurance coverage, limited providers of these treatments, distance, and lack of knowledge by both clinicians and patients of these treatment options. While comprehensive pain programs are known to reduce pain and improve functioning, few patients have access to such programs.[13]

Rural residents suffer from higher rates of chronic pain, are more likely to receive an opioid prescription and experience more comorbidities from chronic pain compared to nonrural-dwelling individuals.[2, 14-16] They are also less likely to receive physical therapy and to be taught pain self-management techniques.[17] Approximately 14% of Americans (or 46 million individuals) live in rural communities and are more likely to face disparities in their chronic pain care and in their health outcomes.

Rural patients with chronic pain present in primary care: Over half of all people with chronic pain receive treatment in primary care,[18, 19] given that demand has outstripped supply of specialty pain care services. This proportion is higher in rural communities. One in five visits in primary care is for chronic pain and has resulted in the over reliance on prescription opioids, despite evidence-based guidelines for care that do not rely on opioids.[20] Managing chronic pain in primary care is complex and has been challenged by a limited primary care workforce.[21] Both patients and primary care clinicians would benefit from interventions and guidance to improve access to evidence-based, non-pharmacologic treatments.

Adapted **Nurse Care Management model** as a solution: Nurse care management (NCM) has been used effectively in other chronic conditions that require coordination between multiple specialties and services to prevent unnecessary hospital and emergency department use, to engage patients in shared decision-making and goal setting, and to alleviate burdens on primary care clinicians.[22, 23] Care managers help communicate to patients and family members, educate them about their chronic disease processes, coordinate interdisciplinary care, and provide assessment and monitoring.[24] To date, NCM has not been widely used for chronic pain despite its potential to improve care and outcomes for patients suffering from chronic pain. **We propose an innovative adapted NCM model where care managers would provide 3 services: 1) care coordination, 2) cognitive behavioral therapy (CBT) and 3) referrals to a remotely delivered exercise program, tele-Enhance Fitness (tele-EF)** (Figure 1)**.** The rationale for using this model is that it

Figure 1: Proposed Adapted Care Management Intervention

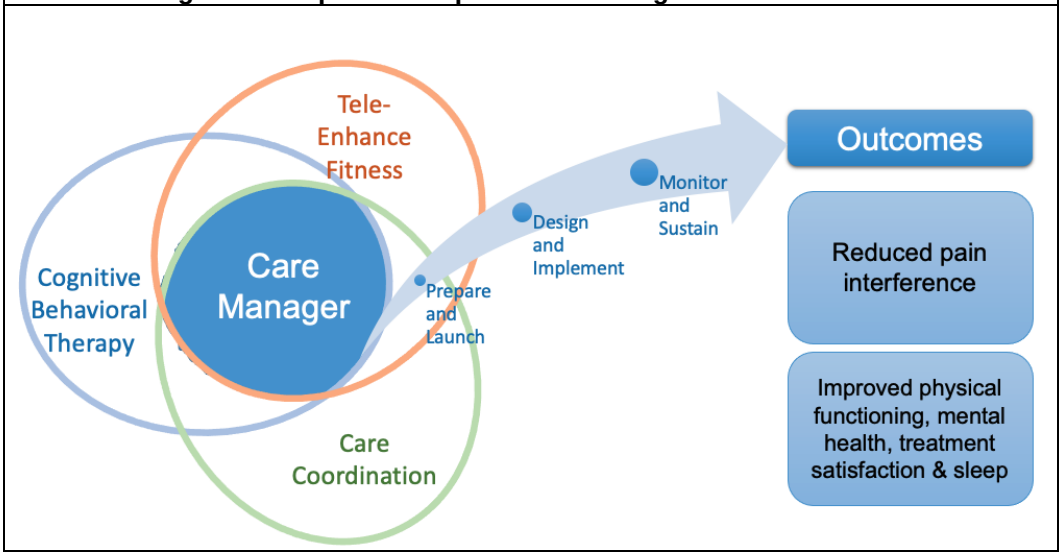
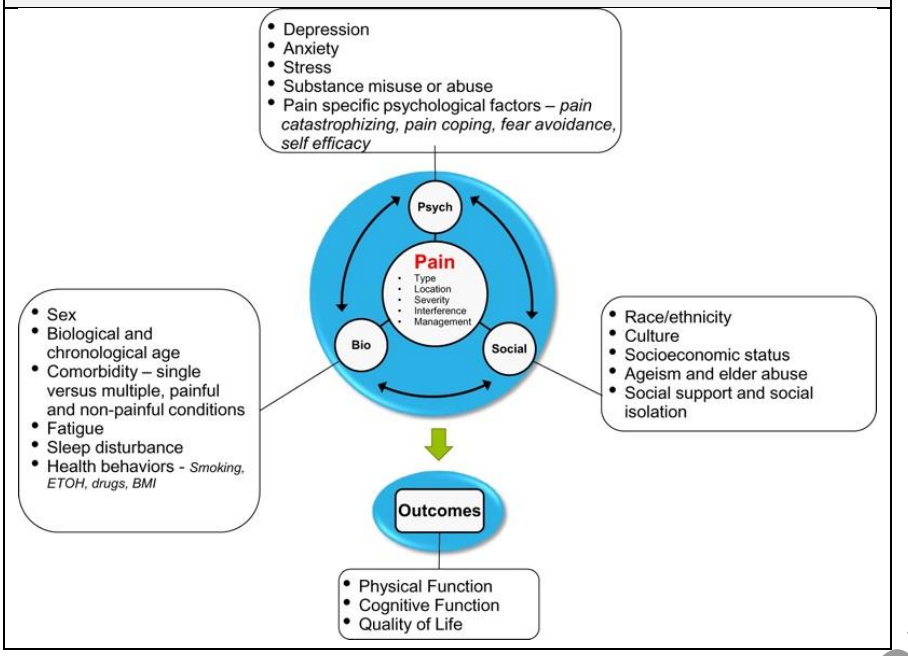


Figure 2: Biopsychosocial model for chronic pain from Miaskowski et al

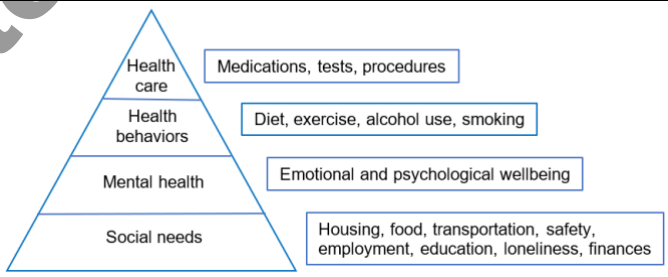


takes into consideration the biological, social and psychological factors that contribute to chronic pain and approaches patients from a holistic perspective.[7, 8, 25]

Conceptual Framework

In AIM-CP, we use the biopsychosocial framework adapted for chronic pain by Miaskowski et al to understand the various predispositions and factors that contribute to the experience of chronic pain.[8] Categorized into biological, psychological and social factors, these interact in a cyclical fashion to affect pain and modify the outcomes of physical function and quality of life (Figure 2). We chose the biopsychosocial framework because prior treatment approaches using this framework have shown improvement in helping patients manage pain and improve functioning.[26-29] For our intervention, we incorporate the understanding of the adapted biopsychosocial model to make use of a modified Maslow's hierarchy of needs.[30] In the modified version (Figure 3), which was developed by Krist et al[31] from pilot work led by Dr. Tong,[32] the hierarchy considered is that of social, mental health and health behavior needs. In this model, social needs (addressed in AIM-CP by care coordination) need to be considered before patients can be effectively engaged in addressing mental health (in AIM-CP by CBT). After addressing mental health needs, patients are then sufficiently engaged in health behavioral changes (in AIM-CP by tele-EF) that can then lead to improvements in chronic disease outcomes.

Figure 3: Hierarchy of social, mental health, health behavior, and healthcare needs



Why address chronic pain with **care coordination:**

Meta-analyses have shown that care coordination for chronic diseases can improve functional status and mental health outcomes.[33, 34] Specifically, care coordination for patients with chronic pain increases pain disability-free days and reduces pain intensity and interference.[35-37] In AIM-CP, the care coordination component will allow for coordination between available specialties and services for chronic pain, and be a means for patients to have their pain assessed and to develop goals of care. In addition, to address the modified Maslow's (Figure 3), we will incorporate social needs screening so that care managers can address social needs that may be affecting chronic pain management. This responds to calls from national organizations to consider and address social needs in health care[38] and to enable patients to participate in the psychological and exercise components of our intervention.

Why address chronic pain with **psychological treatment**: The majority of chronic pain guidelines include psychological involvement as a core part of primary care treatment of chronic pain.[39] Prior studies have demonstrated that behavioral health services improve patient-reported outcomes.[40, 41] Chronic pain often co-occurs with mental and behavioral health conditions.[42, 43] Psychological risk factors are associated with poor outcomes in primary care patients with ongoing chronic pain.[44-47] These include distress, presence of depression or anxiety, passive coping strategies, and fear/avoidance beliefs. Their presence results in greater pain disability and decreased health related quality of life.[48] The presence of depression and anxiety and perception of risk of persistence of lower back pain are most consistently linked with negative outcomes.[49] Over 50% of patients with chronic pain have comorbid depression or anxiety related disorders.[45, 50, 51] Up to 25% of patients with chronic pain have substance use disorders.[45] CBT can help with pain catastrophizing, pain coping, fear avoidance and self-efficacy. In addition, it can be behaviorally activating so that patients are motivated to participate in outside activities including but not limited to exercise programs. Overall, CBT has

been shown to have sustained effects on reducing pain intensity and interference.[40, 52, 53] Prior studies have shown that non-behavioral health professionals can be successfully trained in providing CBT.[54-58] Given the limited access to behavioral health professionals in rural areas, we propose in AIM-CP to train care managers in the provision of CBT to patients with chronic pain.

Why address chronic pain with **a structured physical exercise program**: Physical exercise is recommended for many common painful conditions (e.g., knee osteoarthritis, low back pain).[59-66] Indeed, several meta-analyses and systematic reviews have established that aerobic and strength training improves pain, physical function and other health outcomes among adults with different types of pain conditions.[67-73] Despite clinical recommendations, studies have shown that exercise participation is low among adults with chronic pain.[74-78]

Recognizing the benefits of exercise for chronic pain management, the CDC and other agencies have promoted evidence-based exercise programs that are group-based and led by instructors in the community.[79-81] These programs improve pain and physical function and help address some obstacles to exercise participation, including lack of professional guidance and social support. However, many adults continue to face barriers to engagement in exercise programs.[82-87] Barriers include inclement weather, access to facilities, and transportation. Environmental barriers are particularly challenging for rural residents who are unable to participate in community-based exercise programs because of limited or no access to transportation and exercise facilities.[88, 89] In addition, a major environmental barrier to walking in rural areas is limited pedestrian infrastructure, including long distances between destinations and lack of sidewalks.[90] The COVID-19 pandemic introduced an opportunity to engage rural residents in a virtual manner given the growth in telehealth and virtual offerings for activities.[91] In AIM-CP, we propose to overcome barriers by providing patients access to a virtual group exercise program, tele-Enhance Fitness. Tele-EF will not only overcome many of the barriers previously identified to exercise but also be behaviorally activating with group support and motivation.[92, 93]

Adapting the NCM model to today's nursing shortage:
Recognizing the current nursing workforce shortage that is particularly acute in rural areas,[94, 95] we anticipate some rural health systems may not have sufficient nursing staff to identify a nurse to serve as a care manager. As such, while our preference will be that health systems identify a nurse to serve in such a role, we will work in a flexible manner with health systems to identify appropriate individuals other than nurses to serve in the care manager role as needed. Prior implementation guides have identified characteristics of non-nurses who could serve as care managers.[96]

Summary of study premise:
Rural patients have difficulty accessing non-pharmacologic treatment modalities for chronic pain despite their known efficacy. Our study proposes an intervention that addresses biological, psychological, and social factors contributing to chronic pain using a nurse care management model that offers care coordination, behavioral health treatment and access to a remotely delivered physical exercise program.

II. Innovation

Our proposed intervention is highly innovative for several reasons. First, we are adapting NCM, which has been successfully used to manage other chronic conditions, to patients with chronic pain in rural areas to facilitate the delivery of evidence-based non-pharmacologic treatment modalities. While NCM has been used for chronic pain in the Veterans Affairs system, it has not been widely used in the civilian population.[97] NCM for conditions other than chronic pain has already been implemented in many health systems to help patients with multimorbidity and/or at high risk of complications. Indeed, several of the health systems we are partnering with already have care managers and are enthusiastic about adapting the use of their care managers to manage their high-risk population of rural patients with chronic pain and improve pain-related outcomes.

Second, our study approaches chronic pain using a biopsychosocial framework and uniquely addresses the social component of the framework through a social needs screening and partnerships with community organizations as part of care coordination. To date, most primary care clinicians focus on prescribing medications, whether opioid or non-opioid, to patients with chronic pain. Using care coordination, CBT and exercise therapy will help address chronic pain more comprehensively than medications alone. Through an innovative delivery model, we will expand access to these non-pharmacologic treatment modalities in rural communities where patients are more frequently reliant on medications for chronic pain since there is often limited access to behavioral health providers and/or exercise programs.

Third, we plan to integrate PainTracker, an easy-to-use, patient-centered, online tool to help assess patient reported pain, functioning, mood and sleep, into our care coordination activities.[98] PainTracker has been shown to successfully help patients engage in self-management of their chronic pain, assist care managers

and providers in engaging in shared decision making, and allow patients to better coordinate their care with care managers and providers.

Fourth, we are implementing this project uniquely considering health equity and using a patient-centered approach. We will use the equity framework for addiction research developed by Dr. Tong (MPI) in conjunction with leaders at the National Institute on Drug Abuse and the Agency for Healthcare Research and Quality.[99] Far too often the patient perspective is not considered in chronic pain management and only rarely is shared decision making employed. We will engage patients as members of our learning collaborative in the pilot UG3 phase so we receive patient feedback and engagement in our study protocols and intervention. Then, we plan to implement our intervention in 6 diverse rural health systems: 2 with substantial proportions of Hispanic/Latinx patients and 1 with a large proportion of African American patients. Finally, we will engage a Translation and Dissemination Advisory Group (see Dissemination section for details) composed of patients, stakeholders, policy makers and payers to inform the ongoing dissemination and sustainability of our intervention. Overall, we believe these innovative and unique aspects of our proposed adapted NCM model to care for rural patients with chronic pain will have a transformative effect for patient's pain and functioning.

III. Approach

Project Overview

We propose a 2-phase project to adapt and implement a NCM model with care coordination, CBT and tele-EF for rural patients with chronic pain (Figure 1). In the UG3 phase, we will work with a learning collaborative comprising clinicians, care managers and patients with chronic pain from practices with 2 health systems to refine and pilot our intervention. In the UH3 phase, we will conduct a randomized controlled trial with patients from health systems serving rural areas to test whether the refined NCM model improves pain outcomes.

III.A Team and Sites

Overview of Investigative Team

Our primary team at the University of Washington (UW) includes a multidisciplinary group of investigators with synergistic expertise in the areas proposed for this study. Our team includes diverse backgrounds including primary care, addiction medicine, nursing, epidemiology, psychology, and statistics.

Sebastian Tong, MD, MPH*,* Multiple Principal Investigator (Contact PI), is an Assistant Professor of Family Medicine and a practicing family physician and addiction medicine specialist. He is the Associate Director of the WWAMI region Practice and Research Network (WPRN), a co-investigator in the NIDA-funded Pacific Northwest Clinical Trials Node (CTN) and co-chair of the CTN Practice-Based Research Network Special Interest Group. He has expertise using mixed and qualitative methods and leading studies related to chronic opioid use and in implementation of evidence-based interventions in primary care. Along with Dr. Patel, he will oversee both phases of the study. He will lead the learning collaborative in the pilot phase and be responsible for communicating with WPRN health systems and serving as the liaison to Atrium Health.

Kushang Patel, PhD, MPH, Multiple Principal Investigator, is a Research Associate Professor in the Department of Anesthesiology & Pain Medicine, an epidemiologist, and a gerontologist. He is also the Research Core Director of the CDC-funded Harborview Injury Prevention & Research Center. He is the principal investigator of multiple grants examining group-based exercise therapy for older adults with chronic pain including a NIH-funded trial testing the integration of behavioral therapy with EF for chronic pain (R01AG060992), as well as a CDC-funded non-inferiority trial of tele-EF versus in-person EF (U48 DP006398). He led the adaptation of the EF program for remote delivery using a participatory process, engaging EF users and instructors and the program's national leadership.[100] In addition to overseeing both phases of the study with Dr. Tong, Dr. Patel will be responsible for overseeing the tele-EF component of the intervention.

Kari Stephens, PhD, co-investigator, Associate Professor of Family Medicine, is a practicing clinical psychologist with expertise in pain, addiction and primary care integrated behavioral health, and a biomedical informaticist with expertise in extraction and integration of electronic health record (EHR) data. She serves as Research Section Head and Director of Clinical Research Informatics in the UW Department of Family Medicine and has been funded by the Washington State Department of Labor & Industries to develop/implement a curriculum to train non-behavioral health providers in provision of CBT. She has also served as an NIH Collaboratory Electronic Health Record Work Group member while she was a co-investigator for the LIRE trial (UH3 AR066795). For this grant, she will lead the CBT component of the intervention.

Basia Belza, PhD, RN, FAAN, FGSA, co-investigator, Professor in the School of Nursing and Director of the deTornyay Center for Health Aging, is a nurse investigator with expertise in interventions for managing chronic conditions and exercise therapy. She will provide nursing expertise and help guide the adaptation and implementation of our NCM model.

Laura-Mae Baldwin, MD, co-investigator, is a Professor of Family Medicine, a family physician, and the founding director of the WPRN and the Community Engagement core of UW's Clinical and Translational Science Award (CTSA) program. She founded the Dissemination and Implementation Work Group for the national CTSA Consortium and has led implementation trials in primary care clinics. She has expertise in hybrid effectiveness-implementation trials (R18 HS0237850), rural health disparities, use of EHR data in research, and chronic pain and chronic opioid research in primary care. She will provide expertise in these areas to the MPIs and provide assistance with care manager trainings.
Judith Tsui, MD, MPH, co-investigator, Professor of Medicine, is a general internist, addiction medicine specialist and principal investigator for multiple NIH-funded grants. She brings expertise in the NCM model, opioid misuse/opioid use disorder studies and clinical trials in primary care. She will provide trainings on the care management model to identified care managers.
Bryan Comstock, MS, is a Senior Biostatistician at the Center for Biomedical Statistics and has served as Director of Operations for 25 multi-site studies, including multiple pragmatic, implementation trials. For this study, he will lead the data coordinating center, provide leadership over the biostatistics and data team, and be responsible for all data sharing requirements with the HEAL Initiative.
Mark Sullivan, MD, PhD is a Professor of Psychiatry and Behavioral Sciences and has expertise in clinical trials on chronic pain and opioid tapering. He developed and tested PainTracker, a tool for patients to report on their pain and functioning, which NCMs will use in our trial to assess chronic pain.
William Lober, MD, MS is a Professor of Biobehavioral Nursing and Health Informatics in the School of Nursing. He is the Director of the Clinical Informatics Research Group and will be responsible for overseeing the adaptation of PainTracker for our trial.

The primary team at UW will be supported by a group of experienced investigators at Wake Forest University/Atrium Health.
Dennis Ang, MD, site PI, is the Chief of Rheumatology/Immunology at Wake Forest, and has been the PI of multiple NIH-funded trials on interventions for chronic musculoskeletal pain (i.e., osteoarthritis, fibromyalgia and various chronic musculoskeletal pain conditions) (UG3 NR019196, R21 AR056046, R01 AR054324). He is currently conducting an NIH intervention study that assesses the incremental benefits of web-based cognitive behavioral therapy when added to duloxetine. He will be responsible for overseeing the study at Atrium Health/Wake Forest.
Hazel Tapp, PhD**,** co-investigator, is the Vice Chair of Research in the Department of Family Medicine at Atrium Health and the co-director of the Mecklenburg Area Partnership for Primary Care. As an expert in pragmatic trials in primary care, Dr. Tapp will work with Dr. Ang to implement this study.
Erika Steinbacher, MD, co-investigator, is the Vice Chair of Family Medicine at Atrium Health and brings practice expertise in chronic pain. She will be the lead clinical contact for rural primary care clinics.
Ajay Dharod, MD, co-investigator is the Vice Chair of Informatics and Analytics for the Department of Internal Medicine at Atrium Health/Wake Forest. He will be responsible for developing the EHR algorithm to identify rural patients with chronic pain eligible for the study.
Tom Ludden, PhD, is the lead for informatics at Atrium Health (Charlotte). He will be responsible for identifying rural chronic pain patients from the Atrium Health System.

Proposed Collaboration Plan
Drs. Tong and Patel will alternate leading biweekly co-investigator meetings throughout the entire study. Smaller cross-institution groups will meet separately to discuss the components of the intervention, care manager training, data integration, and dissemination of results as needed. In addition, Dr. Tong will visit Charlotte, NC to work with the Atrium Health/Wake Forest team on an annual basis.

Preliminary Studies/Relevant Team Experience
Our investigative team has completed studies in non-pharmacologic therapies for chronic pain management including CBT and exercise therapy, chronic opioid prescribing, nurse care management and implementation of evidence-based practices in primary care that serve as the foundation for AIM-CP.

<u>Understanding and addressing chronic pain in primary care</u>
Dr. Tong has completed studies examining opioid prescribing and chronic pain management in primary care. In 2017, he received an American Academy of Family Physicians Foundation grant to understand patient and clinician characteristics and primary care clinician perspectives of chronic opioid prescribing. From a sample of over 80,000 primary care patients, he found that 1.1% received chronic opioid prescriptions and that being female, being black and having higher co-morbid risks (such as mental health diagnoses, substance use disorder and/or concurrent benzodiazepine use) were associated with higher rates of chronic opioid use.[101] Dr.

Tong is working with Dr. Stephens on a NIDA CTN-supported study to examine both opioid and buprenorphine prescribing in primary care pre- versus post-pandemic and to explore differences in prescribing using an equity framework.[102] Dr. Tong is also conducting a qualitative interview study, funded by the Osher Center at UW, to explore attitudes about and access to integrative treatment modalities for chronic pain in rural primary care practices. In this study, he is interviewing both primary care clinicians and patients across the WPRN.

Dr. Tong also previously served as the COR (contracting officer's representative) for a series of Agency for Healthcare Research and Quality-funded learning collaboratives to support chronic pain management in older adults in primary care.[103] As part of this contract, he oversaw the development of resources and tools to assist primary care clinicians manage older adults on opioids and with chronic pain.[104]

Nurse Care Management

Building on years of clinical experience implementing NCM models for opioid use disorder, Dr. Tsui conducted a clinical trial investigating the effectiveness of NCM in managing chronic opioids in individuals with co-morbid HIV. The NCM assisted with panel management, education, and coordination of care to specialists. The intervention was found to reduce illicit opioid use.[105, 106] Dr. Ang has also led a trial using NCM to offer CBT and self-management strategies at the Veterans Affairs Health System.[97]

Dr. Sullivan has developed and previously tested PainTracker, a tool to assist patients with chronic pain with self-management.[98, 107] This tool has been implemented in the Center for Pain Relief at UW and has been shown to improve patient engagement in pain management. PainTracker can be used in nurse care management as a tool for care coordination and monitoring patient's pain and functioning.

Cognitive Behavioral Therapy

Drs. Tong and Stephens collaborated in an American Board of Family Medicine Foundation-funded study to examine the characteristics of family physicians who work collaboratively with behavioral health professionals. They found that while 38.8% of family physicians nationwide worked in integrated behavioral health settings, there were significant disparities based on geographic location, practice type and rurality.[108, 109] Stephens has also led the development of a cross-model framework for integrated behavioral health[110] and participated in trials to integrate behavioral health to improve patient-centered outcomes.[111] Most recently, she led, along with Dr. Sullivan, the psychological component of an opioid tapering support study, which found that those with tapering support had improved pain interference and pain self-efficacy.[112] She has also been funded by the Washington State Department of Labor and Industries to develop and implement trainings for non-behavioral health professionals to provide CBT.[113] The CBT trainings were developed in close collaboration with Dr. Sullivan and Dr. Dawn Edhe of UW, who led two randomized controlled trials that improved outcomes for patients with chronic pain, one of which utilized care managers to deliver the CBT intervention.[114, 115]

Enhance Fitness, a structured exercise program

Dr. Patel has led multiple studies of exercise and physical activity, including the adaptation of EF for remote delivery.[77, 93, 116-120] Enhance Fitness is an evidence-based exercise program involving aerobic and strength training that is available in >800 community sites (e.g., YMCAs) nationally and is recommended by CDC for arthritis pain management. Dr. Patel has implemented tele-EF in his current R01-funded trial involving older adults with painful knee OA (current N=182; target enrollment N=280). Thus far, the median tele-EF class attendance rate is 89%, which is excellent for an exercise program held 3 days per week for 1-hour over 16 weeks, and the attrition/withdrawal rate of 10% is low for a multimorbid, older chronic pain population. In addition, he has conducted 2 pilot studies establishing the feasibility and acceptability of tele-EF in rural older adults with knee OA (12-week intervention; N=15) and in rural cancer survivors (16-week intervention; N=39).[92, 93, 116] In both pilot studies, the enrollment rate in tele-EF ranged 64-71% among those who were screened eligible, the median tele-EF class attendance rate ranged 87-90%, and the tele-EF completion rate ranged 87-95%. These favorable implementation outcomes of tele-EF contributed to clinically meaningful improvement in self-reported pain and physical functioning outcomes as well as tests of physical capacity in rural older adults with knee OA (Table 1). Similar gains in physical functioning were observed in rural cancer survivors, but pain interference was lower in this study sample (relative to the knee OA study sample) and did not change.

Table 1: Change in outcomes from baseline to 12-week endpoint among rural older adults with knee osteoarthritis who participated in tele-EF (N=15)

Measures	Mean (SD) at baseline	Mean (SD) at 12-week end point	p-value
Knee Pain (KOOS score, higher is better)	53.6 (21.2)	65.0 (17.7)	0.021
Knee Function (KOOS score, higher is better)	57.6 (22.0)	69.3 (16.3)	0.002
Pain Interference (PROMIS score, lower is better)	58.3 (9.4)	54.7 (8.4)	0.032
Physical Function (PROMIS score, higher is better)	38.8 (6.2)	41.7 (6.9)	0.060
Timed Up and Go test in seconds (lower is better)	12.6 (4.6)	10.8 (3.7)	0.032
5-time sit-to-stand test in seconds (lower is better)	14.8 (4.1)	12.3 (2.8)	0.002

Importantly, exit interviews indicated that tele-EF not only addressed environmental barriers to accessing evidence-based exercise that rural older adults often face, but also participants appreciated the group-based livestream design of tele-EF that facilitated accountability and helped sustain their motivation. Another important feature of tele-EF was the support that participants received not only from exercising with peers but also from the encouragement and guidance given by the instructor. Notably, all participants (100%) were very satisfied with tele-EF classes.[93]

Strategic national directions for future substance use disorder research: Dr. Tong led the development of priorities for chronic pain and addiction health services research while a medical officer at the Agency for Healthcare Research and Quality. These priorities were developed with the consultation of multiple stakeholders including other federal agencies, researchers, clinicians, and patients and concluded with a *New England Journal of Medicine* perspectives article[99] and the publication of a special emphasis notice for research (now listed under another medical officer since he is no longer at AHRQ).[121] The priorities included a focus on comprehensive needs to prevent substance use disorder including the treatment of chronic pain and the need to consider and address equity.

Study Setting and Health Care System Partnerships (Table 2)

Our study will include practices from two geographically diverse practice-based research networks with substantial proportions of rural patients: the WWAMI region Practice and Research Network (WPRN) and Mecklenburg Area Partnership for Primary Care Research (MAPPR) We chose these two health systems because they provide geographic diversity across multiple states and because together they ensure racial/ethnic diversity.

Table 2: Characteristics of Participating Health Systems and Demographics of Rural Patients with Chronic Pain

PBRN	Health System Name	Location	Number of clinics / patients*	% female	% White	% Black	% Hispanic / Latinx	% Asian / Pacific Islander	% other race / ethnicity
WPRN	Clearwater Valley Health – St. Mary's Health	North Central ID	10 / 5,600	51%	94%	1%	1%	<1%	4%
	Health West, Inc.	Southeast ID	9 / 3,000	60%	68%	2%	20%	2%	8%
	Providence Stevens County	Northeast WA	4 / 3,200	51%	95%	1%	3%	<1%	1%
	PeaceHealth Southwest	Southwest WA	4 / 2,800	65%	66%	3%	20%	10%	1%
MAPPR	Atrium Health	NC	10 / 4,000	59%	77%	18%	2%	1%	2%
	Wake Forest Baptist Health	NC	10 / 1,022	60%	95%	2%	2%	<1%	1%

* Number of patients refers to estimated patients with chronic pain who meet our study's eligibility criteria

WPRN: The WPRN consists of over 100 practices across Washington, Wyoming, Alaska, Montana, and Idaho. Dr. Tong is the Associate Director of the WPRN. A large proportion of the practices serve rural communities. A steering committee of clinicians from these practices meets regularly to identify WPRN research priorities and to provide feedback on and approve studies. The steering committee has identified addressing chronic pain and preventing SUD as a high priority and has formally approved our study (see WPRN's letter of support).

For AIM-CP, we are collaborating with four health systems within WPRN (see Letters of Support from each health system). Peace Health consists of 4 primary care clinics in southwest Washington state that serves many rural patients. Health West, Inc. is a federally qualified health center that has nine clinics in the rural region surrounding Pocatello, Idaho. Clearwater Valley Health – St. Mary's Health is a health care system located in North Central Idaho that has 8 practices affiliated with 2 critical access hospitals. Providence Northeast is a system of four health clinics located in rural Northeast Washington.

MAPPR: The MAPPR is a research network of over 266 Atrium Health primary care clinics and has long standing partnerships with the Mecklenburg County Health Department, the county school system and over 60 community-based organizations. MAPPR includes many rural clinics and clinics that serve substantial proportions of rural dwelling patients. We will partner with both Atrium Health and Wake Forest Baptist Health, which includes a catchment area including western North Carolina and southwestern Virginia and extending to Tennessee and West Virginia. Additionally, the primary care practices serve patients from 91 North Carolina counties that include 10 rural counties. The Health System uses a single EHR system that is currently used successfully for recruitment in multiple studies.

III.B Intervention: Adapted Nurse Care Management for Rural Patients with Chronic Pain

Overview of Intervention

Our proposed 6-month long intervention will be an adapted NCM model, which is widely used for other chronic diseases and for patients at high risk of poor health outcomes. Dr. Tsui has previously implemented NCM for patients on chronic opioids with HIV[106, 122] and will provide input into adapting the NCM model for patients with chronic pain. In AIM-CP, participating health systems will identify one or more individuals who will serve as the care manager for patients with chronic pain who agree to participate in the study and are in the active intervention arm of the study. These individuals could be existing nurse care managers who are providing care for patients with other conditions or any other staff who the health system identifies as a suitable care manager. Health systems with substantial Hispanic/Latinx populations will be encouraged to identify care managers who speak Spanish or provide interpretive services for care managers. With ongoing input from our learning collaborative composed of community members and local providers and patients, our study team will train care managers to provide three separate but complementary intervention components: 1) care coordination, 2) CBT, and 3) referral to and enrollment support for tele-EF. This training will include 6 hours of asynchronous video modules, a full day of synchronous virtual training and then 9 hour-long sessions of case-based learning in the first few months of the intervention (see Table 3 for overview).

Patient Eligibility

This study will focus on patients who have chronic pain as identified through an EHR query of participating practices using the U.S. National Pain Strategy-supported methodology described by Mayhew et al.[123] We have previously successfully used this method in EHR data extraction.[124] Our study will target patients with moderate or severe pain interference, which is defined in our study as a Pain, Enjoyment of Life and General Activity scale (PEG) score of ≥4 (see Outcomes section for details about PEG). This definition is based on prior studies in chronic pain.[13] Other inclusion criteria are being 18 years of age and older, being able to communicate in English and/or Spanish, and living in a rural area as defined by the RFA.[125] We will exclude patients who have active cancer, have cognitive impairment severe enough to preclude participation in a behavioral/lifestyle change program, are on palliative care or live in a nursing home or inpatient treatment facility. We intentionally will include patients with active substance use disorder since they comprise up to 25% of patients with chronic pain and, based on our prior experience working with patients with substance use disorder, we believe that these patients will benefit from our intervention.

Collaborating with Primary Care Providers and Health System Staff

Prior to the onset of the study, Drs. Tong, Patel, and/or Ang will briefly present the study and its intervention components to each of the clinics (during a regularly scheduled staff meeting). We will focus on how care managers will communicate with primary care clinicians (email or EHR updates). Clinicians will be given an option to opt their patients out of the study (all patients or specific patients) if desired. They will also be given instructions on how they might refer their patients for the study if desired (see Recruitment section below for more details). Clinicians who have patients in the active intervention arm will be informed when the intervention starts, given updates on a monthly basis (or more frequently if there are substantial changes) and then given a final report at the end of the 6 month intervention.

Care Coordination

Background/Evidence: Care coordination has been widely implemented to manage other chronic conditions and nurse case management has been used successfully for chronic pain in the Veterans' Affairs system (see Significance section). To enhance care coordination, we will use PainTracker, an online questionnaire system asking about pain, mental health and functioning that patients can fill out on a regular basis that will create a report for the care manager to track, assess and manage patients. Using a tool to track patients' pain, mental health, functioning and goals has been shown to improve outcomes.[98, 107, 126] In addition, we will incorporate a social needs survey previously developed by Dr. Tong[32] to assess and manage social needs.

NCM Training: Identified care managers will watch asynchronous videos (previously developed and to be adapted for this intervention by Dr. Stephens) on an introduction to working as a team and care coordination, care manager tracking and monitoring and integrated care best practices (approximately 3 hours total). Drs. Tong and Tsui will then meet with the care managers for a 2-hour virtual training for the care coordination component of the intervention. The training will review the components of care coordination,[22] which include:

- Assessing patients for social service, behavioral health, and specialty care needs
- Linking patients with community resources and responding to social service needs
- Coordinating behavioral health and specialty care needs
- Tracking and supporting patients when care is received outside the practice

Table 3: Overview of NCM Training			
Format	Intervention	Description	Time
Asynchronous, video	Care Coordination	- Introduction to teamwork and care coordination - Care manager tracking and monitoring - Integrated care best practices	3 hours
	CBT	- Pain modules: biopsychosocial model of pain and treatment philosophy, common comorbidities, pain assessment, benefits and skill of self-monitoring, activity, pain self-management strategies, plans for managing pain flare-ups, key messages for patients - Behavioral activation for depression (in case comorbid) - CBT for anxiety (in case comorbid) - Substance use (in case comorbid) - Distress tolerance	3 hours
Synchronous, virtual	Care coordination	- Training on developing care plans for patients, administering and responding to social needs survey, formulating workflow for responding to social needs survey - Training on using PainTracker	3 hours
	CBT	- Introduction to case-based learning and discussion based on asynchronous training	2 hours
	Enhance Fitness	- Introduction to Enhance Fitness, evidence and referrals process	1.5 hours
Synchronous, virtual	Care coordination	- Case-based learning and troubleshooting	3 one-hr sessions
	CBT	- Case-based learning	6 one-hr sessions

- Communicating care plans and results to patients and families (with patient consent)
- Communicating care plans and results to primary care providers

Specifically, care managers will be trained on how to develop care plans for patients with chronic pain and on how to administer and respond to the social needs survey (see patient intervention below for details). Care managers will spend time developing and sharing an action plan to address needs that patients identify on the social needs survey. The workflow may include using existing resources in their practice/health system and/or connecting with new community organizations in the practice's local community. We will also train care managers on how to teach patients to access PainTracker and to use it to assess patients' pain, mental health and functioning in a 1-hour virtual seminar. We will then hold 3 synchronous sessions over the course of a few weeks as care managers administer the intervention to discuss cases and any troubleshooting with care plans, social needs assessments and treatment plans and use of PainTracker.

Patient Intervention: All patients in the intervention arm will receive care coordination. Care managers will schedule an initial 1-hour virtual appointment with each patient in the intervention arm of the study. Prior to the meeting, care managers will review notes from each patient's primary care clinician and available related notes from specialists/consultants. Care managers will also contact the primary care clinician to inform them that the patient will be participating in the intervention and to receive any relevant information from the clinician. Care managers will initially meet with each patient to develop or review (if one already exists from their primary care clinician) their care plan for chronic pain. Care managers will ask patients to review the progression of their chronic pain, list previously tried treatment modalities for chronic pain (including pharmacologic and nonpharmacologic treatments) and categorize each modality by their level of effectiveness. Patients will also be asked to identify their treatment goals for their chronic pain and develop realistic goals/expectations for their pain management.

Patients will work with the care manager to complete a social needs survey, modeled from a survey previously used by Dr. Tong in a social needs study.[32, 127, 128] The survey will include questions about housing, nutrition, exercise, social connections, mental health, financial needs, work/education, safety and transportation. The care manager will use the results from the survey in two ways: first, to inform the context of care for the patients' chronic pain and identify barriers to patients' participation in certain treatment options for their chronic pain and, second, to connect patients with appropriate resources for their social needs. This will vary by the participating health system but may include connection to a practice and/or health system social worker and/or outside community resources found in local volunteer organizations, community centers, libraries, churches, health departments and/or educational centers.

Care managers will contact patients monthly for 6 months via phone or videoconference. A few days prior to each monthly meeting, patients will be prompted via email or phone to complete assessments of their pain in PainTracker. During each visit, care managers will assess patient progress with their chronic pain treatment goals and make any needed adjustments. Care managers will write a brief note in the EHR communicating the care plan with the patient's primary care clinician after the initial assessment and at each check-in.

Cognitive Behavioral Therapy

Evidence: Meta-analyses show that cognitive behavioral therapy for chronic pain reduces pain intensity and interference and improves functional outcomes.[40, 53, 129] Integrating CBT into primary care for other conditions has been shown to improve health outcomes.[110, 130, 131] A recent study from DeBar and colleagues showed that in-person group CBT can be successfully implemented in managed care-provided primary care in non-rural settings and result in sustained reductions in pain and pain-related disability.[52]

Our adapted intervention - NCM training: We propose to train care managers in provision of CBT. The rationale is (a) the limited availability of behavioral health professionals in rural communities[108, 132] and (b) the streamlining of care by using the care manager to provide both care coordination and CBT. Dr. Stephens has previously developed a Washington State Department of Labor and Industries-funded training for non-behavioral health professionals on CBT for patients with chronic pain. This guide includes asynchronous video recordings followed by case-based learning with clinical supervision for feedback. The video recordings include 3 hours of training on topics as identified in Table 3. Care managers will independently watch the video recordings and then work directly with Dr. Stephens in a group over six sessions to do case-based learning. In the first training session, Dr. Stephens will review case selection for the study and format for the trainings and address questions related to the asynchronous trainings. In the subsequent training session, which will begin after a first patient is engaged in care by a trainee, Dr. Stephens will discuss CBT topics in Table 3 and focus on case-based learning through cases presented by the NCM. Care managers will have the ability to gain further input related to CBT treatment skills and delivery through monthly drop-in supervision sessions throughout the study as they continue to treat participants.

Our adapted intervention - Patient receipt of CBT: Patients in the intervention arm of the study who are not already previously engaged in CBT for chronic pain will be offered CBT to address pain self-management, barriers to self-management, and common comorbidities (e.g., depression, anxiety, substance use, etc.). The aim of CBT is to develop strategies to change maladaptive cognition and behaviors around pain. We will use the empirically supported CBT for pain treatment instructor manual developed by Drs. Dawn Ehde and Mark Jensen, who have worked closely with Dr. Stephens and tested these materials in prior RCTs for chronic pain in multiple sclerosis as the foundation of our CBT intervention.[69] This program and the accompanying materials will be adapted from group-based CBT to one-on-one, remote delivery based on feedback from the learning collaborative (UG3 phase, Aim 1).

The CBT intervention will include activities to address pain self-management skills in a patient-centric way. The intervention will require care managers to identify the patient's goals and flex the CBT intervention targets and skills to align with those goals. Patients will participate in a series of 6 to 10, 45-minute weekly individual sessions delivered by the care manager either in person or using a HIPAA-compliant videoconferencing platform.

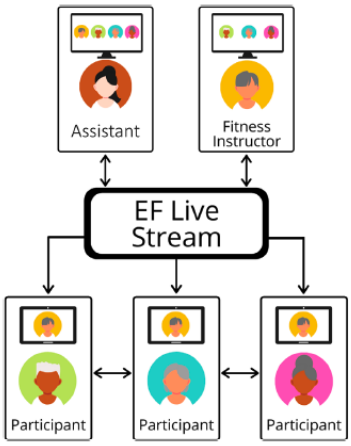
Enhance Fitness

Background/Evidence: Enhance Fitness is a widely disseminated, community-based program recommended by the CDC for arthritis pain management.[80, 133-135] This is an instructor-led, group exercise program that meets for 1-hour, 3 days a week for 16 weeks. Each EF class uses a standardized format that includes a 5-minute warm-up phase, 20 minutes of moderate-intensity aerobic training, 5-minute cool down with balance exercises, 20 minutes of strength training, and 10 minutes of cool down with stretching. Strength training involves progressive resistance exercises, using adjustable 1- to 10-pound cuffed ankle and wrist weights. A sequence of progressively more difficult exercises to improve static and dynamic balance is performed. EF instructors are certified by the American Council on Exercise and receive 12 hours of additional training on the EF program protocol. Instructors are taught how to modify exercises depending on the fitness level of individual participants, including doing exercises in the seated position, if necessary. Fidelity in the delivery of EF is maintained through periodic onsite reviews by master trainers who prepare formal reports providing feedback to the instructors.

As noted earlier, Dr. Patel adapted EF for remote delivery and has demonstrated the feasibility and acceptability of tele-EF in rural populations. This protocol was disseminated to over 800 community sites by the EF national program (see letter of support from Paige Denison).[136] Other than walking for aerobic conditioning

that usually cannot be done at home because of space constraints, all other components of the exercise protocol are the same in tele-EF and in-person EF. In tele-EF, an assistant helps the instructor and participants troubleshoot any technical challenges. In addition, the assistant helps monitor for safety and has participant emergency contact information available. Figure 4 illustrates that the EF instructor, participants, and assistant can all interact during a livestreamed EF class. To facilitate opportunity to interact socially, the assistant or EF instructor opens the virtual classroom 5-10 minutes prior to the start of class and participants will be able to join and see everyone in gallery view. Once it is time to start EF, the Assistant will then spotlight the EF instructor on the screen, who then begins leading the class in exercise. Importantly, however, both the EF instructor and assistant will be able see all participants in gallery view to monitor exercise form and any safety events. At the end of exercising, the assistant will switch everyone back to gallery view and again leave the virtual classroom open for a few minutes to let participants visit with the instructor. There are a variety of videoconferencing platforms (e.g., Zoom) that sites use to deliver tele-EF. The study team will mail the same cuffed ankle/wrist weights that are used by community centers to patients who are referred to tele-EF. In addition, participants with inadequate broadband or computer equipment will be issued a cellular-enabled tablet to facilitate inclusive study participation. Based on prior experience, we estimate up to a third of patients will need a tablet.

Figure 4: Enhance Fitness Live Stream Interactions



NCM Training: Dr. Patel will conduct a 1.5-hour webinar with care managers to describe the tele-EF program and review the process of referring and enrolling patients into tele-EF classes that are offered by community sites around the country.

Patient Intervention: Nurse care managers will refer patients to tele-EF, help them enroll into classes using the Program Locator on the EF website and monitor/encourage their engagement in tele-EF. Once registered, patients will receive cuffed weights (necessary to participate in the program) and, if needed, a cellular-enabled tablet. Prior to starting tele-EF classes, the community EF instructor will hold a "zero session" in which the patient will have a chance to log in to the virtual class, troubleshoot any technology challenges, and undergo a basic functional assessment (e.g., sit-to-stand test) so that the instructor can provide tailored exercise instruction. Patients will exercise for an hour 3 days per week for 16 weeks.

III.C. UG3 Phase: Planning and Pilot

Overview of UG3 phase

The UG3 phase of the study will focus on activities needed to ensure that the full-scale implementation trial can be conducted and completed successfully. We will work with the NIH Collaboratory, other investigators, and our learning collaborative to finalize outcome measures, data extraction processes and participation in Collaboratory workgroups (Aim 1), develop and streamline workflows to adapt the NCM model to rural patients with chronic pain (Aim 2), and pilot test our adapted NCM model, which will include care coordination, CBT, and referrals to tele-EF. Each of the subtasks under each aim below are modeled from our UG3 milestones.

UG3 Aim 1: To finalize outcome measures and data extraction processes through our learning collaborative and participation in NIH Collaboratory workgroups.

1.1 Establish participation in PRISM/Collaborative Work Groups: The MPIs, Drs. Tong and Patel, will work with the NIH Collaboratory and other investigators in the planning phase of this grant. Drs. Tong and Patel will identify project staff who will participate in the PRISM/Collaboratory Work Groups. Our team includes expertise in many of the Work Group areas: Biostatistics and Study Design (Comstock), Electronic Health Records (Stephens, Comstock, Ludden), Health Care Systems Interactions (Tong, Stephens), Patient-Centered Outcomes (Patel, Tsui, Stephens), Health Equity (Tong, Patel, Baldwin, Belza, Stephens) and Implementation Science (Tong, Patel, Stephens, Tsui, Baldwin, Belza).

1.2 Implement approved guidelines for data extraction: Co-investigators Stephens, Comstock and Ludden have extensive experience extracting and synthesizing EHR data from multiple health systems and applying quality control methods and tools. They will work with the Collaboratory to implement approved guidelines and practices for data extraction and quality control and develop a plan for data sharing with the NIH Collaboratory.

1.3 Finalize outcome measures: Both Drs. Tong and Patel will attend the two Health Care Systems Research Collaboratory program meetings in the first year and the subsequent annual meetings. In addition,

either Dr. Tong or Patel will attend the annual HEAL Investigators meeting. Drs. Tong and Patel will work with the NIH Collaboratory and other investigators to finalize outcome measures and refine estimates for sample size, number of sites, site to site heterogeneity and implementation timetable as needed. Our study proposes primary and secondary outcomes from the Common Data Elements identified by NIH HEAL Initiative investigators and other pain research experts. We will work with the Prism Coordinating Center and NIH to coordinate with other studies. In addition, we will engage patient and provider stakeholders in our Learning Collaborative as we finalize our outcome measures (Learning Collaborative further described in UG3 Aim 3.4).

UG3 Aim 2: To refine trainings, identify community-based partners and streamline workflows to adapt the NCM model to rural patients with chronic pain.

In this Aim, we will refine trainings, identify community-based partners, and streamline workflows for each component of our intervention.

2.1 Adapt and re-record asynchronous training videos: Dr. Stephens will update the training materials that she developed for the Washington State Department of Labor and Industries to tailor it for delivery by care managers. She will re-record the updated materials (which cover 3 hours of training on care coordination and 3 hours of training on CBT provision [see intervention description above for details]).

2.2 Streamline referrals and enrollment process for tele-EF: Dr. Patel will work with Sound Generations, the non-profit that manages EF nationally, to develop a streamlined workflow for enrolling patients into tele-EF (see letter of support from Ms. Denison). This will involve engaging community EF sites about the project, establishing payment mechanisms for individual tele-EF instructors or for community centers (e.g., YMCAs) that offer tele-EF, and ensuring updated class offerings in the Program Locator on the EF website.

2.3 Adapt PainTracker for our study: Dr. Sullivan, who created the PainTracker tool, will work with Dr. Lober, who oversees the Clinical Informatics Research Group, to modify and adapt PainTracker for use by care managers for tracking patients' chronic pain, mental health and personal goals. Some assessment tools in the current PainTracker will be changed since they are the same outcome measures identified by the HEAL Initiative Common Data Elements (e.g., the PEG, our primary outcome, will be replaced in PainTracker with the 4-item PROMIS Pain Interference scale to avoid any potential measurement biasing effect).

2.4 Obtain IRB approval for all sites: Drs. Patel and Tong will finalize the single Institutional Review Board (with University of Washington as the single IRB of record) for all sites where research activities are to take place. A single IRB is required for all multisite studies. See our Humans Subjects Plan for further details.

2.5 Establish community-based partnerships: Our **community engagement plan** includes seeking out organizations that meet the following criteria:

- Be based in communities served by our collaborating health care systems (ideally, we would find one in each of our 5 health care systems' local communities);
- Includes local community representation in its leadership, staff and/or board of directors; and
- At least one of the following 4 criteria:
  (a) assist patients with social needs as identified from our social needs survey;
  (b) assist patients with limited health literacy to access services referred by our care managers;
  (c) provide technology assistance to patients who may need help with accessing tele-EF and/or remote CBT; and/or
  (d) provide input on our study design, analysis, results and/or dissemination

We have already established a partnership with Sound Generations, which is a nonprofit that disseminates evidence-based programs nationally, including EF, and provides social support services to older adults in Seattle and King County, WA (see letter of support). Ms. Denison directs the health programs for Sound Generations, including EF, and she has an extensive network of colleagues who lead local community-based and national non-profit organizations (e.g., YMCA of the USA) that provide community support services. Dr. Patel, who has partnered with Sound Generations on several projects since 2015, will work with Ms. Denison to connect with community organizations that serve the catchment areas of our partnering rural-serving health care systems. We will also engage the health care systems themselves to identify community organizations that support their rural patients.

We have set aside funds in each year (Yrs 1-2 $25,000/yr and Yrs 3-5 $50,000/yr) to establish and support collaborations with community-based partners. As part of this milestone, we will also develop vendor and/or subcontract agreements with each community-based partner. We will identify a champion from one of our community-based partnerships to attend our biweekly co-investigator meetings to provide input on study design, analysis, interpretation of results and dissemination.

2.6 Identify care managers from each health system: In order to identify care managers from each system, we will first finalize any vendor and/or subcontract agreements with each participating health care system. The

WPRN has a history of facilitating agreements with its member health care systems and we will use this experience to establish these agreements with the 4 participating WPRN health care systems. We already have a subcontract as part of this application for Atrium Health. Each health system will be responsible for identifying at least one care manager. This can be an existing nurse care manager or other care manager who works with other chronic diseases and/or risk factors or another identified individual who can be trained to provide care management functions. Health systems will choose whether to have care managers centralized to serve all the system's participating practices or different care managers for different practices. Identified care managers will undergo training (see Table 3) at the beginning of the UH3 phase.

UG3 Aim 3: To pilot test the adapted NCM model that includes care coordination, remotely delivered CBT and tele-EF for rural patients with chronic pain in 2 health systems.

We propose to conduct a small pilot to refine our adaptations of the NCM model for wider implementation and to obtain stakeholder feedback on all elements of our NCM model and evaluation. To accomplish this aim, we will engage a learning collaborative consisting of clinicians, patients, and care managers in adapting and implementing the NCM with 30 patients in 2 of our health systems. Learning collaboratives are commonly used to support the implementation of innovation, clinical evidence, and models of care.[137] Dr. Tong has successfully led learning collaboratives to implement social needs screening,[32] improve care for older adults on opioids,[103] and implement medications for opioid use disorder in primary care. The purpose of our learning collaborative is to support the pilot adaptation and implementation of the adapted NCM model while obtaining feedback for our larger implementation trial. For the pilot, we plan to use Peace Health in southwest Washington, where we will recruit 20 patients, and Atrium Health in North Carolina, where we will recruit 10 patients. We will use the RE-AIM framework to assess implementation outcomes in our pilot. Developed by Glasgow, the RE-AIM framework is commonly used to measure implementation outcomes framed around Reach, Effectiveness, Adoption, Implementation and Maintenance.[138, 139]

3.1 Recruit learning collaborative members: We will recruit one provider, one other staff member, and one patient (who meets inclusion criteria for the study) from each of the two systems as well as identified care mangers from each system. We will use our existing practice champions to identify providers, staff members and patients, and health system leadership will assist with determining which individuals will serve as care managers. All learning collaborative members will be reimbursed per session for their time.

3.2 Train care managers for UG3 pilot phase testing: We will train care managers from the two health systems using the training adapted as described in Table 3.

3.3 Recruit 30 patients from 2 health systems to participate in pilot: We will use two separate mechanisms to recruit patients for this trial: 1) provider referrals and 2) EHR data query.

Provider referrals: Prior to the beginning of the pilot, Drs. Tong, Patel, and/or Ang will give a presentation to participating clinic providers and staff at a regularly scheduled staff meeting (or another meeting as preferred by the clinic staff) on the study and its interventions. Providers will be given the opportunity to opt out all or specific patients. They will also be given flyers to refer their patients to the study. Providers will be able to hand out these flyers to patients who will then be instructed by the flyer to reach out to the study coordinator by phone and/or email. The study coordinator will then screen them for other eligibility criteria.

EHR data query: For each of the two health systems, we will build a data query that identifies patients with chronic pain who are 18 years or older, live in a rural area as defined by the RFA, and do not have cognitive impairment. We have previously identified patients with chronic pain using an EHR algorithm and co-investigators Comstock, Stephens, Ludden and Dharod have experience building EHR-based data queries for studies. The participating health systems will send eligible patients an introductory letter on their letterhead with an opt-out option and, after 2 weeks, if patients do not opt out, they will be contacted by phone by the research coordinator (up to 5 contact attempts per eligible patient) until we reach our recruiting goal of 20 patients from Peace Health and 10 patients from Atrium Health. Patients we reach will be screened for eligibility using the PEG (eligibility = PEG $\geq$ 4). We will also confirm other eligibility criteria including rurality.

Those who are eligible and agree to participate will be consented over the phone. We will collect demographic information as per the HEAL Initiative Common Data Elements Program (date of birth, sex at birth, gender identity, ethnicity/race, highest level of education, employment, relationship status, annual household income, disability insurance application status, pain duration, and ZIP code). As there is no randomization in the pilot, all participants will then be connected with their health system's identified care manager. We conservatively estimate that we will be able to recruit 5% of the patients we contact. Dr. Stephens previously successfully recruited 23% in a comprehensive pain treatment trial for opioid tapering.

3.4 Conduct learning collaborative and implement pilot: The pilot and learning collaborative will happen simultaneously. The learning collaborative will meet 4 times during the 2-year UG3 phase, each time for 1.5

hours on a videoconferencing platform. The learning collaborative and pilot processes are described in Table 4. During the discussion of the various components of the study (training, recruitment, intervention components), we will focus the prompts in the discussion on needed adaptations for patients with chronic pain and rural populations, considerations for equity, successes to date and challenges with implementation. The intervention details are described in more detail above.

Table 4: Pilot and Learning Collaborative Activities

Period	Learning Collaborative Material	Pilot Implementation Process
Yr 1, Q3	- Introduction to learning collaborative, biopsychosocial approach to chronic pain and proposed intervention - Review of training and recruitment processes	- Identified care managers receive training - Patients are identified via EHR data query and recruitment/baseline data collection begins
Yr 1, Q4	- Discussion of care coordination and CBT components of intervention (specifically, challenges with implementation, needed adaptations for rural areas and successes to date)	- Patient recruitment/baseline data collection ongoing - Intervention begins
Yr2, Q1	- Discussion of Enhance Fitness component of intervention (specifically, challenges with implementation, needed adaptations for rural areas and successes to date)	- Intervention continues - Immediate post-intervention data collection occurs
Y2, Q2	- Discussion of preliminary results - Sharing of lessons learned and feedback for improvement	- Pilot study completed

3.5 Collect implementation outcomes using the RE-AIM framework[138]:

Reach – We will measure the proportion of patients who we reach out to who agree to participate in our study by tracking number of patients identified as eligible who are sent introductory letters, patients opting out, patients called, patients reached by phone call, patients enrolled by provider referral, and total patients enrolled. Specifically, we will track the demographic characteristics of patients (using the HEAL Initiative preferred demographics) to determine if specific subpopulations are more easily reached and enrolled in our study.

Effectiveness – In the UG3 phase of our trial, we will not be able to determine effectiveness but will focus on the feasibility of collecting outcome measures. We will collect outcomes at baseline and 6 months (i.e. immediately post-intervention). Six-month follow-up data collection is not feasible within the UG3 time period.

Patient Data Collection: In the initial interaction with the research coordinator, patients will be asked if they prefer baseline data collection to occur online (via email or text), mail or phone. The phone option allows patients with limited literacy to participate. For those who prefer the phone option, we will administer the instruments at the time of consent. For those who prefer online, we will email the link to REDCap to complete the outcome tools. For those who prefer mail, we will mail paper copies of tools to them after consent. Patients will be reimbursed $25 for initial data collection. At 6 months (i.e. post-intervention), patients will be emailed, mailed or called by phone for subsequent repeat data collection and be reimbursed $30 (at 6 months) for completion of outcome measures.

Outcomes: Our outcome measures are modeled off the HEAL Initiative's Common Data Elements[140] and reflect our study's focus on patient-reported outcomes. The primary outcome is pain interference as measured by the PEG scale. The PEG is a validated 3-item, 0-10 numerical rating scale that measures pain intensity and pain interference with enjoyment of life and general activity.[141] We have chosen to use the PEG to measure our primary outcome since it is easy to administer and is the NIH HEAL Initiative's preferred instrument for pain interference.[142] Secondary outcomes including the remaining NIH HEAL Initiative core pain domains: pain intensity, physical functioning/QOL, sleep disturbance, pain catastrophizing, depression, anxiety, global satisfaction with treatment and substance use disorder (See Table 5 for proposed measures to be finalized with NIH Collaboratory). In addition, we will track pharmacologic treatments (medication names, doses and, if opioid, morphine milligram equivalents/day) from the EHR and patient-reported health care utilization over the course of the intervention period (number of hospital admissions, emergency department visits, urgent care visits and primary care visits).

Adoption – We will measure the proportion of patients in the pilot trial who engage in each of the 3 components of the intervention. To measure engagement from providers, we will also track communication between care manager and primary care providers in this trial through care manager notes of any interactions with the primary care clinician and office staff.

Implementation – We will measure care manager fidelity with all 3 components of the interventions through review of care coordination templates that the care manager completes. For the care coordination component, we will track and evaluate adherence with completing PainTracker assessments prior to the care coordination
meetings, number of care coordination visits, whether a pain management plan was developed, whether the social needs survey was administered, how identified needs were addressed and substantial variations between patients in the intervention (i.e., visit durations, types of plans, etc.). For the CBT component, we will track the consistency of the delivery of the CBT intervention between individuals, the level of adherence to the study manual, patients' adherence to CBT visits and any necessary adaptations based on patients' needs or expressed desires during visits. For the Enhance Fitness component, we will track patient attendance to tele-EF classes over 4 months. EF instructors record attendance data, and these data are uploaded to Sound Generations, our community-based partner.

Table 5: Effectiveness Outcomes and Measurement Tools

Outcome	Measure	Data Source
Pain interference	PEG	Patient report
Pain intensity	PEG	Patient report
Physical Functioning	PROMIS Physical Functioning Short Form 6b	Patient report
Sleep	PROMIS Sleep Disturbance 6a + Sleep Duration Question	Patient report
Pain Catastrophizing	Pain Catastrophizing Scale	Patient report
Depression	PHQ-9	Patient report
Anxiety	GAD-7	Patient report
Global Satisfaction with Treatment	Patients' Global Impression of Change scale	Patient report
Substance Use Disorder	TAPS 1	Patient report
Pharmacologic Treatments	Medication name, dose, and, if opioid, morphine milligram equivalent	EHR
Health care utilization	Hospital admissions and Emergency Department, urgent care and primary care visits	Patient report

Maintenance – We do not plan to evaluate maintenance at 6 months post-intervention in our pilot due to time constraints. We will evaluate maintenance in our UH3 phase trial.

UG3 Milestones

Milestones for the three UG3 phase aims are listed in Table 6 and described above. Our team will meet biweekly during the UG3 phase to track milestones progress. More details are in the Milestones attachment.

Table 6: UG3 Milestones and Project Timeline

Milestones	Y1				Y2			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Aim 1: *To finalize outcome measures and data extraction processes through our learning collaborative and participation in NIH Collaboratory workgroups.*								
1.1 Establish participation in Collaboratory Workgroups	X	X	X	X				
1.2 Implement approved guidelines for data extraction	X	X	X	X				
1.3 Finalize outcome measures	X	X	X	X				
Aim 2: *To refine trainings, identify community-based partners and streamline workflows to adapt the NCM model to rural patients with chronic pain*								
2.1 Re-record asynchronous trainings	X	X						
2.2 Streamline referral and enrollment process for Enhance Fitness	X	X						
2.3 Adapt PainTracker for our study	X	X						
2.4 Obtain IRB approval for all sites	X	X						
2.5 Establish community-based partners	X	X	X	X				
2.6 Identify care managers from health system for UH3 phase					X	X	X	X
Aim 3: *To pilot test an adapted nurse care management model*								
3.1 Recruit learning collaborative members	X	X						
3.2 Train care managers for UG3 pilot phase testing			X					
3.3 Recruit 30 patients from 2 health systems for pilot participation			X	X	X			
3.4 Conduct learning collaborative and pilot implementation			X	X	X	X		
3.5 Collect implementation outcomes using RE-AIM framework			X	X	X	X	X	X

III.D. UH3 Phase: Individual Randomized Controlled Trial

Overview of UH3 phase

In the UH3 phase of the study, we will implement an individual-level randomized controlled trial to test our adapted NCM model in 6 health care systems that serve substantial numbers of rural patients with chronic pain (see Table 2 above for characteristics of health care systems). Our UH3 aims are to: 1) determine the effectiveness of the adapted NCM model vs. usual care in improving pain interference with daily functioning, 2) evaluate the implementation of the adapted NCM intervention and 3) explore disparities by examining heterogeneity in treatment effects via subgroup analyses of the primary outcome, secondary outcomes and implementation outcomes.

Sampling and Power Analysis

We plan to recruit 416 patients with chronic pain with the eligibility criteria listed in the patient eligibility section above. Assuming a two-sided type 1 error rate of 0.05, conservatively estimated follow-up rate of 85% at 6 months, and a correlation between baseline and 6-month PEG scores of 0.3, this study can detect a (small) standardized effect size of d=0.33 on the PEG with 90.6% power.[143] Using a conservative Bonferroni correction, the study has >90% power to detect standardized effect sizes of $d \geq 0.40$ on the 7 secondary outcome measures of Aim 1. We conservatively anticipate being able to recruit 5% of patients we contact and as such estimate that we will need to reach out to approximately 8,320 patients to recruit for this trial.

Recruitment Contingency Plan: We have engaged 6 health care systems so that we have more than enough patients to recruit from and in the unlikely chance that one of the health care systems decides they are unable to participate in the trial. Between the 6 health care systems, we have approximately 19,622 patients who would be eligible for this trial (see Table 2). As such, we have an excess of 11,302 patients between our health care systems. In the highly unlikely event that we are unable to recruit from our identified partnering health care systems, the WPRN, which has a network of over 100 primary care practices, would assist us in identifying another health care system (see WPRN letter of support).

Patient Recruitment

We will use the eligibility criteria outlined above with recruitment techniques refined from the UG3 phase. In brief, we will use both the EHR query and provider referrals. Providers will be asked to refer patients when the study is first described to them at a practice staff meeting. For the EHR query, we will identify patients with chronic pain from health systems with methodology as described by Mayhew.[123] Like in the UG3 phase, the health systems will send eligible patients an introductory letter on their letterhead with an opt-out option and, after 2 weeks, if patients do not opt out, they will be contacted by phone by the research team (up to 5 contact attempts per eligible patient). We seek to recruit 266 patients from the 4 WPRN health care systems and 150 patients from Atrium Health. We will intentionally oversample from racial/ethnic minorities, those who identify as female and those who live in highly rural areas. Patients we reach will be screened for eligibility using the PEG (eligibility = PEG $\geq$ 4) and other eligibility criteria. Those who are eligible and agree to participate will be consented over the phone and then required demographic information as per the HEAL Initiative Common Data Elements Program will be collected.[142] Baseline data collection will occur via email/text (online REDCap surveys), mail or phone depending on patient preference.

Randomization

After patients complete the baseline assessment, research staff will randomize eligible patients using a centralized web-based portal that provides the next available assignment once an eligible patient consents for study participation. Randomization assignments will be generated by the UW Data Coordinating Center. Patients will be randomly assigned to either the intervention or usual care using permuted block randomization with random block sizes of 2, 4, 6, and 8. Using block randomization ensures that equal numbers of participants are randomized to each arm and that the two groups are balanced at enrollment intervals.

Intervention Group

Patients assigned to the intervention group will be contacted by identified care managers from each health system. The care managers will have been identified in the UG3 phase (UG3 Aim 2.6) and will receive training refined from the UG3 phase as per Table 3 within 3 months of the start of the UH3 phase. Modified with feedback from the UG3 phase learning collaborative, the intervention will last 6 months in duration.

Usual Care Group

Those randomized to usual care will continue to follow-up with their usual care team for chronic pain management. At the close of the trial (i.e. after the 12 month data collection timepoint), if the patient's health

care system decides to continue the NCM model for chronic pain, they will be eligible to receive the intervention from the identified care manager. See below for sustainability and next steps plan.

UH3 Aim 1 Outcomes, Data Collection and Analyses

To determine the effectiveness of the adapted NCM model vs. usual care in improving pain interference with daily functioning.

Outcomes

As described in the UG3 phase section, our outcomes are based on the NIH HEAL Initiative Common Data Elements. We will use the PEG to measure our primary outcome of pain interference. Secondary outcomes and their respective measures are listed in Table 5. In addition to the Common Data Elements identified outcomes, we will include receipt and dose of pain medication prescriptions (to include acetaminophen, any NSAIDs, numbing or NSAID creams, neuropathic agents, muscle relaxants and opioids), if any opioids, morphine milligram equivalent/day, and health care utilization (frequency of hospital admission, emergency department use, urgent care use and primary care visits). All outcomes will be refined in collaboration with other grantees, the NIH HEAL Initiative and learning collaborative members from our UG3 phase.

Data Collection (see Table 5 above in UG3 section)

Patient data collection: In addition to our baseline data collection, we will collect the outcome measures from patients in the week following the intervention and then 6 months following the intervention (or, for comparable time points, for those in the usual care group at 6 and 12 months after baseline data collection). Data collection will take place via email/text (online REDCap surveys), mail or phone depending on the patient preference. Patients will be given a $25 gift card incentive for the baseline data collection, $30 initial follow-up data collection and $50 for the final data collection time point. In addition to the measures, we will ask patients if they have been admitted to the hospital, visited the emergency department, gone to urgent care or visited primary care since the previous data collection point and if yes, how many times for each.

EHR data extraction: We will obtain prescription data from the EHR at baseline and then complete another EHR extraction at 12 months after the baseline data collection to identify pain medication prescriptions and dose. This will capture both pain medication changes at 6 and 12 months.

Analytic Plan

The primary evaluation for Aim 1 will utilize an intention to treat (ITT) approach, where patients' data are analyzed according to their randomized treatment assignment. For the primary analysis, PEG scores post-randomization at 6 months will be analyzed using an analysis of covariance model (ANCOVA) adjusting for the PEG score pre-randomization and recruitment site. All analyses will use robust standard errors to generate treatment effect estimates and two-sided 95% confidence intervals. In secondary analyses, we will use linear mixed models to characterize the average time-specific PEG outcome, PEG(j), where j= 6, 12 and the treatment-group-specific mean trajectories over time. To account for potential missing data at one or more follow-up times, we will use linear mixed models to characterize the mean time-specific PEG outcome and treatment-group specific mean trajectories over time. From the longitudinal model we will estimate the mean difference in the time-averaged outcome by averaging the time-specific treatment group differences.

For secondary outcomes, we will use generalized linear regression models (linear, log-linear, logistic, Poisson, as appropriate for each outcome) to evaluate differences between treatment groups at 6 and 12 months, including physical function, sleep disturbance, pain catastrophizing, depression, anxiety, treatment satisfaction, substance use disorder, pain medication use and dosage including opioids, and health care utilization. We will use the Benjamini-Hochberg procedure to correct for statistical tests of multiple secondary outcomes.

Non-adherence - Our primary analysis sample will be the ITT sample defined according to the treatments to which an individual is randomized regardless of treatment received. An ITT analysis will include all subjects in the analysis and account for any missing data using methods detailed below to address the causal question of whether adapted NCM is superior to usual care in improving pain interference with daily functioning. Non-adherence can bias an intention-to-treat analysis towards a null conclusion and in such cases, Detry et al[144] recommends both an ITT and careful, per-protocol analysis that addresses non-adherence to randomization. Using marginal structural models, we will compute the probability of protocol adherence for each participant and use these as inverse weights to estimate regimen-specific means using methods detailed by Hernan and Robins[145] and overviewed by Hernan and Robins.[146] Per-protocol analyses will thus focus on the causal estimate associated with complete adherence to NCM in the entire cohort.

Missing Data - As summarized in NEJM guidance,[147] we will employ three primary strategies that are recommended to address missing data. First, the Data Coordinating Center will work with the study team to minimize the amount of missing data since prevention of missing data is preferable to any attempted analysis

correction. Second, we will use inverse probability weighting[148] to inflate the weights of cases that are under-represented in the analysis due to selective attrition and/or non-participation. We will conduct a descriptive analysis that characterizes enrolled participants who do not provide data due to attrition, and we will use observed covariates to construct a weighted model using logistic regression. Third, the strategy that the Data Coordinating Center has used in three recent primary trial publications[149-151] and which we will adopt for our primary analysis, is the use of tenfold multiple imputation to assess the robustness of the results when missing data are imputed and allowing all participants to be included in ITT analysis. Our primary approach is to use multiple imputation since it provides flexibility in inclusion of relevant baseline and follow-up data.

UH3 Aim 2 Outcomes, Data Collection and Analyses

To evaluate the implementation of the adapted NCM intervention.

Outcomes

As in our UG3 phase, we will use the RE-AIM framework to assess the implementation of the adapted NCM intervention. We will also conduct 30 qualitative interviews with patients in the intervention arm of the study to assess their experiences with the intervention and to provide feedback for future dissemination of our intervention.

RE-AIM Framework Outcomes:

Reach – Unchanged from UG3 phase. We will measure the proportion of patients who we reach out to who agree to participate in our study and the demographic characteristics of patients reached and enrolled in our study.

Effectiveness – See UH3 Aim 1 for effectiveness outcomes. See UH3 Aim 3 for an exploration of subgroup characteristics that may affect the effectiveness outcomes.

Adoption – Unchanged from UG3 phase. We will measure the proportion of patients who engage in each of the 3 components of the intervention and engagement with primary care clinicians.

Implementation – Unchanged from UG3 phase. We will continue to measure fidelity to each of the 3 components of the intervention.

Maintenance – We plan to evaluate maintenance of our intervention in two ways. First, at a patient level, we will determine maintenance of change in our primary outcome (and any secondary outcomes in which there is a significant change) at 12 months (i.e., 6 months post-intervention). Second, at a systems level, we will measure the proportion of the health systems/clinics where our intervention has been implemented that choose to continue the intervention when they no longer have financial support from the study for the care manager.

Qualitative interviews:

Qualitative interviews will elucidate multiple elements from within the RE-AIM framework in greater detail. We will conduct 30 interviews with patients (20 from the 4 WPRN health care systems and 10 from Atrium Health) at the conclusion of the intervention. We will recruit patients via phone with a $50 incentive offered to those who agree to and complete the interview (this incentive is in addition to other incentives offered to patients for completion of data measures). We will intentionally sample patients of diverse gender, race/ethnicity, and geographic location, and if feasible, both patients who have attended the majority/all of the intervention sessions and those who have attended fewer sessions of the assigned intervention. The interviews will be conducted by our qualitative research scientist and will query the experience of participants in the intervention group. We will ask patients about their experience of chronic pain, the perceived effect of the intervention on chronic pain/medication/opioid use, thoughts about facilitators and barriers to accessing the intervention, feedback about the intervention, and comments about potential future adaptations. Semi-structured interviews will be conducted using an interview guide.

Data Collection

RE-AIM outcomes: For the reach and adoption measures, we will record all interactions with clinics and recruitment efforts via a template to document different types of interactions in REDCap. This database will be maintained by our research coordinators. For the implementation measures, the care managers will record attendance at individual visits and CBT sessions. Furthermore, the NCMs will take notes immediately following each meeting with patients. Data on Enhance Fitness class attendance will be available through Sound Generations' online data portal.

Qualitative interviews: We will audio record and transcribe all the qualitative interviews.

Analytic Plan

RE-AIM outcomes:

R*each:* We will use descriptive statistics to summarize the proportion of patients contacted who agree to participate in the study. In addition, we will use chi-squared analyses to determine if there are differences by age (grouped by tertiles in the data), gender (male, female, nonbinary), degree of rurality (as defined using the Rural-Urban Continuum Codes[94]), and race/ethnicity.

E*ffectiveness:* See Aim 1 and 3 Analytic Plan.

A*doption:* Descriptive statistics will be used to summarize the proportion of patients who participated in each element of the intervention.

I*mplementation:* We will use descriptive statistics to summarize the proportion of visits attended. We will also use chi-square analyses to complete subgroup analyses to see if there are differences in adherence and fidelity to the intervention based on age, gender, race/ethnicity, and degree of rurality. While we may not detect differences because we are not powered for subgroup analyses, we may observe trends.

M*aintenance*: See Aim 1 Analytic Plan to describe sustained change in outcomes at 12 months.

Qualitative Interview Analysis: An immersion-crystallization process will be used to identify key themes in the data.[95] The themes will describe patient experiences of the intervention, effects of the interventions on their chronic pain, pain medication use and health care utilization, and patients' perceived facilitators and barriers to accessing the intervention. A codebook will be created that combines emergent and a priori themes derived from the interview guide. Two coders will independently code each transcript. Coders will meet weekly throughout the coding process. If any new themes emerge during the coding process, these will be discussed as a team and may be added to the codebook. A random subset of 5 (15%) transcripts will be selected for cross-checking by a 3rd coder to ensure the two coders are using the codebook in a consistent manner. Any disagreement in coding will be resolved by consensus including a third coder. Once all interview transcripts have been coded, the coders will meet with the investigators on two separate occasions to discuss the themes, search for patterns and overarching interpretations in the themes, seek alternative interpretations, and ask whether the themes and patterns may be interpreted in a different manner. This process will continue until no further interpretations are generated. Qualitative software, Atlas.ti, will be used by the team to code the transcripts and organize the data.

UH3 Aim 3 Outcomes, Data Collection and Analyses

To explore if there are disparities in response to the NCM intervention by examining heterogeneity in treatment effect in the primary (pain interference) and secondary outcomes.

Outcomes

We will explore subgroup analyses with the NIH HEAL Initiative Common Data Elements required demographic information. This includes age, sex at birth, gender identity, race/ethnicity, highest level of education, employment status, relationship status, annual household income, disability insurance application status, pain duration and RUCA code (identified from querying patient zip code).

Data Collection

Demographic data will be collected from patients on intake and recorded in REDCap.

Analytic Plan

Subgroup analyses will be considered exploratory and heterogeneity of treatment effect (HTE) of NCM will be assessed through the CATE (conditional average treatment effect) analysis framework. Using features and patient characteristics (X) at baseline (e.g. race/ethnicity, gender identity, comorbidities, degree of rurality, and insurance status), and for each outcome Y, we will fit generalized random forests (R function: causal_forest) to estimate the difference in potential outcomes E[Y(NCM) – Y(Usual care) |X=x] under each corresponding treatment group.[152] In estimating CATEs, we will hold out folds of data so that an individual's own outcome does not influence its subgroup assignment. Using the CATE estimates, we will then estimate the Targeting Operator Characteristic curve which compares the benefit of treating only a certain fraction *p* of units to the overall average treatment effect. The Rank-Weighted Average Treatment Effect (RATE) is a weighted sum of this curve and identifies prioritization rules that effectively targets treatment and can be used to test for the presence of heterogeneous treatment effects. If HTE exists, the curve will start high for the individuals with the highest expected benefit and declines until it equals the average treatment effect (e.g. when *p*=1 and everyone is included). The area under this curve gives an immediate impression of whether there is HTE or not, as the area under the curve will be a large number in the presence of HTE or zero in the absence of HTE. If there is evidence of HTE for select subgroups, we will present CATE estimates, 95% confidence intervals, and Benjamini-Hochberg corrected p-values for multiple testing.[153]

UH3 Milestones

Milestones for the UH3 phase are listed in Table 7 and described above. Our research team will meet biweekly during the 3 years of the UH3 phase to track progress. See more details in the Milestones attachment.

Table 7: UH3 milestones and timeline

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Train identified nurse care managers	X	X										
Conduct EHR queries to identify eligible patients	X	X										
Recruit and randomize patients for study		X	X	X	X	X	X					
Collect baseline demographics and outcome measures		X	X	X	X	X	X					
Deliver NCM intervention			X	X	X	X	X	X	X			
Collect post-intervention patient surveys				X	X	X	X	X	X	X		
Conduct post-intervention EHR queries										X		
Conduct qualitative interviews									X	X		
Complete Aim 1 (primary outcome) analyses										X	X	
Complete Aim 2 (implementation outcomes) analyses											X	
Analyze qualitative interviews											X	X
Complete Aim 3 (subgroup analyses) analyses											X	X
Disseminate preliminary findings from UG3 phase	X	X	X	X								
Prepare dissemination products for UH3 phase											X	X

III.E. Dissemination and Other Considerations

Summary of Resource Sharing Plan

Our data coordinating center has previously worked on NIH HEAL Initiative funded studies and have experience with the data sharing requirements from the HEAL Initiative Public Access and Data Sharing Policy. The costs listed for the data coordinating center include those associated with data sharing to the NIH HEAL Initiative. Further details are provided in our Resource Sharing Plan.

Potential Limitations and Mitigations

1) Recruitment and retention: To mitigate potential problems with recruitment and retention of health systems, we are partnering with health care systems with a known history of collaboration with the WPRN and with MAPRR. Each health system has provided a letter of support indicating the availability of institutional resources and suitability of patient populations for the proposed intervention. See our Recruitment Contingency Plan above for further details.
2) Patient sample bias: Patients who agree to participate in this study may be more motivated than patients in the general population. We will mitigate this by using embedded care managers and encouraging primary care clinicians to refer their patients to our study. In addition, future studies to disseminate this model will be at the health system level instead of the patient level to mitigate additional bias concerns.

Dissemination, Sustainability and Potential Impact

At the conclusion of our trial, we will strongly encourage health care systems to continue offering NCM for patients with chronic pain and identify ways it can be financially sustainable in their local context. Building on sustainable interventions that Drs. Stephens, Belza and Baldwin have done in rural health settings, we will engage a Translation and Dissemination Advisory Group with the goal of facilitating sustainability beyond the study and other translational/dissemination opportunities and goals. Members will include policymakers, payors, health system leaders and community leaders that represent minority groups. Starting in year 2 of the UH3 phase, this group will meet every 6 months to discuss translational opportunities and goals, identify barriers/facilitators to implementation and sustainability, problems solve identified barriers and develop action plans for dissemination and sustainability.

We believe our adapted NCM model for chronic pain will substantially change the ways in which chronic pain is conceptualized and addressed for patients in rural communities. Our adapted NCM model uses a biopsychosocial approach to chronic pain management previously not widely used in rural primary care practices to serve patients with chronic pain. Incorporating exercise, cognitive behavioral therapy and care coordination, our intervention has the potential to transform care for patients with chronic pain in rural communities by improving access to evidence-based non-pharmacologic treatments.

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RESOURCES AND DATA SHARING PLAN

Resources

The University of Washington (UW) research team will co-lead development of all policies, practices, materials, and tools for facilitating data collection and sharing to target facilitation of collaboration between Co-I's, reuse data, and replication of the project. All members of the research team will abide by the UW IRB and the NIH HEAL Initiative Public Access and Data Sharing requirements (https://heal.nih.gov/about/public-access-data).

Data Sharing Plan

Electronic Health Record (EHR) Data Privacy and Confidentiality. The UW will serve as the data coordinating center for all EHR data involved in the trial. The UW team has extensive experience with data access, privacy protection, and management. All health care system partners will de-identify data, removing PHI, except for service dates and year of birth, before sending data extractions to the University of Washington (UW) research team for analyses. UW will facilitate secure transfer of the data from the health care systems to a HIPAA compliant computing environment supported by the Department of Family Medicine and the Institute of Translational Health Sciences. All data sharing protocols will be IRB approved by the single IRB governance provided by UW. Each health care system partner will also complete a Data Use Agreement to support use of their EHR data for the trial and any defined ancillary studies deemed to be in scope by the Co-PIs. Any data shared out with other partnered institutions in support of completing ancillary studies will be done through a clear data management plan and technical infrastructure for rigorous data handling and safety monitoring, led by the UW team and vetted through the UW IRB.

We will prepare and share a final research data set that the accepted primary pragmatic trial publication is based upon. The final data set will be structured to maximize future scientific value while protecting patient and health system privacy. The UW research team will remove or de-identify all of the 18 HIPAA-specified direct identifiers in the final dataset. The aim of our data sharing policy is to strive for the least restrictive plan possible while providing appropriate protection for participant privacy, health system privacy, and scientific integrity.

The final research data set will be stored separately from the operational study database in a secure HIPAA compliant database platform, where access and downloads can be easily monitored and the data are downloadable securely by the research analytics team at UW in a variety of formats (Excel, R, SAS, Stata, SPSS). A comprehensive data dictionary will be available alongside the final research database. The data sharing plan will be executed within the final year of funding. The overhead required to support this data sharing plan is minimal and therefore no additional budget is requested to cover its costs.

Within 9 months of the end of the final year of funding, a final study data set will be accessible via a supervised private data enclave. Access will be limited to registered users who submit proposed specific questions or analysis plans and sign a data use agreement. "Supervised" indicates that individual requests are reviewed to protect the intellectual property rights of the project investigative team by restricting external development of manuscripts using the study data that substantially overlap with those that are already in development by study investigators. We will form a publications committee, with investigator representatives from core research sites to establish manuscript development and publication guidelines.

Qualitative Data Privacy and Confidentiality. These data will include surveys, interviews, and field notes that will be stored securely at OHSU in accordance with IRB protocol and de-identified from name identifiers. Voice recordings will be stored in HIPAA compliant servers, where they will be transcribed for the qualitative team's analyses efforts. Raw qualitative data with identified voices and names will not be shared beyond the OHSU research team.

Consistency with HEAL Initiative Public Access and Data Sharing Policy

Our data coordinating center has previously worked on NIH Collaboratory studies and is budgeted to include work to meet all data sharing requirements. We will work with NIH staff to ensure that our data sharing plan meets HEAL Public Access and Data Sharing Policies, that our data meets FAIR principles and that we submit required forms to the HEAL Clinical Data Elements Program. We have chosen primary and secondary

outcomes that are in concordance with the HEAL Clinical Data Elements Program to better facilitate this transfer of data.

Academic Presentation and Publications

Sharing of data generated by this project is an essential part of our proposed activities and will be carried out in several different ways. We plan to make our results available both to the community of scientists interested in improving chronic pain management in primary care settings to avoid unintentional duplication of research. Conversely, we would welcome collaboration with others who could make use of the findings, materials and resources developed in the study. Below are several ways we expect to specifically share data.

Presentations at national scientific meetings. It is expected that the Co-PIs and Co-Is will spearhead national conference presentations throughout the project to present works in progress, methods, and final outcome analyses. In addition, we will share methods and insights at meetings of the NIH Collaboratory. We also anticipate participating in the NIH Dissemination and Implementation Annual Conference and other relevant conferences sponsored by organizations with interest in the trial (e.g., Society for Behavioral Medicine, Academy Health, North American Primary Care Research Group).

Publications and Release of Data. All efforts will be made to rapidly release data through publication of results in peer reviewed journals as quickly as it is possible to analyze the outcomes of the study. Data used in publications will be released publicly in a timely manner. This project will generate data about chronic pain management from the participating health care systems. It is our explicit intention that these data will be placed in a readily accessible public database with health care system identifiers removed.

Community partners. We will work with our community partners as well as the WPRN and MAPPR to share results from our study.

PROTECTION OF HUMAN SUBJECTS

The protection of human subjects' plan that we propose is designed to adequately protect all research participants. The main risk, which we have minimized, is a breach of privacy and confidentiality. If effective, our intervention will improve pain and functionality for those with chronic pain who live in rural communities. All study activities will be approved by the University of Washington Institutional Review Board.

1. Risks to the Subjects

Human subjects' involvement, characteristics, and design: In the UG3 phase, our study design is a pilot trial where all participants will receive the intervention. In the UH3 phase, our study design is a randomized controlled trial with 416 primary care patients as participants. The patients will meet the following inclusion criteria: age 18+, having a diagnosis of chronic pain as defined in our research strategy, having a PEG score of 4 or greater, live in a rural area as defined by the RFA and are English and/or Spanish speaking. We will exclude patients who have dementia, active psychosis, and/or active substance use disorder (except tobacco use disorder), are in palliative care, or live in a controlled setting (i.e. assisted living, nursing home or inpatient treatment facility). While it is possible that pregnant persons may be included as part of the sample, we will not be intentionally targeting pregnant persons. In the UH3 phase, patients who agree to participate with be randomly assigned to one of two groups: 1) psychological intervention (n = 208), or 3) control (i.e. usual care) (n = 208). Patients will be recruited using one of two methods: 1) referral by primary care provider or 2) data extraction from electronic health records (EHR) followed by phone call recruitment by our research coordinators.

Study Procedures: There are two intervention arms in our 3-arm trial. The psychological intervention arm will consist of weekly virtual visits in a group setting for 8 weeks during which an adapted CBT intervention will be used. The social navigation intervention will consist of weekly virtual visits with the social navigator in an individual setting.

Study Materials: We will use 5 data sources to address the questions in our specific aims: EHR data queries (baseline and post-intervention), patient surveys (at baseline, immediately post intervention and 6 months post intervention), study care coordinator notes, notes from learning collaborative meetings, and select patient semi-structured interviews. EHR data of all potential subjects will be used to identify the sample for recruitment, patient demographics and pain medication use/dosing. Identifiable data is needed from the EHR because we will need to contact patients to recruit them. EHR data is considered previously collected data and will be linked with living individuals. Our data coordinator center will have access to identifiable EHR data.

Potential Risks: Overall, the potential risks associated with participation in this study is low. Overall, the primary potential risks are limited to breaches of privacy and confidentiality. For the CBT intervention, a potential risk may involve discussion of issues that may raise psychological distress. Enhance Fitness could possibly be associated with pain flare-ups and muscle soreness, although there is evidence that engaging in physical activity helps to manage pain symptoms.

2. Adequacy of Protection Against Risks

Informed Consent and Assent: There are three points in the study where we will either seek a waiver of consent or seek informed consent:

(a) Eligible patient identification: To identify eligible participants for study recruitment, we will need to obtain identifiable data from the EHR (including name, date of birth and phone number) of the two participating clinics. We are seeking a waiver of consent for obtaining the EHR data. Each participating clinic will send an initial letter by mail allowing patients two weeks to contact the clinic to opt out of having their EHR data released if patients do not want their data released to study personnel. This step of the study could not be practically done if it required obtaining informed consent prior to contacting patients since we need to have their identifiable data before we can contact them.

(b) Study learning collaborative participation in UG3 phase: We will obtain informed consent from each of the patients, clinic staff and clinicians participating in the learning collaborative. For each participant, the study research coordinator who is recruiting learning collaborative members will overview the informed consent process over the phone when they are being recruited and send each participant the document via email (preferred) or mail (if participants request). The risks overviewed will include potential breaches in privacy and confidentiality. Participants will return the signed consents via email (or mail if preferred).

(c) UG3 pilot trial or UH3 implementation trial participation: We will obtain informed consent from each of the patients participating in the trial. For each participant, the study coordinator who is recruiting patients to the study will overview the informed consent process over the phone when they are being recruited and send each participant the informed consent document via email (preferred) or mail (if participants request). The risks overviewed will include potential breach in privacy and confidentiality, transient muscle soreness with Enhance Fitness, and potential psychological distress (depending on issues discussed over the course of the intervention). Participants will return the signed consents via email (or mail if preferred).

Protection against risk.

Privacy and Confidentiality: To protect patient privacy and confidentiality, we will utilize protections to manage the data from the EHR, patient surveys, interview transcriptions and other study notes. The process results in researchers who have access to personal health information not having access to any personally identifiable information, and research staff who have access to personal identifiable information not having access to any personal health information. The process for this project is described in detail below.

For this study, the EHR data extractions will be generated by each health system's information technology (IT) staff. Data will be imported into a password-secure file and sent to the UW or Wake Forest research team. The patient identifiers will be their name, date of birth, address, phone number and email. To reduce the risk of breaches of confidentiality, we replace this information in the research databases with a subject key code. This key code will be used for linking EHR data with patient survey data. The subject key code link is stored separately from all other data and is retrievable only by one member of the team. By compartmentalizing data access to potential identifiable data, similar protocols have been approved as posing minimal risks to patients' privacy and confidentiality. Following recruitment, all personal identifiable data for non-recruited patients from the participating clinics will be purged.

For surveys, patients who choose to complete the surveys by email will be sent an individualized link to a REDCap survey that links data only to the patient's subject key code. Those who participate by mail will be mailed the surveys with only the subject key code on the survey documents. The project manager will take these mailings and enter the responses directly into the REDCap survey, which is linked only to the subject key code. Those who participate by phone with the project manager will have the project manager enter the responses directly into the REDCap survey which is only linked to the subject key code.

For interview transcriptions, any individually identifying information will be removed from the transcripts, except for a key code to link the transcripts with other datasets. Transcriptions and qualitative data analyses will be stored in password protected files, and recordings will be erased and/or destroyed after they are analyzed.

For other study notes (such as notes from the care manager and interaction notes from the project coordinator), these will be stored in REDCap using only the patient subject key as identifier.

All electronic data will be securely stored in a password restricted database. Paper surveys and interview audio recordings will be physically secured in locked file cabinets until destroyed.

Psychological Distress: Psychological distress may result from either intervention since participants will be discussing their experiences with chronic pain in the context of how to overcome pain. When psychological distress occurs, the care managers will try to address this in the context of the current session. If this is ongoing by the end of the session, the participant will be offered individual resources and connections to address this psychological distress. In the highly unlikely event of a participant voicing suicidal or homicidal thoughts during the intervention session, they will be offered the appropriate clinical referrals using input from Dr. Stephens.

Pain flare-ups and muscle soreness: Muscle soreness is normal after exercise, particularly in those who are sedentary. In addition, musculoskeletal injury may occur as a result of the exercise intervention, but a clinical trial of 454 overweight adults with knee OA had no serious injuries or serious adverse events associated with a more intensive strength training exercise program (Messier SP, Mihalko SL, Legault C, et al. *JAMA*. 2013;310:1263-1273). Further, a review of 12 clinical trials of exercise among older adults with increased risk of falls reported no cardiac events or falls during these trials (Gardner M, Robertson C, Campbell A. *Br J Sports Med*. 2000;34:7-17). In addition, only 4 of the 12 trials observed mild adverse events such as muscle soreness or minor sprains. More recently, an exercise trial of 298 older adults involving 12 weeks of exercise reported only 4 mild adverse events (e.g., muscle soreness) and no serious adverse events (Brach J, Perera S, Gilmore S, et al. *JAMA Intern Med.* 2017;177:1437-1444). Finally, in our experience in delivering Enhance Fitness classes to over 150 older adults with chronic pain, we have had no reports of serious injury or hospitalization related to this exercise program.

Vulnerable Subjects: Our study excludes prisoners, institutionalized individuals, children, neonates and fetuses. While it is possible that we will have a pregnant individual in our study, we are not specifically targeting such participants. There are no increased risks from our proposed interventions for pregnant individuals.

3. Potential Benefits of the Proposed Research to Research Participants and Others

Many patients with chronic pain have limited functionality and poorer overall health outcomes. Our study is designed to implement evidence-based non-pharmacologic treatments that might otherwise be inaccessible to patients in rural communities. Participants (and others in the future) could reduce pain intensity and interference (primary outcomes) and improve functionality. These potential benefits are appropriately balanced with the measures described above to minimize risks to breach of patient privacy and confidentiality, temporary muscle soreness and potential psychological distress.

4. Importance of Knowledge to be Gained

The purpose of this proposed study is to determine if non-pharmacologic, evidence-based treatment modalities can be implemented in rural communities to reduce pain intensity and interference. The knowledge to be gained is well balanced with the measures described to minimize the discussed risks to subjects.