Study Title: Integrating the Patient Voice Into Comparative Effectiveness Trial of Communication Strategies in the Management of Chronic Pain

Management	**A Randomized Controlled Trial**
Document Date	**April 20th, 2018**
IRB Protocol Number	**Pro00049085**
ClinicalTrials.gov ID	**NCT03301623**
Principal Investigators	**Brennan Spiegel, MD MSHS**
Other Investigators	**Itai Danovitch, MD MBA** **Teryl Nuckols, MD MSHS** **Teresa Dean, MD**
Sponsoring Institution	**Patient-Centered Outcomes Research Institute (PCORI)** **1828 L Street NW** **Suite 900** **Washington, DC 20036**

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PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

PCORI Contract Number CDR-1602-34521
Modification 002- Milestones and Scope of Work

April 20, 2018

CEDARS-SINAI MEDICAL CENTER
Cedars-Sinai Medical Center
8700 Beverly Blvd
Los Angeles, California 90048

Re: Modification to PCORI Contract for Funded Research Project, entitled "Integrating the Patient Voice into a Comparative Effectiveness Trial of Communication Strategies in the Management of Chronic Pain"- PI: Dr. Brennan Spiegel

Dear Stacy Miller:

Based on PCORI correspondence regarding the requested Milestones and SOW modifications, this letter confirms approval of certain modifications to the PCORI Contract for Funded Research Project entered into by and between Patient-Centered Outcomes Research Institute ("PCORI") and CEDARS-SINAI MEDICAL CENTER ("Recipient") effective as of March 13, 2017 (the "Contract").

To this end, PCORI approves the following modifications to the Contract:

1. The PCORI-Approved Project Plan in Attachment A to the Contract is modified as follows:
   a) IRB has approved passive collection of data elements to allow rapid enrollment.
   b) Eliminate COMRADE, but measure patient satisfaction with CG-CAHPS, which is considered more generalizable as part of routine care throughout the U.S.
2. Attachment C to the Contract is replaced by Attachment C-R below.

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Attachment A-R1: PCORI-Approved Project Plan

Integrating the Patient Voice into a Comparative Effectiveness Trial of Communication Strategies in the Management of Chronic Pain
RESEARCH STRATEGY

A. EXECUTIVE SUMMARY. This proposal aims to positively disrupt how chronic pain treatments are currently discussed and managed between patients and providers. Extensive research shows that communication barriers create a mismatch between provider and patient expectations for the treatment of chronic pain.[1-7] These communication challenges between patients, their families, and their providers impede discussions about the risks and benefits of opioid medications and their alternatives in the management of chronic pain. Together with patients, consumer advocates, addiction specialists, and primary care providers (PCPs), we will assess the comparative effectiveness of two evidence-based techniques to catalyze dialogue between patients and their PCPs about managing chronic pain: (1) Engaging PCPs with **Clinical Decision Support (CDS)** at the point of care, activating reminders through the Electronic Health Records (EHR) when there is risk of inappropriate opioid prescribing, thus leading to informed decision-making with the patient about alternative treatments; *versus* (2) Engaging patients prior to their PCP visit using **Patient Education and Activation Tools (PEATs)** administered via REDCap and encouraging discussion about treatment preferences, values and treatment goals at the time of the visit, thus leading to shared decision-making with the provider. Our CDS intervention will use the widely promulgated "Choosing Wisely" guidance developed by the American Board of Internal Medicine (ABIM), and our PEAT intervention will use material developed by Consumer Reports and the American Chronic Pain Association (ACPA). Both CDS and PEAT approaches are widely used and evidence-based,[8-13] but have never been tested in a head-to-head comparative effectiveness trial. We will conduct a pragmatic, cluster-randomized trial to measure outcomes that are important to patients, their families, and caregivers, with a focus on balancing two intertwined goals: reducing the impact of pain on patients' lives and reducing opioid overuse. Moreover, the findings from this study will help identify unintended consequences of CDS and PEAT strategies. **We are interested in identifying whether CDS or PEATs may reduce opioid prescriptions but leave patients with lower quality of life.** To accomplish our goal of improving patient communication and outcomes for chronic pain in primary care, we are collaborating with patient partners, the ACPA, Consumer Reports, and PCPs in a large, integrated, urban healthcare delivery network. Our main Patient Partner, Tom Norris, leads chronic pain support groups, including a statewide support group for elderly patients with chronic pain. Having managed chronic pain for more than 30 years, Mr. Norris is familiar with the treatment challenges faced by many chronic pain patients. Our Co-Investigator, Dr. Teresa Dean, is a PCP with expertise in chronic pain treatment and part of the Chronic Pain Working Group at Cedars-Sinai, which will be advising us throughout the study. Our multidisciplinary study team combines expertise in primary care, patient-reported outcomes, mental health, addiction medicine, health services research, patient activation, and health information technology. By conducting our study in primary care offices that serve a diverse group of patients, we will ensure the results of this study are broadly applicable and exportable to other practices.

B. BACKGROUND

B1. A Public Health Crisis: The Overuse of Opioids for Treating Chronic Pain. A 2015 Perspective piece in the *New England Journal of Medicine* noted that the sole focus on eliminating pain through opioids has proven detrimental to patients and providers, leading to high levels of opioid use disorder, opioid-related overdoses, and creating a chasm of trust between patients and providers.[14] In the past decade, the use of opioids for chronic non-cancer pain has increased at an alarming rate. From 1999 to 2008, prescription opioid sales increased by 300%.[15] In 2000, 11% of primary care visits resulted in an opioid prescription; in 2010, the percentage increased to nearly 20%.[16] In addition, while the number of outpatient visits for chronic pain decreased from 14.8 million in the late 1990s to 12.2 million in the early 2000s, the prevalence of visits for which an opioid was prescribed doubled during the same time period.[17] High rates of opioid prescribing have been accompanied by a concomitant increases in opioid use disorders as well as opioid overdoses.[18] Opioid use disorder is associated with decreased health related quality of life (HRQOL) and increased risk of death.[19] **The highly addictive nature of opioids and their resulting overuse has created a public health crisis in the U.S. Overdose**

deaths related to opioids now outnumber deaths from heroin and cocaine combined.[15] In 2007, nearly 30,000 unintentional drug overdoses occurred in the U.S., approximately one death every 19 minutes.[20] The opioid crisis has reached many American families: A 2015 Kaiser Family Foundation poll found that more than 50% of Americans report knowing someone who took a prescription painkiller that was not prescribed to them, know an individual with an addiction problem, or know someone who has died as the result of an overdose of opioid medications.[21] **It is vital to address the problem of opioid overuse in a way that maximizes benefits for patients while minimizing harms.**

There are many provider, patient, and health system factors driving the high rate of opioid prescriptions in the U.S. Providers describe lack of knowledge about opioids, lack of alternatives for chronic pain, conflicting guidelines, insufficient education, the issue of the "inherited patient" already on opioids, and a concern for patient satisfaction.[22-28] From the patient perspective, perceived pain control needs, knowledge and beliefs about the risk of opioid addiction, and a variety of predisposing characteristics are associated with the use of opioid medications.[29-35] Encouraging patients and providers to discuss risks, benefits, and patient treatment goals can result in improved HRQOL.

B2. The Burden of Chronic Pain in the United States. More than 100 million Americans suffer from chronic pain.[36] Chronic pain is defined as the presence of pain that persists beyond the expected tissue healing time, three to six months.[37] In addition to experiencing the physical symptom of pain, patients with chronic pain endure a multi-dimensional illness affecting biopsychosocial health broadly, including energy, cognitive functioning, sleep, physical health, mental health, and social functioning.[31,38-43] As a result, patients with chronic pain interact with the healthcare system frequently: one in five visits to a PCP is related to pain.[15] Moreover, many patients undergo diagnostic tests, treatments, and medication regimens that are not evidence-based and may actually worsen outcomes.[44-46] Historically, providers have focused mainly on addressing pain and often overlook other key factors that are important to patients in making decisions.[14] Research shows that communication difficulties between providers and patients pose a significant barrier to helping patients find pain management strategies that are effective.[2,47-53] Moreover, communication breakdowns impede patient engagement, leading patients, families, caregivers, and providers to feel frustrated and dissatisfied.[52,54] Aligning expectations for pain management through improved communication can help both patients and providers identify strategies that maximize effectiveness while reducing harm.

B3. Engaging Patients in the Chronic Pain Discussion. While policymakers and medical societies are currently devising strategies to stem the overuse of opioids,[55] it is imperative to incorporate the patient perspective into these discussions. For carefully selected patients, opioids may relieve debilitating pain and meaningfully improve HRQOL. A recent meta-analysis of 20 randomized controlled trials examining the use of opioids for chronic low back pain, however, found that opioids may provide some short-term relief but evidence on long-term efficacy is sparse.[56] Moreover, at least of half of study participants stopped taking opioids due to side effects or lack of efficacy. Decisions surrounding opioid prescriptions involve balancing patient needs for effective and safe pain management with the potential for adverse events and possible abuse. Long-term opioid use can lead to cognitive impairment, fatigue, nausea, constipation, and hypogonadism, which can result in depression, anxiety, infertility, osteoporosis, lowered muscle mass, impotence, lowered libido, and an increased risk of fractures.[57] Moreover, the discussion about chronic pain treatment should move beyond solely focusing on pain scores to encompass other outcomes central to the lives of patients. Treatment strategies should address fatigue, mental health, cognitive functioning, sexual health and other relevant factors. **Communication strategies that prompt patients and providers to identify and address these patient outcomes are critical to improving chronic pain management and considering alternatives to opioids when appropriate.**

Communication challenges are highly prevalent in chronic pain management. Many patients believe that they must put forth special effort to feel understood and taken seriously when discussing pain with their providers.[47,53,58,59] Patients must negotiate with the healthcare system and prove legitimacy of their claims of pain for treatment to occur, an experience not reported with many other chronic conditions.[52] **In a recent ethnographic analysis, our research group found that chronic pain patients report a high burden of side effects from opioids and often believe they are not able to communicate important HRQOL issues with their providers.**[60] We also found that individuals taking opioids are likely

to modify their regimens without consulting their provider and resort to non-evidence based measures.[60] Our findings, as well as results from other investigators,[51,59,61,62] identify opportunities for improved provider-patient communication.

B4. Addressing Gaps in Provider Knowledge of Chronic Pain. One of the main challenges faced by healthcare providers is the struggle to balance the potential risks and benefits of chronic pain treatments.[63] Yet, despite the importance of this decision, providers still have difficulty knowing whether and when opioid therapy is indicated, particularly because they often perceive pain to be subjective and difficult to quantify.[63] Providers also express that they rely on impressions of patients' trustworthiness and intuition when making decisions regarding pain medication rather than relying strictly on guidelines.[63]Moreover, providers establish fewer goals for chronic pain relief compared to acute postoperative pain or cancer pain, indicating that chronic pain may be inadequately addressed and undertreated.[64]

B5. Current Gaps in Communication Strategies for Chronic Pain (RQ-1). Health systems have implemented a variety of communication and surveillance strategies to support appropriate use of opioid medications and reduce misuse. Opioid treatment agreements – which have statements about dose compliance, the safe-keeping of opioid medications, and often include clauses about routine urine drug testing – are not consistently used in part because many providers believe they exist primarily for liability purposes and are not effective in preventing misuse.[65] A systematic review of studies assessing the usefulness of treatment agreements found their effectiveness to be weak.[66] Furthermore, such communication strategies focus solely on the use of opioids and fail to include other important patient outcomes. For example, treatment agreements typically do not present alternatives for patients who continue to have high pain severity or are experiencing side effects from opioid medications.

B5.a. Patient Education and Activation Tools (PEATs): Our group conducted a literature search to find studies that evaluate patient education tools in chronic pain management **(RQ-1)**. We identified several systematic reviews demonstrating the effectiveness of PEATs in chronic pain. For example, a 2009 review concluded that education tools for pain improve knowledge and attitudes, reduce pain intensity, and reduce worst pain intensity.[67] The review noted that PEATs are underused, despite their proven effectiveness.[67] There is also evidence that PEATs can significantly improve patient-provider dialogue **(RQ-1)**. A systematic review found that communication-based interventions are associated with improved clinician and patient communication behaviors.[68] Another study examined methods specifically designed to elicit patient preferences in decision-making;[69] it showed that when patients receive PEATs, they not only prime patients for their visit, but also prompt *providers* to introduce more themes at the time of the visit. **In short, there is extensive data supporting the efficacy of PEATs to improve outcomes in chronic pain management, justifying its inclusion as a comparator arm in this study.**

B5.b. Clinical Decision Support (CDS) Tools for Chronic Pain: In 2014, as part of the Choosing Wisely campaign, the American Society of Anesthesiologists released two recommendations on the use of opioid analgesics for chronic pain. The first recommendation noted that opioids should not be prescribed as first-line therapy for chronic pain, while the second recommended that opioids should not be prescribed as long-term therapy until risks are considered and discussed with the patient.[70,71] While useful, the mere existence of such guidelines has been shown to be ineffective. A recent analysis in *JAMA* found little to no change in the use of inappropriate tests and medications as a result of the release of the Choosing Wisely guidelines.[72] **Without guidelines available at the point of care, typically in the EHR itself, providers and patients are often unable to make informed decisions guided by evidence. Given the limited evidence associated with the use of prescribing guidelines for opioids, the US Department of Health and Human Services' Office of the Assistant Secretary for Planning and Evaluation has called for "a better understanding of how to optimally operationalize them."**[73,74]

A variety of organizations, including Cedars-Sinai Medical Center, have operationalized evidence-based guidelines, such as the Choosing Wisely, using CDS tools embedded in the EHR that can help providers and patients make better decisions at the point of care. **In 2014, Cedars-Sinai became the first healthcare system in the nation to configure its EHR to include more than 180 Choosing Wisely recommendations.**[75] These recommendations are activated when a provider, nurse, or pharmacist attempts to order a treatment that is referenced in the Choosing Wisely list. For example, a provider that orders a benzodiazepine medication for a patient already taking opioids is alerted that the American

Society of Anesthesiologists recommends: "Providers should be cautious on co-prescribing opioids and benzodiazepines." The Choosing Wisely CDS algorithms developed by Cedars-Sinai are now being used in over 100 hospitals around the U.S. with more than 30,000 combined healthcare providers.

A 2012 systematic review found that CDS is markedly effective at improving health care processes across diverse settings.[76] A variety of health care systems have implemented CDS to improve opioid prescription safety, in particular. Kaiser Permanente uses CDS for opioid prescribing for its more than 4 million members.[77] At the Veterans Health Affairs system, efforts have also been made to provide CDS for chronic pain management.[78-80] **In short, there is extensive literature supporting the effectiveness of CDS across healthcare settings, explaining its widespread use for optimizing opioid prescribing at the point of care and justifying its inclusion as a comparator arm in this study.**

C. SIGNIFICANCE

C1. Significance of the Proposed Study. We will evaluate and compare two broadly used strategies to catalyze dialogue between patients and their PCPs about managing chronic pain. Although previous studies have assessed the use of these two communication strategies alone, there is no existing comparative effectiveness study that evaluates them head-to-head, particularly using modern EHR implementation strategies. **Moreover, most studies evaluating these strategies in isolation have focused solely on how they change opioid prescribing rather than on patient-centered outcomes.**

C2. Patients, Families and their Caregivers. From the perspective of **patient stakeholders**, this study will add to the decision-making literature and demonstrate whether engaging patients can foster productive dialogue and treatment planning. The study will demonstrate whether chronic pain patients are better able to address infrequently discussed issues such as sleep, energy, mental health and cognitive function, in addition to pain management, as a result of these communication strategies. Our own research shows that clinicians prescribing opioids often do not discuss important side effects such as opioid-induced constipation.[60] Encouraging patients and providers to discuss issues such as constipation, concentration, and mood can help patients and providers better tailor treatment options. Most importantly, we will compare widely used CDS strategies and freely available PEATs, so findings from this research can be used in any pain-related clinical setting. **We will also identify unintended consequences of opioid-reduction strategies, critically important to patients. We have worked closely with our patient partners and consumer advocates to create a proposal of value to patients, their families, and their caregivers.**

C3. Patient and Consumer Advocates. For **patient and consumer advocacy stakeholders**, our study will examine for which populations the competing strategies are most effective. This will create opportunities to disseminate effective communication strategies in a targeted manner. Additionally, the study will promote collaboration aimed at modifying strategies so that they are accessible and effective for more patients. By partnering with these stakeholders, we will optimize the dissemination and implementation of our findings.

C4. Clinicians and Health Systems. From the perspective of **provider and health system stakeholders**, this study will demonstrate which strategies are most effective in helping providers communicate the risks and benefits of a variety of treatment options, including high-risk medications such as opioids. **Given the wide media coverage about the opioid overdose crisis, many institutions are implementing opioid medication interventions without knowing their effectiveness. Findings from this study can help health systems and provider groups focus on efforts that result in improved patient-centered outcomes as opposed to implementing programs that can increase costs to patients and may not be effective. Most studies focused on CDS have focused on outcomes such as reducing the use of high-risk medications and have not addressed whether patient outcomes, including satisfaction with care, are affected.** We will also track high-risk opioid prescribing measures to assess whether patients who are encouraged to discuss risks and benefits with their providers select different medications to manage their chronic pain and reduce high-risk opioid usage. These findings can help health systems select strategies that maximize benefits while reducing risks to patients.

C5. Health Information Technology Developers. For **developers of CDS systems**, this study will help prioritize which alerts are most effective to providers, reducing alert fatigue and improving provider performance. Furthermore, the study will lay groundwork for assessing how health information technology can improve patient-centered care.

C6. Responsiveness to PCORI Priorities and Mission. We believe this research proposal is responsive to PCORI priorities and mission. Specifically, the two comparators will support people in making informed healthcare decisions by addressing documented gaps in the communication process. We will compare two methods of communicating information to the patient-provider dyad in the setting of modern health information systems. **Our team of patient advocates, professional societies, and PCPs will generate results that can help patients, clinicians and healthcare systems adopt strategies that are responsive to patient needs and guided by patient priorities.**

D. STUDY POPULATION (RQ-3, RQ-4)

D1. Study Population Characteristics. Our aim is to compare communication strategies for individuals who have initiated opioid treatment in the primary care setting. We selected this study population because we aim to improve communication for any patient considering long-term opioid use, including those individuals who have recently started an opioid prescription and those who may have taken opioids for longer periods of time. As a result, we will recruit individuals with at least six weeks of opioid use.

We will employ broad inclusion criteria so as to maximize the study's external validity. Many studies assessing chronic pain and opioid management exclude individuals with any pain related to the treatment of cancer or focus on only on specific types of pain, such as low back pain or neuropathic pain. In consulting with our patient partners, however, we believe that it is appropriate to address communication for individuals with all forms of chronic pain except those in certain specific circumstances, such as active cancer treatment, palliative care, or end-of-life care. In accordance with the CDC guidelines, palliative care "is defined in a manner consistent with that of the Institute of Medicine as care that provides relief from pain and other symptoms, supports quality of life, and is focused on patients with serious advanced illness. Palliative care can begin early in the course of treatment for any serious illness that requires excellent management of pain or other distressing symptoms."[20] End-of-life care is defined as "care for persons with a terminal illness or at high risk for dying in the near future in hospice care, hospitals, long-term care settings, or at home." Additionally, the CDC guidelines state that "patients within the scope of [recent] guideline include cancer survivors with chronic pain who have completed cancer treatment, are in clinical remission, and are under cancer surveillance only."[20] Given the unique therapeutic goals of active cancer treatment, end-of-life care, and palliative care, we believe that the communication strategies proposed in this study do not apply to these patient populations.

The population impacted by this research thus encompasses individuals with many different types of chronic pain conditions, including, but not limited to, complex regional pain syndrome, neuropathic pain due to non-active cancer treatment or diabetes, musculoskeletal pain (such as chronic low back or neck pain), osteoarthritis, fibromyalgia, carpal tunnel syndrome, chronic daily headaches, rheumatoid arthritis, and migraine headaches. This study has the potential to impact a large proportion of the population. The burden of chronic pain in the United States is substantial. Between 14% and 30% of the US population suffers from chronic pain,[81-84] affecting individuals at all stages of life. More than 60% of individuals with chronic pain are women, and although the point prevalence for chronic pain increases with age, 35% of individuals 45-54 years of age report some form of chronic pain condition.[16,84] In terms of race and ethnicity, 81-85% of individuals with chronic pain report their race and ethnicity as non-Hispanic White, 8-9% identify as non-Hispanic Black, 5-9% identify as Hispanic, and 3-5% report as Other race/ethnicity.[16,84]

D2. Study and Exclusion Inclusion Criteria

Inclusion Criteria: We will recruit individuals at least 18 years of age that meet the following criteria: ≥30 days of prescriptions for opioid medications, ≥2 opioid prescriptions in a three-month period, or a ≥700 morphine milligram equivalent dose in the first prescription. A study that appeared in the March 17, 2017 Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Report found that the largest continuation in probability of continued opioid use was found after the thirty-first days on opioid therapy, after a second prescription, after a ≥700 morphine milligram equivalent dose, and first prescriptions with 10- and 30-day supplies (6). Given that this study aims to target individuals who are on chronic opioids (defined as 90 days of opioid use) or who may become chronic opioid users, based on this important new evidence, we have decided to modify our eligibility criteria to best target this population. In order to capture patients who have a primary care provider within the CSMG system (and not just patients who see a

physician once and then leave the system), we will include patients who have had 2 or more visits to a CSMG physician in the year prior to the study start date and at least 1 visit during the follow-up year. This will ensure that we have a relatively stable population, which will be critical in calculating the rates outlined in Aim 3 of the study. Prescribed opioid medications include: codeine, dihydrocodeine, tramadol, morphine, hydromorphone, oxymorphone, tapentadol, buprenorphine, methadone, oxycodone, fentanyl, and remifentanil.

Exclusion Criteria: We will exclude individuals less than 18 years of age because the communication comparators include Choosing Wisely and CDC guidelines that do not address the use of opioids in minors. Exclusion criteria also include individuals with treatment for chronic pain during (1) active cancer treatment, (2) palliative care, or (3) end-of-life care. Patients who do not see their primary care provider during the study period will be excluded retroactively from the study.

D3. Study Population. We will conduct this study in the Cedars-Sinai Medical Network, a large, urban, integrated delivery system serving a diverse population. The Cedars-Sinai Medical Network services a large cohort reflective of the national population with regards to insurance coverage as well as chronic pain prevalence and opioid use.[85] A quality improvement claims-based analysis of patients served by the network found that 30% of individuals at Cedars-Sinai have a chronic pain condition, approximately 22,800 patients in total, consistent with national chronic pain prevalence estimates.[81] Using national chronic pain prevalence data, we estimate that the population for this study is distributed by race and ethnicity as described in **Table 1: (RQ3, RQ4)**

Table 1. Estimated Race-Ethnicity Distribution of the Study Population for Proposed Study

	National Chronic Pain Prevalence Data[71]	Estimated Study Population Race-Ethnicity Distribution
Non-Hispanic White	81%	18468
Non-Hispanic Black	8%	1824
Hispanic	5%	1140
Asian	1%	228
Mixed Race	3%	684
Other	3%	684

With respect to gender, the prevalence of chronic pain has been found to be higher in women than in men, so we estimate that 62%, or 14,130 are women and 8,660 are men. Women are more likely to be prescribed pain relievers, be prescribed higher doses, and use these medications for longer time periods than men.[86,87] Based on national prevalence data, we estimate that 13% of the study population are 18-34 years of age, 42% are 35-54 years of age, and 46% are 55 years of age and older.[84] In terms of physician-diagnosed pain conditions, we estimate that 18% of patients with chronic pain in our population have low back pain, 16% osteoarthritis, 6% rheumatoid arthritis, 36% migraine headaches, and 21% carpal tunnel syndrome.[84]

E. STUDY DESIGN

E1. Specific Aims

Aim 1: To assess the comparative effectiveness of two communication strategies aimed at generating conversations between patients and providers about appropriate use of opioid medications and their effects on patient-reported outcomes. We will compare two strategies: (1) Engage PCPs with **Clinical Decision Support** at the point of care, raising active alerts through the EHR when there is risk of inappropriate opioid prescribing, thus leading to informed decision-making with the patient about alternative treatments; *versus* (2) Engage patients prior to their PCP visit using **Patient Education and Activation Tools** administered via EHR portal, helping patients to prepare for their visit and encouraging discussion about treatment preferences, values and treatment goals at the time of the visit, thus leading to shared decision-making with the provider. Our CDS intervention will use "Choosing Wisely" and CDC guidelines, and our PEAT intervention will use widely disseminated material developed by Consumer Reports and the ACPA. Informed Decision-Making (IDM) using EHR-based "Choosing Wisely" CDS alerts about appropriate opioid use, and (2) Shared Decision Making (SDM) using PEATs developed by the ACPA and Consumer Reports and delivered via REDCap. We will assess whether improved communication and patient activation through these strategies improves patient-reported outcomes related to pain interference and HRQOL. To assess these outcomes, we will use NIH Patient Reported Outcome Measurement Information System (PROMIS®) questionnaires to capture health domains identified by our patient

partners as most important. Using PROs will also help capture whether use of either of these strategies leads to unintended consequences for patients when opioids are reduced and other pain management strategies – including non-pharmacological strategies – are not substituted.

Rationale: Communication about chronic pain and pain management is one of the most widely reported challenges for both patients with chronic pain and their healthcare providers.[1,2,48,88-90] There is a gap in the literature on the comparison of strategies and tools that are effective in guiding communication about benefits and risks of opioids. Improving communication can help identify which treatment strategies are best for each patient,[49,69,90,91] thus improving patient-reported outcomes.[1] There is evidence that in order to implement self-management strategies successfully, patients must have a clear understanding of their condition and treatment approaches, both of which require high-quality, contextually appropriate communication between patients and providers.[92] Furthermore, patient activation is strongly associated with patient outcomes, including utilization and health outcomes.[93]

Aim 2: Understand how patient-level factors such as age, gender, mental health comorbidities such as depression and prior substance abuse disorder, race, and ethnicity are associated with patient outcomes in the treatment and management of chronic pain **(RQ-4)**. Understand how physician-level factors such as gender and years of practice may interact with patient-level factors.

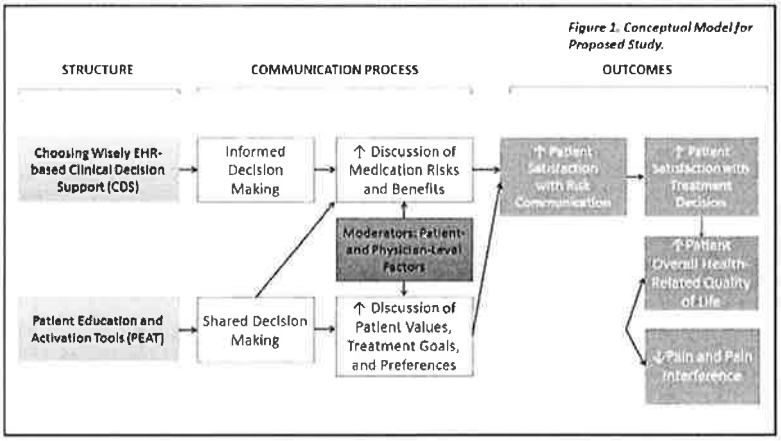
Rationale: A variety of patient-level and healthcare level-factors are thought to impact communication for chronic pain management and subsequent outcomes. These include patient-level factors such as age, gender, race, and ethnicity.[94] Previous research reveals that African-American patients are less likely to receive adequate pain management[34,95] and that providers may be less likely to engage in shared decision-making with patients of non-White race/ethnicity.[94] Other studies have found that women, particularly young women, experience more skepticism from their providers about their chronic pain conditions[94] and report feeling dismissed and doubted,[59] particularly for less visible conditions such as fibromyalgia.[53,59] In terms of provider-level factors, studies indicate that female and younger providers are more likely to engage patients in decision-making.[94] Additionally, the presence of mental health conditions can negatively impact communication between patients and providers. Patient preferences may also play an important role: some patients may be more satisfied with their provider shaping difficult decisions.[96] One study of information and decision-making preferences among hospitalized cancer patients found that one quarter of patients – mostly older, male patients – preferred for their clinician to drive informed decisions.[96]

Aim 3: Compare the impact of CDS vs. PEATs on reduction of high-risk medication use, as measured by: (1) percentage of patients with an opioid prescription of more than 90 milligrams morphine equivalents, and (2) co-prescription of benzodiazepines and opioid medications.[20]

Rationale: One factor identified for the overuse of opioids is providers' focus on pain management at the expense of addressing other important patient outcomes such as sleep, energy, and concentration.[3,14] Presenting a variety of treatment strategies through better communication can help reduce the use of high-risk medications without compromising pain management.[12] The CDC guidelines state that clinicians "should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day"[20] because high doses can lead serious harm.[20] Additionally, CDC guidelines state that clinicians should avoid co-prescribing opioids and benzodiazepines whenever possible, given that both medications cause central nervous system depression and the combination increases risk of death. Compared to opioid monotherapy, concurrent use of a benzodiazepine with an opioid increases the risk of overdose death fourfold .[97]

E2. Conceptual Model for Proposed Study. Our study design is based on an adaption of Donabedian's Quality of Care Model, which states that quality improvement results from casual links between structure, processes and their associated outcomes. In our conceptual model (**Figure 1**), communication strategies implemented by health care systems lead to different communication processes, which in turn affect patient outcomes. Health care systems that implement the comparators we selected for this study – CDS and PEAT – set into motion two types of communication processes: *informed decision-making* and *shared decision-making.* Reminding a physician through EHR-based CDS to evaluate appropriate opioid medication use, assess HRQOL outcomes, and explore treatment alternatives leads to the informed decision-making process. First, the clinician receives a timely reminder to explain the risks and benefits of available treatment options. Then, the patient considers the options presented, optimally in partnership with their clinician.[94] Previous literature suggests that reminding providers to engage in informed decision-making can encourage more discussion of risks and benefits.[98] In the case of chronic pain management, a clinician might discuss the risks and benefits of opioids and, depending on pain scores, recommend an alternative medication or other pain-reduction strategies. A thorough discussion of treatment risks and benefits is hypothesized to increase patient satisfaction through an effective and timely communication of risk, thus increasing overall satisfaction with the treatment decision.[99,100]

Figure 1. Conceptual Model for Proposed Study.



In contrast, using PEATs encourages a different type of communication process: shared decision-making. In this process, patients are proactively encouraged to discuss their treatment preferences, values, and specific treatment goals through patient-facing assessments.[12] For example, a patient using PEATs might highlight concerns about energy and concentration, which are affected by opioids, and might collaborate with the clinician to explore a different dose or treatment strategy. Shared decision-making also has the potential to increase self-management and coping skills among patients with chronic illnesses,[101] including fibromyalgia,[102] which has been shown to help improve HRQOL.[92] A 2008 systematic review found that shared decision-making is effective in the management of chronic illnesses.[103] Potential limitations of shared decision-making, however, are that it requires additional preparation on the part of the patient and additional time from providers. For these reasons, PEATs are not universally employed despite their effectiveness.

E3.

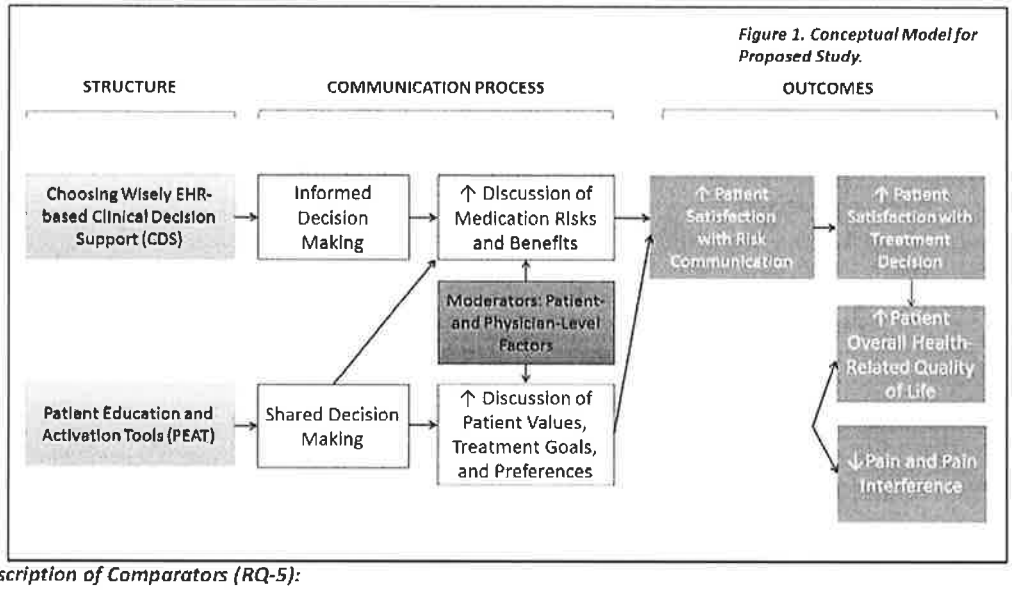


Figure 1. Conceptual Model for Proposed Study.

Description of Comparators (RQ-5):

1. CDS vs. PEAT

Description: The CDS intervention will test the use of existing guideline-based EHR alerts related to the prescription of opioids. CDS alerts employ computer algorithms that account for patient characteristics and diagnoses to deliver reminders of appropriate use when a provider enters an order for a medication. For this study, we will examine the following Choosing Wisely CDS alerts to help prompt discussions about chronic pain treatment:

(1) *Discussion of Risks and Benefits of Opioid Analgesics as Long-Term Therapy for Patients with Chronic Pain and Establishment of a Treatment Goal.* This alert is triggered whenever a refill for a long-acting or extended-release opioid is entered or when any new opioid prescription is ordered.

(2) *Evaluation of Risk Factors for Opioid-Related Harms.* This alert is triggered whenever there is an existing diagnosis of prior substance abuse disorder, history of overdose, history of sleep apnea, renal or hepatic insufficiency, age over 65 years, or a diagnosis of depression, anxiety disorder, or Post-Traumatic Stress Disorder in the setting of opioid use.

(3) *High-Risk Opioid Co-Prescribing: Co-Prescribing of Benzodiazepines and Opioids.* This alert is triggered whenever an order for a benzodiazepine is entered in the setting of a preexisting opioid prescription, or vice versa.

Figure 2 presents a schematic demonstrating the process flow for a CDS alert, using the example of the co-prescribing alert. The process begins when a provider places the medication order in the EHR. The Choosing Wisely algorithm, powered by Stanson Health, a CDS developer used by Cedars-Sinai to power its EHR alerts (www.StansonHealth.com), then evaluates over 30 patient-level data elements to determine whether an alert should be triggered. If there is evidence of potentially inappropriate co-prescription, then the EHR displays a "pop-up" reminder with language supported by Choosing Wisely guidelines. The provider may override the alert by selecting one of several pre-populated reasons (e.g. "end-of-life care") and the system records the rationale. The system also allows the provider to offer open-ended comments explaining the reason for override. Conversely, the provider may choose to cancel the order and back out from initiating a prescription. Through an analytics dashboard supported by Stanson Health and already used by our health system to monitor system performance with Choosing Wisely alerts, we will track: (1) which provider activated the alert, (2) whether the provider overrode the alert or canceled the order, and (3) for which patient

the alerts were triggered. In this manner, the system offers hard metrics that are already embedded and operating within our EHR data analytics system, offering real-time process measures for the CDS arm.

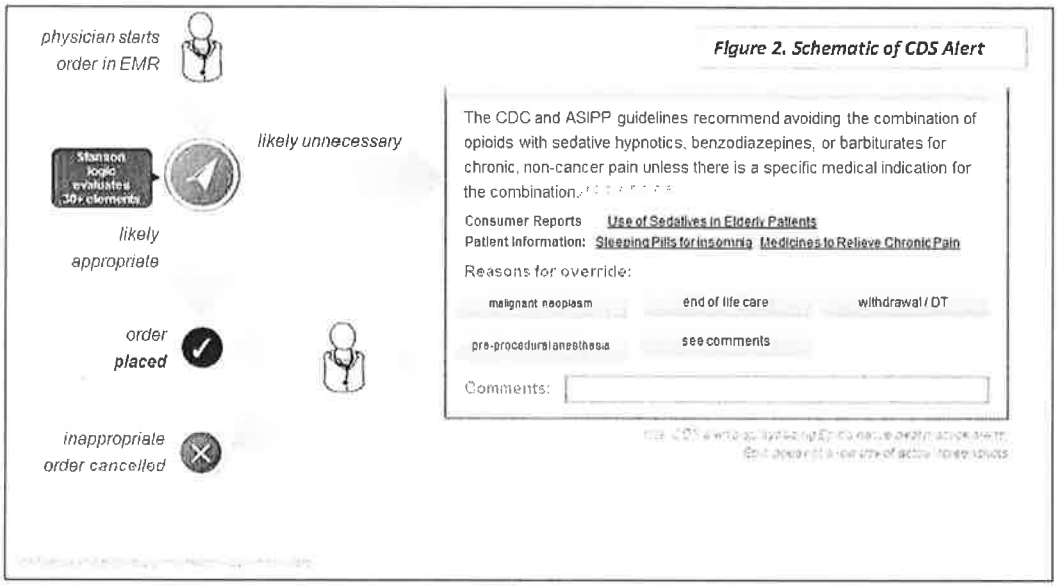


Figure 2. Schematic of CDS Alert

Specific Health Decision the Comparator is Intended to Inform: The Choosing Wisely CDS alerts directly address the question of whether continuing an opioid prescription is appropriate in patients with chronic pain, particularly for those individuals at high risk for drug-drug interactions, at risk for addiction, or for whom opioids may not be effective for long-term pain relief. The decision should include patient and provider discussion of medication risks and benefits.

Evidence of Widespread Use: The alerts powered by Stanson Health **are already in use by more than 100 health care systems with more than 30,000 combined physicians.** Other large healthcare systems such as Kaiser Permanente are currently using similar CDS systems to reduce inappropriate opioid prescribing for their more than 4 million members.[77]

Evidence of Effectiveness: At Kaiser Permanente, the CDS-based alerts function very similarly to the alerts used at Cedars-Sinai: when a provider attempts to submit an order for certain high-risk opioid prescriptions, the EHR triggers an alert detailing the risks of the medication and offers links to evidence-based guidelines. Partly as a result this intervention, prescriptions for oxycodone decreased at Kaiser Permanente by 70 percent in two years.[77] In a 10-week pilot study examining the effects of CDS alerts of benzodiazepine use in patients 65 years and older, a specific Choosing Wisely recommendation, Cedars-Sinai reduced prescriptions of benzodiazepines in the patient population by 32%.[104]

2. CDS via PEAT.

Description: Consumer Reports Health, a patient advocacy organization, has created education materials aimed at patients with chronic pain. The patient education materials we selected for this study, "Pain Management: Which Treatment is Right for You" (Appendix I), include information about opioids along with alternatives to opioids, including nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin and acetaminophen. **Additionally, the materials present information about non-pharmacological treatments for chronic pain, many of which are recommended in recent CDC pain management guidelines.**[20] The Consumer Reports education tool was informed by patient needs, is written with easy-to-understand language, and discusses the addiction risks, side effects and long-term effectiveness of opioids.

study is to examine which comparator is most effective under *everyday care* conditions. We applied the PRECIS criteria and the 1-5 scale, where "5" is a purely pragmatic design and "1" is a purely explanatory design:

1. Participant eligibility criteria. Pragmatic trials allow the enrollment of "all participants who have the condition of interest, regardless of their anticipated risk, responsiveness, co-morbidities, or past compliance." We will include all individuals who have an opioid prescription for more than 6 weeks (save for the exclusions outlined previously) and will not exclude patients based on chronic pain type, comorbidities, responsiveness, anticipated risk, or past compliance with interventions. Score = 5.

2. Experimental intervention flexibility. PRECIS notes that instructions on how to apply the experimental intervention for pragmatic trials "are highly flexible, offering practitioners considerable leeway." In this study, patients will receive the PEAT materials via REDCap (described further, below) and providers will also receive the CDS alerts via EHR, but in both cases clinicians are given wide leeway in how to apply these tools in their practice. Score = 5.

3. Experimental intervention practitioner expertise. In purely pragmatic trials, "the experimental intervention typically is applied by the full range of practitioners and in the full range of clinical settings, regardless of their expertise, with only ordinary attention to dose setting and side effects." In this trial, we will restrict the intervention to PCPs, as most chronic pain patients discuss pain management with their PCP, but we do not exclude providers based on expertise. Score = 3.

4. Comparison intervention. Purely pragmatic trials offer "usual care" as a comparison. In this trial, given the previously established effectiveness of both study comparators against "usual care" and the purpose of the study (comparative effectiveness), **we do not offer "usual care" as a comparator. Moreover, "usual care" is difficult to define in the context of chronic pain decision-making in primary care given the widespread practice variation.** However, since we are comparing both interventions in the usual clinical care context, we do not employ the use of a "placebo" and thus retain the pragmatic design of this trial. Score = 4.

5. Comparison intervention practitioner expertise. Pragmatic trials do not standardize which and how practitioners implement the intervention. In this case, we will cluster-randomize all of the PCPs in our practice to the intervention and will not standardize who or how they will implement the communication strategies. Score = 5.

6. Follow-up intensity. Purely pragmatic trials do not have any formal follow-up visits of the individuals and use passive administrative databases to detect outcomes. Given the importance of patient-reported outcomes in this study, we will use a combination of passive and active follow-up methods to ascertain outcomes; these have low respondent burden and only require the completion of short questionnaires. Score = 4.

7. Primary trial outcome. Pragmatic trials select outcomes that are meaningful to study participants. Our main outcome will be pain interference, or how pain interferes with a patient's daily life, an outcome identified as meaningful by our patient partners. This outcome is important because while we seek to prevent inappropriate overuse of opioids, the flip side – discontinuing appropriate use of opioids – should also be prevented. The net outcome – pain interference – reflects a balance between inappropriate overuse and underuse of effective pain treatments. Score = 5.

8. Participant compliance with "prescribed" intervention. Pragmatic trials measure little or no patient "compliance" with the intervention. When we administer the questionnaires, we will ask whether individuals have received and read the PEAT materials via REDCap but we will not measure adherence to or use of PEATs. Score = 4.

9. Practitioner adherence to study protocol. Trials with pragmatic designs use unobtrusive or no methods to measure practitioner adherence to the study protocol. We will measure when and for whom the CDS alerts are activated, but will not report feedback to providers. Score = 4.

10. Analysis of primary outcome. PRECIS notes that pragmatic trials include all enrolled patients in the final analysis and there is no separation of the intention-to-treat (ITT) vs. per protocol (PP) patients. We will conduct both ITT and PP analyses for sensitivity analysis purposes. We will ask patients whether they received and read the PEAT materials and will examine when the CDS alerts were fired and for which patients to conduct a PP analysis. Score = 3.

E4.b. Unit of Randomization. We will randomize the study on the provider level. We will use a random number generator to assign offices to study arms, and will employ multi-level hierarchical models to adjust for clustering within the physician level, described in more detail below.

E4.c. Study Design Overview.
We will auto-enroll all eligible patients to participate in the pragmatic trial and will administer baseline questionnaires as further detailed in the Recruitment Procedures and Outcome Measurement sections below. Patients within the physicians randomized to the CDS arm will not receive the PEAT materials; their physicians will receive the Choosing Wisely alerts via the EHR (Epic Systems, Verona, Wisc.) when appropriate. Patients within the physicians randomized to PEAT will receive the engagement materials via REDCap two days prior to their PCP office visit, supplemented by duplicate paper copies sent via express delivery. For both study arms, patients will receive Clinician and Group Consumer Assessment of Healthcare Providers and Systems (CG-CAHPS) one day after their office visit. They will receive the PROMIS questionnaires every month throughout the study period. We will track follow-up visits through the EHR reports. In all instances, patients may refuse to participate by either not using the PEATs sent via REDCap, or not completing outcome questionnaires.
3. Analysis, Dissemination, and Implementation. In Year 3, we will conduct the statistical analyses and will collaborate with our patient partners to determine the implications of the study results. We present our Dissemination and Implementation plan in full detail below.

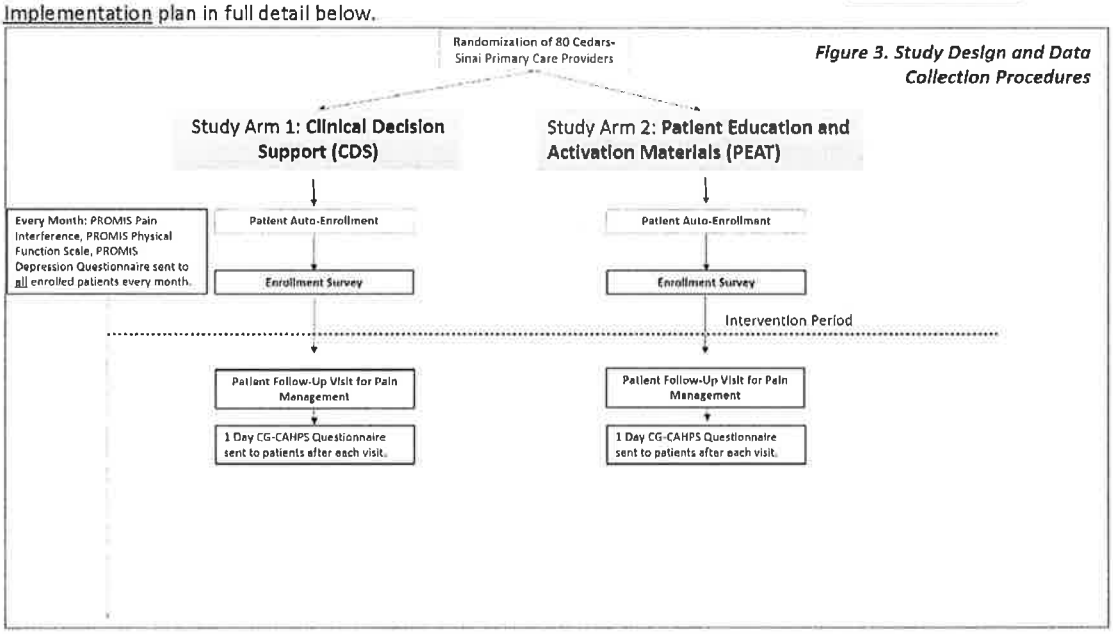


Figure 3. Study Design and Data Collection Procedures

E4.d. Recruitment Procedures (PC-2). Patients meeting inclusion criteria who are managed by one of the 80 participating PCPs at the Cedars-Sinai Medical Network will be auto-enrolled in the study. Patients will receive a written notification via mail of their inclusion in the study and at that time they will be told about the study details, including research procedures and requirements for follow-up, as well as the risks and benefits of study participation. At this time, patients will have the opportunity to actively opt out of receiving the education materials (if they are randomized to PEAT arm). Patients who do not opt out will receive education materials and their care will proceed as usual. Patients who are passively enrolled will receive the study questionnaires via REDCap. We estimate that out of the 4,000 patients eligible for the study (calculated from a quality improvement project based on claims data), approximately 30% will complete all of the questionnaires, which is in line with our sample size calculations. Once the patients complete monthly questionnaires, we will provide a $5 gift card for filling out the enrollment survey. We have budgeted $25 per patient as

a financial incentive for completing the questionnaires (Appendix I, **Table 1** for Recruitment Plan and **Table 2** for Passive Enrollment Estimates).

Our study team has extensive expertise conducting pragmatic trials, including using PEAT, CDS, and EHR-based interventions. For example, the PI, Brennan Spiegel, conducted a successful VA Merit Award CER trial evaluating PEATs for colonoscopy preparation,[110] and a second VA Merit evaluating CDS for safe NSAID prescribing.[111] More recently, Dr. Spiegel's research team conducted clinical trials that were used by the Food and Drug Administration as evidence of efficacy for a medical device,[112] performed trials of EHR-based interventions to improve patient-provider communication at the point of care,[113] and conducted large validation trials for the NIH PROMIS® consortium,[114] demonstrating experience across varying and complex trial designs.[112,115] Biblana Martinez, MPH, the team's Principal Research Manager, has extensive experience creating and implementing protocols for all of these studies conducted by the team, and will oversee the enrollment procedures for this trial as well. Our statistician, Roger Bolus, was the principal analyst for most of these previous trials and has been with the team for over a decade, including as principal analyst for our NIH PROMIS research. Our other collaborators and research associates have extensive experience, as described in Research Team and Environment, below.

E6.d. Outcome Measurement (IR-4, RQ-6). We will use a variety of data sources, including questionnaires delivered via REDCap, inherent EHR data, and analytic data on CDS implementation, to measure outcomes and covariates. Our Patient, Provider and Intervention Data Elements and Sources are outlined in detail in Appendix I, Table 3.

2. HRQOL Questionnaires. We collaborated with our primary patient partner, Tom Norris, to identify outcomes that were important to patients with chronic pain and their caregivers. Tom has been living with chronic pain for nearly 30 years and has had numerous interactions with a variety of clinicians. In addition to pain management, Tom stressed that it was important that we address energy, fatigue, and concentration. He shared his experiences taking a variety of medications to manage his chronic pain and **identified that providers often forget to discuss whether medications affect how and whether the side effects of medications such as opioids allow him and other patients to be active participants in their lives.** For example, Tom discussed his experiences taking fentanyl and shared how it left him so tired, unsteady, and fatigued that he could not function. We collaborated with Tom to find survey instruments that would address these important issues and proposed using the PROMIS Pain Interference Scale. **This instrument will allow us to track whether improving communication strategies through our comparators affects metrics that are critical to patients, including how pain affects an individual's day-to-day activities, ability to participate in social and leisure activities, and overall health, including pain, fatigue, energy and concentration.** Dr. Spiegel is currently an NIH PROMIS PI and developed PROMIS® instruments for the NIH.[114] Dr. Bolus was the principal statistician for this work. Thus, our team has experience scoring and implementing PROMIS®.

The PROMIS Pain Interference Scale has been used in diverse clinic populations[116] and research settings to measure interventions aimed at improving chronic pain (Appendix I).[117,118] It measures the degree to which pain interferes with other activities in life in adults.

In addition to the PROMIS Pain Interference Scale, our Institutional Review Board has approved a passive data collection method that allows us to collect key PROMIS measures currently collected as part of routine care at Cedars-Sinai. We will also collect PROMIS Physical Function and Depression scale scores to round-out our biopsychosocial HRQOL assessments and sample from the items in the PROMIS Global Health scale. These three scales are currently administered and serve as valid, reliable, and contextually appropriate PROs for the study intervention.

The PROMIS Physical Function Scale measures self-reported ability, this includes the functioning of upper and lower extremities as well as activities of daily life.

The PROMIS Depression Questionnaire measures self-reported negative mood, views of self, and decreased positive mood and engagement.

3. Communication Questionnaire. Use of CG-CAHPS Surveys for Primary Outcome (IR-5). We will evaluate patient experience data as measured by Clinician and Group Consumer Assessment of Healthcare Providers and Systems (CG-CAHPS) Adult 6-Month Visit survey (version 3.0) that is already being collected by the Cedars-Sinai Medical Network. Use of CG-CAHPS will ensure generalizability of the results, as many health systems rely on the survey to assess patient satisfaction. Broadly, CAHPS surveys are premised upon systematic and standardized measurement and are widely regarded as the national standard for collecting and reporting information from patients about care experiences. CG-CAHPS asks patients to report on their experiences with healthcare providers from their most recent office visit using items related to physician-patient communication. CG-CAHPS is itself widely used, tested, and validated, featuring prominently in CMS's Value-Based Purchasing (Pay for Performance) initiatives.[133] In studies, CAHPS surveys have been found to display excellent psychometric properties at the individual level and practice site level, and reliably assess the experiences of large samples of patients across diverse healthcare settings.[134] Employing standardized questions and data collection protocols, CG-CAHPS produces measurements in the following domains of patient experience:

- How Well Providers Communicate With Patients.
- Providers' Use of Information to Coordinate Patient Care

And

- Patients' Rating of the Provider

Accordingly, a number of CG-CAHPS' individual items are particularly relevant to our purposes (i.e. as measures of physician communication) including Items 11 ("Provider explained things in a way that was easy to understand"), 12 ("Provider listened carefully to patient"), and 20 ("Someone from provider's office talked about all prescription medications being taken"). Evidence from the literature suggests CG-CAHPS captures many of the communication related behaviors commonly exhibited by high-performing physicians: involving office staff in communication with patients; spending enough time with patients; listening carefully; providing clear, simple explanations; and devising an action plan with each patient.[135] Given this, we feel confident CG-CAHPS can adequately assess the quality of communication between patients and physicians as described in our conceptual and measurement models.

4. EHR Data and Pharmaceutical Health Claims Data. In order to capture medication use related to chronic pain treatment, including use of opioids, we will link patient EHR data to the other data sources using Medical Record Numbers and date of birth **(IR-2)**. We will employ our EHR Data Warehouse to collect ICD-10 codes for comorbid chronic conditions such as hypertension, hyperlipidemia, allergies, arthritis, depression, anxiety disorders, diabetes, asthma, coronary artery disease, thyroid disorders, and chronic obstructive lung disease. These conditions were identified by AHRQ as the most prevalent chronic conditions among adults 18 years and older.[136] Because comorbidities might impact HRQOL and medication use, we will use these chronic conditions to evaluate whether the study arms are balanced in terms of comorbidities and will also conduct sub-group analysis on mental health comorbidities. In addition, we will collect opioid prescription information using pharmaceutical claims data. We will also collect information on medications commonly used by individuals with chronic pain conditions. Finally, we will also use data pulled from the CDS analytics dashboard to estimate the number of times that the CDS alerts were triggered in response to high-risk opioid prescriptions.

E4.e. Data Collection (RQ-2). Upon auto-enrollment, we will extract the following variables from the electronic health record: chronic pain condition, length of time with chronic pain diagnosis, race and ethnicity, language, marital status, history of pharmacologic treatment, surgical history related to chronic pain condition, past injuries related to chronic pain condition, and length of time with current primary care provider[137]. When the intervention period is initiated, all eligible patients who have any follow-up visits during this 12-month period in both study arms will be sent the questionnaires. We will also capture depression scores via the Patient Health Questionnaires -PHQ-2 and/or PHQ-9 in the EHR. Furthermore, to determine if conversations about opioid medications took place during the visit that was

informed by either the CDS or the PEATS, we will conduct a structured review of a random sample of charts from both study arms.

E5. Statistical Analysis

E5.a. Descriptive and Exploratory Analyses. We will use frequencies and means for univariate descriptive analyses. We will use chi-square tests and paired t-tests to determine whether there are differences between the two study arms; using these bivariate analyses, we will identify covariates and patient- and physician-level moderators to use in the regression models. We will also consult with our Patient Partner to ensure that all appropriate patient-level covariates are included in the final models.

E5.b. Multi-Variate Regression Models. To evaluate the effectiveness of the comparators on the selected outcomes, we will use hierarchical linear regression models to measure changes in the outcomes over time using growth modeling statistical techniques[138] and will adjust for clustering at the patient, provider, and provider office level. Growth modeling allows the testing of individual differences in outcomes over time. In this study, we will examine HRQOL and communication scores over 12 months for the two study arms. We will adjust for patient- and provider-level covariates to account for potential confounders and also to identify whether there is heterogeneity of the treatment effect (see below). The proposed models are outlined here. We will test both fixed effects and random effects.[139] **(IR-3):**

Primary Outcome: Model 1: Hierarchical Linear Model (Longitudinal Analysis)

Question: **Which communication strategy used during the clinical encounter is more effective in reducing pain interference over time for patients with chronic pain who were taking opioids at baseline?**

Dependent variable: Pain interference as measured by PROMIS Pain Interference Score (T-Scored, Continuous)

Independent variable: Comparator received, CDS vs. PEAT (Dichotomous)

Potential Covariates: Age, gender, race, ethnicity, mental health comorbidities, chronic pain diagnosis, use of other pain medications (neuropathic pain medications, NSAIDS, antidepressants), benzodiazepine use, number of office visits during intervention period, baseline HRQOL, encounter month, physician years of practice, physician gender, employment, SES.

Moderator Analyses: We will use statistical interactions examining the moderating effects of patient age, race, ethnicity, mental health comorbidities, chronic pain diagnosis, physician years of practice and physician gender on the relationship between comparator and pain interference.

Mediation Analyses: We will test whether confidence in decision and satisfaction with communication as measured by COMRADE Scores mediates the relationship between the comparator used and the pain interference outcomes.

Primary Outcome: Model 2: Hierarchical Linear Model (Longitudinal Analysis)

Question: **Which communication strategy used during the clinical encounter is more effective in improving how satisfied patients feel over time after communicating with their physician about chronic pain treatment risks and benefits?**

Dependent variable: CG-CAHPS

Independent variable: Comparator received, CDS vs. PEAT (Dichotomous)

Potential Covariates: Age, gender, race, ethnicity, educational level, mental health comorbidities, chronic pain diagnosis, use of other prescribed pain medications (neuropathic pain medications, NSAIDS, antidepressants) benzodiazepine use, number of office visits during intervention period, baseline HRQOL, encounter month, physician years of practice, physician gender, employment, SES.

Subgroup Analyses: We will use statistical interactions examining the moderating effects of patient age, race, ethnicity, education level, mental health comorbidities, chronic pain diagnosis; and physician years of practice and gender on the relationship between comparator and pain interference.

Secondary Outcome: Model 3: Hierarchical Linear Model

Question: **Which communication strategy used during the clinical encounter is more effective in improving patient's Health Related Quality of Life over time?**

Dependent variable: PROMIS Physical Function, PROMIS Depression, and PROMIS Pain Interference Scores (T-Scored, Continuous)

Independent variable: Comparator received, CDS vs. PEAT (Dichotomous). *Potential Covariates:* Same as Model 2.

Secondary Outcome: Model 4: Hierarchical Generalized Linear Model

Question: **Which communication strategy used during the clinical encounter is more effective in reducing opioid prescriptions of more than 90 Morphine Milligram Equivalents (MME) over time?**

Dependent variable: Opioid Prescription over 90MME (Dichotomous)

Independent variable: Comparator received, CDS vs. PEAT (Dichotomous). *Potential Covariates:* Same as Model 2.

Other Analyses: We will also perform a differences-in-differences analysis at the beginning and the end of the intervention to determine which strategy resulted in greater reduction in high-risk prescriptions.

Secondary Outcome: Model 5: Hierarchical Generalized Linear Model

Question: **Which communication strategy used during the clinical encounter is more effective in reducing co-prescriptions of opioids and benzodiazepines over time?**

Dependent variable: Opioids and Benzodiazepines Co-Prescribed (Dichotomous)

Independent variable: Comparator received, CDS vs. PEAT (Dichotomous). *Potential Covariates:* Same as Model 2.

Other Analyses: We will also perform a differences-in-differences analysis at the beginning and the end of the intervention to determine which strategy resulted in greater reduction in high-risk prescriptions.

E5.c. Power Calculations. Guided by previous work in chronic pain interventions,[140] we calculated sample size using an intracluster correlation coefficient of 0.02, an α level of 0.05, 90% power, and detection of a mean (SD) difference of 0.3 standard deviations on the PROMIS Pain Interference scale. We calculated a sample size of 320 patients per study arm, for a total of 640 patients. To compensate for predicted loss to follow-up, multiple variables in the final multi-level models, as well as sub-group analyses, we inflated the sample size by 50% to 960. Since we will be examining the effect of the interventions on a variety of sub-groups within the study sample, such as diagnoses of mental health conditions, race, ethnicity, gender, and chronic pain diagnosis, we will be adequately powered to detect meaningful differences. In our original proposal, we calculated a sample size of 320 patients per study arm for a total of 640 patients. To compensate for predicted loss to follow-up and non-response we had inflated the recruitment target size by 50% to 960. Under the current modification – and given the absence of changes to the assessment schedule, the estimated intracluster correlation coefficient, and the expected mean difference - the sample size required to adequately power the analysis remains unchanged. We believe the recruitment target will also remain consistent, and potentially even fall due to the ability of study staff to call passively enrolled patients and remind them to respond to assessments. We therefore anticipate being adequately powered to detect meaningful differences between the two arms.

E6 Heterogeneity of Treatment Effect (HT-1, HT-3, HT-4)

After reviewing the literature and consulting with our patient partners, we identified specific subgroups we plan to analyze to identify whether there is a heterogeneity of the treatment effects. Below we detail our planned sub-group analyses, our hypotheses, and our plans for statistical analysis for each subgroup. In order to address the problem of multiplicity, a Bonferroni correction will apply to all analyses.

- ***Race/Ethnicity.*** *Hypothesis:* Previous literature finds that providers might be less likely to engage in shared decision-making with non-White patients.[94] It is plausible that the interventions, particularly the PEATs, may be less effective for non-White patients as a result of provider-level factors. Lower satisfaction with communication should result in lower improvements in HRQOL. This analysis can inform future development of CDS or PEATs. *Outcomes analyzed:* Communication satisfaction scores as measured by CG-CAHPS and HRQOL scores as measured by the PROMIS Physical Function, PROMIS Depression, and PROMIS Pain Interference Survey. *Statistical analysis plan:* Statistical interaction in regression models
- ***Mental Health Diagnosis of Depression, Anxiety Disorder, Prior Substance Abuse Disorder or PTSD.*** *Hypothesis:* Patients with diagnoses of depression, anxiety disorder, Substance Abuse Disorder, or PTSD should see improved

communication scores as measured by CG-CAHPS in the CDS arm because one alert specifically targets these conditions and prompts physicians to discuss risks and benefits of opioids for these patients, who are at higher risk of opioid abuse disorder. *Outcomes analyzed*: CG-CAHPS scores, high-risk opioid prescriptions at the end of the intervention. *Statistical analysis plan*: Statistical interaction in the regression models.

- ***Gender.*** *Hypothesis*: Prior studies have found that women are more likely to encounter providers who do not believe their pain is real or who believe that they are exaggerating their pain.[53] We believe that female patients in the PEAT arm will see greater effect on their HRQOL as a result of shifting the conversation from pain alone to other important Patient-Reported Outcomes such as fatigue, appetite, mood. *Outcomes analyzed*: HRQOL scores. *Statistical analysis plan*: Statistical interaction in the regression models.

E7. Data Source Adequacy (IR-1). We plan to collect several types of data for this study. For the PROs, we will collect data directly from patients through web-based questionnaires. We will collect some data on comorbidities and medication use through data collected for clinical care and billing purposes through the EHR. Given that this data is not collected for research purposes, errors, particularly with regards to ICD-10 codes, are possible. We will work with our data warehouse to ensure that the data are cleaned prior to analysis and our statistical analysis team, led by Dr. Roger Bolus, who has experience with clinical data collection and analysis,[141] will also conduct extensive exploratory data analysis to identify potential errors in the data.

E7. Missing Data

a. Methods to Prevent and Monitor Missing Data. We anticipate two sources of missing data: the failure of patients to complete the initial set of questionnaires and the loss of patients to follow-up. Monitoring of missing questionnaire data will occur in real-time as online questionnaires are completed, completed partially, or never started. For enrolled patients who do not respond to the questionnaires after baseline, we will conduct two follow-up phone calls to attempt to collect data. After the intervention study period has ended, we will attempt one last follow-up phone call with a sub-sample of non-respondents to see if they are similar to respondents **(MD-1)**. If so, for the hierarchical linear model, maximum likelihood estimation will be consistent as long as the data are missing at random **(MD-3)**.[137] We are aware of the potential between failure to complete survey elements, failure to use the educational tools, and reduced HRQOL. These hypothesized patterns will receive close scrutiny in the analysis of the mechanisms.

b. Statistical Methods to Handle Missing Data and Sensitivity Analyses. If the data is not missing at random, we will use multiple imputation techniques to impute missing data for respondents **(MD-2)**. We plan on using the *mi impute mvn* command in Stata and will generate 20 datasets compatible with the regressions planned for the final analyses. To insure that the imputation has proceeded as expected, we will visually inspect parameters from successive iterations of the model to determine if they have reached a stationary distribution. We will conduct sensitivity analyses with the dataset that includes imputed data as well as with a dataset that does not include imputed data to determine the effect of the multiple imputation and plan on reporting both results. These precautions will serve to identify autocorrelation in the inputed data and allow for proper maintenance of uncertainty in imputed values **(MD-3)**.

c. Reporting Reasons for Dropout and Missing Data. We will drop data from patients who do not have any visits with their PCP during the intervention period or are lost to follow-up, but will compare descriptive statistics for these patients to patients with at least one visit to their PCP for sensitivity analysis **(MD-4, MD-5)**.

E9. Project Milestones and Timeline.

Table 3. Study Activities Timeline

Activity	Year 1 Q1-Q2	Year 1 Q3-Q4	Year 2 Q1-Q2	Year 2 Q3-Q4	Year 3 Q1-Q2	Year 3 Q1-Q2
Kick-Off Activities: Train Project Staff	X					
IRB Approval	X					
Study Protocol Refinement	X					
Patient Auto-Enrollment Recruitment		X	X	X		
Intervention Period			X	X		
Data collection: EHR		X	X	X	X	
Data collection: Patient Surveys		X	X	X		
Data Analysis					X	X
Dissemination Activities						X
Manuscripts and Reports						X

During the first 3-6 months of the study project, we will train the project staff, refine the study protocol, develop the data dictionaries, and obtain IRB approval. We will hold monthly meetings with our patient partners to finalize the study design and discuss issues related to IRB approval. In Year 1, Q4, we will passively enroll eligible patients in the two study arms. In the 4 weeks before the intervention period, we will send baseline questionnaires via REDCap. In Year 2, we will begin the intervention. We will conduct weekly reports from our EHR data warehouse to determine enrolled patient visits. Enrolled patients will be sent CG-CAHPS survey one day after each primary care visit. Enrolled patients will also receive the PROMIS questionnaires once a month. We will perform monthly checks to assess the completeness of data to minimize missing data and will complete one set of interim data analyses in Year 2 to assess whether there are any issues with missing data. Full data analysis will take place in Year 3. We will collaborate with our patient partners to develop implications of the study results and will work collaboratively on manuscripts, briefs, and patient-facing reports about the study in the second half of Year 3.

F. Threats to Internal Validity and Generalizability (IR-6) The main threat to internal validity with this study design is the possibility of external events or initiatives influencing the outcomes. Given the widespread media coverage of the opioid epidemic, it is possible that patients will proactively discuss the risks and benefits of their opioid medications with their physicians or that physicians will bring up these risks and benefits without the use of the communication strategies or tools. However, we have built in several controls for this issue. First, we have included a measure of communication via the CG-CAHPS questionnaire. If we see improved HRQOL scores and a reduction in high-risk opioid prescribing practices without a corresponding increase in the communication scores, we may conclude that initiatives or events outside of the study influenced the outcomes. We will use CG-CAHPS scores for sensitivity analysis to test whether improved communication results in better health outcomes. The study setting – primary care practices located in an urban, diverse healthcare system – is a strength of this study, but does reduce the generalizability with regards to study replicability and findings in rural or low-income settings. For example, patients within our study population are more likely to be employed, have higher levels of overall education and health literacy, and may have higher incomes. However, given that the majority of patients in the U.S. are insured, and most are covered by private insurance or Medicare,[85] we believe that it is important to study the proposed interventions in this populations.

F. Research Team and Environment

Principal Investigator: Brennan M. R. Spiegel, MD, MSHS, is Director of Health Services Research for Cedars-Sinai Health System. Dr. Spiegel has extensive experience with patient-reported outcomes development and measurement. Dr. Spiegel has worked on a multitude of studies in the areas of healthcare decision-making,[142,143] clinical trial design,[112,115] EHRs, and quality measurement.[144] Dr. Spiegel is an NIH PROMIS investigator, and a current member of the PROMIS Steering Committee. He has received VA Merit Award and NIH funding for studies using PEAT, EHR communication interventions, patient reported outcomes, and CDS. For this study, Dr. Spiegel will oversee the development of the study protocol, patient recruitment and screening, data collection, data analysis, and manuscript and report development.

Co-Investigator: Teresa Dean, MD is a practicing PCP at the Cedars-Sinai Medical Network and has experience in epidemiological research. She served as an Epidemiology Fellow for the Centers for Disease Control and Prevention. Dr. Dean will lead the study protocol development with regards to incorporating the study materials into the clinical workflow. Dr. Dean will also be involved in data management and analysis, manuscript development, and dissemination activities.

Co-Investigator: Itai Danovitch, MD, MBA, chair of the Department of Psychiatry and director of Addiction Psychiatry at Cedars-Sinai, has begun a two-year term as president of the California Society of Addiction Medicine. Dr. Danovitch is a member of the American Academy of Addiction Psychiatry, American Society of Addiction Medicine, and is a past recipient of the American Psychiatric Association GlaxoSmithKline Fellowship for national leadership in the field of psychiatry. Dr. Danovitch will assist with the refinement of the study protocol and will serve as a key member of the data analysis team with regards to the analysis of mental health conditions. Dr. Danovitch will also be involved in the dissemination of the results through his widespread network of addiction medicine physicians and addiction specialists.
Co-Investigator: Teryl Nuckols, MD, MSHS is Director of General Internal Medicine for Cedars-Sinai Medical Center and an established Health Services Researcher. Dr. Nuckols has extensive research experience in opioid guideline analysis and appropriate opioid use.[145,146] Dr. Nuckols will work closely with the project manager and data analysis team to select appropriate covariates based on her work on high-risk opioid prescribing. Dr. Nuckols will also play an important role in the data analysis.
Biostatistician: Roger Bolus, PhD, is a biostatistician with substantial experience in clinical trial design,[141] multi-level model data analysis, and the development and use of Patient-Reported Outcomes.[114] He was the primary analyst for our lab's foundational work with NIH PROMIS, and has worked on many pragmatic trials including EHR-based, CDS-based, and PEAT-based interventions. Dr. Bolus will assist with the clinical trial design, statistical analysis and data linkage portions of the project and will help develop the EHR-based data reports for the study.
Primary Patient Partner: Tom Norris, is a Patient Advocate and individual with chronic pain. Mr. Norris has been a member of the ACPA for more than 20 years and leads multiple chronic pain support groups in the Los Angeles Area. Mr. Norris will also meet regularly with the study team to monitor implementation to provide input on the patient experience. Mr. Norris will be embedded in our data analysis team by helping to interpret the study results. Mr. Norris will also play an important role in the dissemination and implementation phase by presenting the study results to patient groups, patient advocacy organizations, and leaders at other health care teams.
Patient Advocacy Partner: Penney Cowan, is the Founder and Executive Director of the ACPA. Ms. Cowan has worked closely with researchers on a variety of projects, including PCORI-funded studies. She has also worked on the development of patient education, communication, and activation materials for individuals with chronic pain. For this study, Ms. Cowan will work closely with the Investigator Team to develop the study protocol. She will also be heavily involved in the dissemination phase of the study, particularly with regards to the development of patient-facing reports highlighting the study findings and their implications for patients.
Consumer Advocacy Partner: Dominic Lorusso and Doris Peter, PhD. Mr. Lorusso is the Director of Health Partnerships at Consumer Reports and leads several Health Impact campaigns, including Choosing Wisely, at Consumer Reports. In this role, Mr. Lorusso works with national and regional partner groups in developing unique methods to reach each of their members or constituents. For this study, Mr. Lorusso will lend his expertise in dissemination methods to assist the study team on the dissemination phase of the study. Dr. Peter is the Director of the Consumer Reports Health Ratings Center. He will work with the team during the data collection and analysis phases of the study and will work with the study team to disseminate the study results by leveraging Consumer Reports' existing partnerships.
Project Director: Michelle S. Keller, MPH, is a Health Services Researcher with experience in claims data analysis, multi-level modeling, and project management. Ms. Keller will work closely with Dr. Dean and the Patient Partner, Tom Norris, to refine the study protocol. Ms. Keller will also work with Dr. Bolus to clean and link the data sets and will also be involved in the statistical analysis. Ms. Keller will also serve as the primary liaison between the Investigator Team and the Patient Partners and will organize and coordinate meetings.
Research Manager: Bibiana Martinez, MPH, is a Health Services Researcher with experience with Community-Based Participatory Research, protocol development, IRB applications, and data analysis. In addition to leading the IRB application process, Ms. Martinez will work closely with the patient partners on dissemination strategies.
Environment: Cedars-Sinai Center for Outcomes Research and Education (CS-CORE). Cedars-Sinai provides an ideal laboratory for the proposed study given its strong commitment to research. CS-CORE is focused on health services research specifically in the fields of patient-reported outcomes, physician-patient communication, and implementation

and dissemination research. CS-CORE's software and computer capabilities strengthen the team's ability to perform in-depth research. CS-CORE also has access to the main data and research facilities at Cedars-Sinai, including a staffed research library, a team of biostatisticians, experts in the fields of multiple specialties, and data analysts and programmers from the Enterprise Information Systems (EIS) work group, which manage all data for Cedars-Sinai. CS-CORE is located near the Medical Network, which will facilitate recruitment and study implementation.

G. Engagement Plan (PC-1). In accordance with PCORI's principles of Patient Engagement, this study includes patient engagement in all stages of the study, from the study design, outcomes selection, recruitment development, intervention implementation, data analysis and dissemination of results. All team members will have an equal voice in the process and all contributions will be valued. The investigator team will communicate regularly with study partners via scheduled and unscheduled meetings and conference calls to elicit input from the stakeholders. Our primary Patient Partners, Mr. Norris and Ms. Cowan, will review study protocols, consent materials, and will contribute to manuscripts.

G1. Stakeholder Identification. We have initiated a number of collaborative partnerships with a wide range of stakeholders for this proposal, all of whom have important and distinct perspectives on chronic pain management. These groups include those receiving care for chronic pain, such as patients and individuals representing patient support groups; those providing care, such as clinicians and mental health professionals; and those that support the interaction between these two groups, such as consumer advocacy organizations.

1. Patient Partners: The ACPA has developed a variety of communication tools, including one of the communication tools used in this grant proposal, to assist patients in communicating their values and goals with their health care providers. Ms. Cowan has presented the communication tools to dozens of Veterans Health Affairs organizations through the Veterans in Pain project and has also spoken to patients and health care system leaders about the importance of improving physician-patient communication.

2. Care Providers: **Cedars-Sinai Medical Network (CS-MN)**: Part of the Cedar-Sinai Medical Center, the CS-MN serves 10,000 patients per month. PCPs represent one of the most important actors in the patient-physician chronic pain management interaction. **Pain Management Working Group**: The Working Group consists of a group of PCPs concerned with chronic pain management and opioid misuse. **Dr. Teresa Dean**, who is the current head of the Working Group, will serve as the group's representative for this study.

3. Professional Organization: **Consumer Reports**: Consumer Reports Health works to create tools and educational materials aimed at supporting and empowering patients and facilitating interactions with their clinicians. The organization's priority is to ensure that patients and consumers have unbiased, clear information that can empower them in complicated decision-making processes. **Mr. Dom Lorusso and Dr. Doris Peter** will collaborate with the study investigators to represent Consumer Reports Health's voice in this study.

G2. Stakeholder Engagement. **Phase 1: Planning the study.** We began collaborating with our stakeholders even before the grant-writing process and their input and feedback has guided the development of our current study design. **Table 4** outlines the process through which our study design was developed in collaboration with our partners.

Phase 2: Conducting the Study. We will collaborate with our Patient Partners throughout the study planning and implementation phases to ensure that we develop patient-centered communications. We will hold monthly meetings prior to the study to develop protocols. During the data collection phase, we will monitor data collection for quality and completeness and will update our stakeholders to discuss issues that may arise.

At the conclusion of the implementation period, we will collaborate with our stakeholders during the statistical analyses to discuss the results. We will also create a Patient Advisory Board. We will invite patients who have previously participated in other chronic pain studies in our group to participate in a patient advisory board. They will receive information about the study via a newsletter and will be invited to make suggestions and changes throughout the study implementation period.

Table 4. Stakeholder input in Study Design and Development

Activities	Stakeholder Input
Outcome selection	Patient Partner: Tom Norris - Patient-provider communication suggested as primary outcome - Identified pain interference and overall health related quality of life as critical primary outcomes Patient Partner: American Chronic Pain Association - Suggested Patient-Reported Measures of communication/patient satisfaction as study outcomes
Research refinement	Clinician Partner: Pain Management Working Group - Guided development of eligibility criteria based on understanding of high-risk patients
Study design	Patient Partner: Tom Norris - Provided guidance on instrument selection - Provided input on timing of the delivery of patient-facing education and activation materials Consumer Reports Health - Guided selection of education material Clinician Partner: Pain Management Working Group - Guided study design and protocol development

Phase 3: Disseminating the Study Results. We will collaborate with our stakeholders to disseminate the study results. Our Patient Partners will collaborate on the development of manuscripts, presentations, and patient-facing materials – including a website that details the results of the study. We will work with the ACPA and Consumer Reports to create a communication strategy to disseminate the study through the lay media – a powerful opportunity for widespread dissemination. Additionally, the investigators will present the study findings alongside Mr. Norris and Ms. Cowan at national and professional conferences.

C. Stakeholder Meetings. Regular, standing meetings will be held with stakeholder partners through all 3 years of the study. In order to facilitate participation, meetings will take place either in person or by phone. See **Table 5.**

Table 5. Meeting Schedule for the Proposed Study.

Meeting Schedule	Weekly	Monthly	Biannually
Year 1: Planning and patient recruitment	• Investigator Team, Pain Management Working Group	• Investigator Team, Patient Partners, Pain Management Working Group	• Investigator Team, Patient Partners, Consumer Reports, Pain Management Working Group
Year 2: Study Implementation	• Investigator Team, Pain Management Working Group	• Investigator Team, Patient Partners, Pain Management Working Group	• Investigator Team, Patient Partners, Consumer Reports, Pain Management Working Group

Attachment C-R: Milestone Schedule

	Milestone Name	Description	Projected Completion Date
A	**Project Start Date**	-	**3/13/2017**
B1	Stakeholder engagement meeting	Stakeholder engagement kick-off meeting	3/30/2017
B2	Patient eligibility data pulls	EIS Data Analyst to create a list of eligible patient population	4/30/2017
B3	Study protocol completed	Final trial protocol completed - submit a copy to PCORI	5/30/2017
B4	Patient eligibility data pulls	EIS Data Analyst to finalize list of eligible patient population and other data pulls	5/30/2017
B5	IRB Approval Obtained	Obtain IRB approval for study and submit approval letters to PCORI	7/30/2017
B6	DSMB Meeting 1	Set safety protocols and standards for data safety monitoring	7/30/2017
B7	Integration of questionnaires into patient portal	EIS Data Analyst to integrate questionnaires into MyCSLink	7/30/2017
B8	Select and register project at appropriate site for the study design (Clinicaltrials.gov, RoPR, or other as approved by PCORI before study start date)	Study Identification Number and the Primary Research Completion Date must be sent to PCORI.	7/30/2017
B9	Randomization of clinic sites	Randomization of Cedars-Sinai network offices completed; 50% to CDS arm and 50% to PEAT arm of trial	7/30/2017
B10	Passive patient recruitment begins	Passive data enrollment begins for study participants (N=960) / Study begins	8/1/2017
B11	Pharmacy data collection begins	EIS Data Analyst to begin pull data for passively enrolled patients on pharmacy data for data monitoring purposes	8/1/2017
B12	Patient baseline questionnaires	Enrolled patients begin filling out PROMIS patient reported outcome questionnaires	8/1/2017
B13	Stakeholder engagement meeting	Stakeholder engagement meeting to update on IRB submission and patient eligibility protocols and baseline data collection	8/31/2017
B14	Engagement Update	For the 6-month time intervals (i.e., 6 months, 18 months, 30 months, etc. but not at 12 months or 24 months), provide specific examples of the impact of engagement on project activities during the reporting period. Report this in the Engagement Report section of the PCORI interim progress report.	9/13/2017
B	**Report Submission**	**Submit 6-month Interim Progress Report, Using PCORI Interim Progress Report Template**	**9/13/2017**
C1	Study intervention begins	Study intervention begins	1/1/2018
C2	Stakeholder engagement meeting	Updates on study implementation	2/28/2018
C3	DSMB Meeting 2	Review safety monitoring standards and plan interim data analysis	3/1/2018
C4	Engagement Report	For each **annual** report (i.e., at year 1, year 2, etc. but not at 6 months or 18 months), additional descriptive information on engagement of patients and/or other stakeholders should be reported at https://live.datstathost.com/PCORI-Collector/Survey.ashx?Name=Engagement_Report_Login. Confirmation code should be reported in the Engagement Report section of the PCORI interim progress report.	3/13/2018
C	**Report Submission**	**Submit 12-month Interim Progress Report, Using PCORI Interim Progress Report Template**	**3/13/2018**
D1	25% enrollment	Completion of 25% of study enrollment/recruitment (240/960)	6/15/2018

D2	50% enrollment	Completion of 50% of study enrollment/recruitment (480/960)	8/15/2018
D3	Pharmacy data collection continues	EIS Data Analyst to pull monthly for enrolled patients on pharmacy data for data monitoring purposes.	9/13/2018
D4	Engagement Update	For the 6-month time intervals (i.e., 6 months, 18 months, 30 months, etc. but not at 12 months or 24 months), provide specific examples of the impact of engagement on project activities during the reporting period. Report this in the Engagement Report section of the PCORI interim progress report.	9/13/2018
D	**Report Submission**	**Submit 18-month Progress Report, Using PCORI Interim Progress Report Template**	**9/13/2018**
E1	75% enrollment	Completion of 75% of study enrollment/recruitment (720/960)	10/15/2018
E2	100% enrollment	Completion of 100% of study enrollment/recruitment (960/960)	12/31/2018
E3	Interim analysis	Data cleaning, linking, merging, specification of statistical models, data dictionary and codebook development	1/31/2019
E4	Stakeholder engagement meeting	Review of interim data analysis, study implementation, missing data issues, potential safety issues	1/31/2019
E5	DSMB Meeting 3	Board reviews interim data analysis to examine potential safety issues	1/31/2019
E6	50% follow-up data collection	Completion of 50% of follow-up data collection	2/1/2019
E7	Pharmacy data collection continues	EIS Data Analyst to pull monthly for enrolled patients on pharmacy data for data monitoring purposes	3/13/2019
E8	Engagement Report	For each **annual** report (i.e., at year 1, year 2, etc. but not at 6 months or 18 months), additional descriptive information on engagement of patients and/or other stakeholders should be reported at https://live.datstathost.com/PCORI-Collector/Survey.ashx?Name=Engagement_Report_Login. Confirmation code should be reported in the Engagement Report section of the PCORI interim progress report.	3/13/2019
E	**Report Submission**	**Submit 24-month Interim Progress Report, Using PCORI Interim Progress Report Template**	**3/13/2019**
F1	75% follow-up data collection	Completion of 75% of follow-up data collection	6/15/2019
F2	DSMB Meeting 4	Board reviews data collection	7/30/2019
F3	Stakeholder engagement meeting	Update on intervention, data collection	7/28/2019
F4	Engagement Update	For the 6-month time intervals (i.e., 6 months, 18 months, 30 months, etc. but not at 12 months or 24 months), provide specific examples of the impact of engagement on project activities during the reporting period. Report this in the Engagement Report section of the PCORI interim progress report.	9/13/2019
F	**Report Submission**	**Submit 30-month Interim Progress Report, Using PCORI Interim Progress Report Template**	**9/13/2019**
G1	Stakeholder engagement meeting	Discussion of preliminary research findings and implementation issues	10/25/2019
G2	Completion of follow-up data collection	Completion of follow-up data collection (100%).	12/15/2019
G3	EHR data pull	Final data pull from EIS Data Analyst with all encounters, covariates, and pharmacy data	12/15/2019
G4	Statistical analysis	Data cleaning, linking, merging, specification of statistical models, data dictionary and codebook development	1/30/2020
G5	Primary completion date	A Primary Research Completion Date must be provided when registering the study in Clinicaltrials.gov. For studies that are not clinical trials or observational studies registered on ClinicalTrials.gov, the Awardee and PCORI shall agree on a primary completion date as a milestone that precedes the agreed-upon date to submit a Draft Final Research Report.	1/30/2020

G6	Stakeholder engagement meeting	Discussion of findings and implications, Creation of detailed dissemination strategy and specific roles of each team member	2/3/2020
G7	Website development	Development of sub-site with study findings and implications	2/30/2020
G8	Engagement Report	For each **annual** report (i.e., at year 1, year 2, etc. but not at 6 months or 18 months), additional descriptive information on engagement of patients and/or other stakeholders should be reported at https://live.datstathost.com/PCORI-Collector/Survey.ashx?Name=Engagement_Report_Login. Confirmation code should be reported in the Engagement Report section of the PCORI interim progress report.	3/13/2020
G9	Website launch	Launch of study findings website	3/13/2020
G10	Patient-facing reports development	Development of patient-facing reports by Patient Partners and Investigators	3/13/2020
G11	Manuscript development	Development of primary outcome/specific aim manuscripts	3/13/2020
G12	Press release development	Collaboration with Patient Partners to create press releases for lay media	3/13/2020
G13	Dissemination presentations	Presentations by Investigators and Patient Partners	3/13/2020
G14	De-identified dataset	EIS Data Analyst to create de-identified dataset for data sharing	3/13/2020
G15	Stakeholder engagement meeting	Discussion of next steps and future dissemination activities	3/13/2020
G	**Research Project Period End Date**		**3/13/2020**
H	**Final Progress Report Submission**	**Submit Final Progress Report, Using Final Progress Report Template. Submit Expenditure Report (See Contract for Instructions)**	**3/13/2020**
I	**Results submitted to ClinicalTrials.gov or appropriate database.**	**Awardee ensures results are submitted to ClinicalTrials.gov or appropriate database. For ClinicalTrials.gov, the generated tables are a required section in the Draft Final Research Report.**	**9/1/2020**
J	**Draft Final Research Report Submission**	**Submit Draft Final Research Report according to instructions found at *http://www.pcori.org/awardee-resources*** ***Draft Final Research Report must be submitted no later than 30 days from when results are posted to clinicaltrials.gov or other applicable website.***	**10/1/2020**
K	**Final Research Report**	**Upon receipt of written summary, and as applicable, PI will make revisions and submit revised Draft Final Research Report for acceptance as directed by PCORI.**	**See Description**
L	**Approval / sign off of the Lay Abstract**	**Sign off must be no later than 90 days beyond the date PCORI accepts the final report**	**3/31/2021**
M	**Contract Term End Date**		**3/31/2021**
N	**Final Expenditure Report**	**Submit Final Expenditure Report (See Contract for Instructions) 90 days from Contract Term Date**	**6/30/2021**
O	**Notification of Public Acceptance**	**See Contract for Instructions**	**Within 30 Days of Acceptance**

Except as and only to the extent explicitly modified by the terms and provisions of this letter of modification, all terms and provisions of the Contract are ratified and confirmed in all respects and shall hereby remain in full force and effect.

If these modifications to the Contract are acceptable to you, please counter-sign, scan and PDF this letter of modification, and return to PCORI at fundedpfa@pcori.org. We will provide a fully executed copy for your files.

Sincerely,

PCORI:

_____

Name: Lauren Massey
Title: Administrator, Contract Management
Date:

_____

Name: Regina Yan
Title: Chief Operating Officer
Date:

Accepted and agreed to by:
CEDARS-SINAI MEDICAL CENTER

_____

Name: Stacy Miller
Title: Sr. Grant and Contract Officer/AOR
Date: June 21, 2018

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Name: Lauren Massey
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Date: JUN 25 2018

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Title: Sr. Grant and Contract Officer/AOR
Date: June 21, 2018