Prioritizing Comparative Effectiveness Research Questions for the Long-Term Use of Opioids for Chronic Pain:

A Stakeholder Workshop on Multimodal Treatment Options, Risk Mitigation Strategies, and Opioid Dependency Meeting Summary

Overview

On June 9, 2015, PCORI brought together a wide range of stakeholder groups to identify, refine, and prioritize comparative effectiveness research (CER) questions regarding the long-term use of opioids for chronic pain whose findings could improve patient-centered outcomes. Chronic pain is extremely common and defined as pain lasting longer than three months. Chronic pain affects more than 100 million Americans, and opioid prescriptions have increased threefold over the past 20 years. Opioids are associated with a number of harms, including overdose, abuse, addiction, diversion, sedation, impaired cognitive function, depression, constipation, and nausea (Topic Brief). Workgroup participants were tasked with identifying the most relevant CER question that focuses on the use of long-term opioid therapy for chronic pain and addresses current gaps in knowledge. University of Texas Health Science Center's Director, Dr. Barbara J. Turner, chaired the meeting. A wide range of stakeholders attended, and the meeting was audio recorded and open to the public via teleconference and webinar.

Key Questions

Questions for discussion were submitted by workshop participants prior to the meeting and refined by PCORI staff to yield a total of 24 comparative effectiveness questions that were reviewed by two opioid panels. Panelists in this group discussed multimodal treatment options, risk mitigation strategies, and opioid dependency.

Morning Session

During the workshop's morning session, attendees were asked to prioritize and discuss the top-ranked questions using PCORI research prioritization criteria. Conversation revolved around each question's relation with each of the following criteria:

- **Patient-Centeredness**: Is the comparison relevant to patients, their caregivers, clinicians, or other key stakeholders, and are the outcomes relevant to patients?
- **Impact of the Condition on the Health of Individuals and Populations**: Is the condition or disease associated with a significant burden in the U.S. population, in terms of disease prevalence, costs to society, loss of productivity, or individual suffering?
- **Assessment of Current Options**: Does the topic reflect an important evidence gap related to current options that is not being addressed by ongoing research?
- **Likelihood of Implementation in Practice**: Would new information generated by research be likely to have an impact in practice?
- **Durability of Information**: Would new information on this topic remain current for several years, or would it be rendered obsolete quickly by new technologies or subsequent studies?

The following questions were discussed:

Category 1: Studies that Include Non-pharmacologic Options – High-level question: In patients with chronic pain, what is the comparative effectiveness of opioids versus non-pharmacological options versus opioid or non-opioid interventions alone on outcomes related to pain, function, quality of life (QOL), and doses of opioids used?

Question 1.1 What are the comparative benefits and risks of a multimodal approach (physical therapy injections, and cognitive behavioral therapy) and non-opioid analgesics versus long-term opioid analgesics for adults with chronic pain? Outcome measures include QOL indices (better mobility, better sleep, better mood, improved daily function) and pain reduction.

The panel agreed that is an important broad question. Some participants noted specific concerns with the practicality of the implied approach as well as issues with the proposed study population.

Comments included:

- The scope of research should be broadened to include pediatric populations.
- The study may not be feasible as non-opioid analgesics are often not covered by insurance. Therefore, access to non-pharmacologics can be a barrier. Additionally, these treatments are not often as immediately effective as opioids, so it will be important to incorporate strategies (e.g., health coach, app) to keep patients engaged.
- The scope of the research should be expanded to include opioid-inclusive versus non-opioid options.
- Study outcomes should also include healthcare utilization.
- Women of childbearing age should also be included.

Question 1.2 What are the comparative benefits and risks of a combined approach using yoga, mind-body practice, and non-opioid analgesics versus long-term opioid analgesics in patients with chronic generalized pain? Outcome measures include QOL indices (better mobility, sleep, mood, function) and pain reduction.

The panel agreed that this question should be merged with Question 1. Some panelists identified differences in patient perceptions to pain, noting that no single integrative medicine approach would be appropriate for all patients.

Comments included:

- Yoga may not be appropriate for all chronic pain patients.
- A multidisciplinary approach may be the optimal way to treat chronic pain.
- It is unclear if it is feasible to have a study arm without opioids. Several panelists suggested a multimodal approach in which opioid therapy would be included across all study arms.
- Function is an important outcome and should include social aspects (e.g., sense of purpose, feelings of control) as well.
- An education component should be included.

Question 1.3 What is the impact of parallel versus sequential timing of multimodal/integrative pain treatment (including opioids and non-pharmacologic treatments) on measures of pain and functional status in patients with chronic pain, stratified by treatment modality and underlying disease state?

Overall, the panelists questioned whether this study would be feasible due to the complexity of the research question.

Comments included:

- Stratifying by underlying disease state is important as not all chronic pain is the same.

- The research question seems very complicated with numerous permutations possible.
- Studying sequential versus parallel timing of multimodal treatment is important because it may demonstrate how complementary medication could alleviate some of the side effects of opioid treatment.
- The study design could be simplified by comparing two multimodal approaches or using an adaptive design.

Question 1.4 What are options for improving long-term function and pain in opioid-using persons with chronic pain? Considerations include:
a. Population: *Patients with chronic non-cancer musculoskeletal pain. (3+ months) prescribed >1 month opioid therapy (consider a minimum dose such as greater than 20mg morphine equivalent)*
b. Option 1: *Non-pharmacologic, evidence-based interventions (stretching/massage group education) in a primary care clinic with case management to facilitate and promote engagement and the long-term maintenance of activities at home*
c. Option 2: *Similar curriculum/support offered several times weekly by a community-based organization such as the YMCA. This program must be at no or low cost and include peer coach support to encourage engagement and the maintenance of activities along with an incentive/competition for completion.*
d. Outcomes: *Function (e.g., 6 min. walk test, sit to stand 5x), QOL, patient satisfaction, mental health (Patient Health Questionnaire [PHQ-9], anxiety), pain (10 pt. scale), and change in dose of opioid looking at repeated measures overt three, six, and 12 months*
e. *Study must involve a multidisciplinary team (primary care, pain specialty, physical therapy, kinesiology, psychology/psychiatry) to ensure that the interventions offer high levels of motivation and patient self-management education while coordinating closely with the primary care provider.*

The panel agreed that this is an important question, but its potential impact may be limited by barriers regarding access to care.

Comments included:

- Option 1 may not be feasible as patients may not be able to return to the primary care clinic for multiple appointments. Additionally, utilizing community-based organizations (Option 2) such as the YMCA is important, but patient access may be a barrier.
- It is unclear what the target population for this study would be. It would be important to include those that routinely visit hospitals/clinics.

Question 1.5 Opioid risk reduction in persons initiating opioids for chronic non-cancer pain
a. Population: *Patients with musculoskeletal pain who meet eligibility criteria for initiating opioid therapy (e.g., failed alternatives such as PT, non-opioid drugs, injections). This project must include vulnerable populations who are more likely to be undertreated for pain but who suffer disproportionately from pain (NHANES) including minorities and low-income groups.*
b. Option 1: *Patient-centered medical home structure that takes advantage of an electronic medical record (EMR) support package and case management to offer support and ensure high-quality care. The EMR must offer tools to evaluate the risk of opioid abuse/misuse and the ability to monitor total opioid dose/daily dose as well as concurrent treatment with potentially risky drugs such as psychotherapeutics (e.g., benzodiazepines, hypnotics) and antidepressants.*

c. Option 2: *Low opioid dose therapy and referral to a practice-based pain champion—such as a physician, physician's assistant, or registered nurses—who have received advanced training in an evidence-based pain management program. The patient visits the clinic specialist at least every six months (to supplement care from a primary care physician). This arm offers basic EMR support (ORT, OA agreement). Both arms offer collaborative care with appropriate specialists (PT, pain experts).*

d. Outcomes: *Opioid dose, functional measures (6 min. speed walk, 50 ft. speed walk, sit to stand 5x), mental health (PHQ9)/mental functioning (symbol digit test) measures, patient satisfaction, and measures of opioid misuse (early refill requests, dose escalation)*

The panel questioned the feasibility of this research question due to standard (but not guideline-concordant) practices.

Comments included:

- The patient population should be revised as patients who have "failed" alternative treatments would have already initiated opioid therapy.
- There is a lack of data supporting the use of patient-centered medical homes for pain patients.
- This question does focus on important vulnerable populations. Vulnerable populations should include patients with low health literacy.
- The study may not be feasible as these options may not be covered by insurance.

Question 1.6 Cognitive behavioral therapy
a. Population: *Patient with chronic non-cancer pain >3 months without achievement of functional goals*
b. Option 1: *Individual cognitive behavior therapy (CBT) directed by primary care clinic–based counselor (e.g., case manager trained in a pain management program—consider a refinement of the general CBT model such as the Acceptance and Commitment Therapy (ACT) 1) provided in-person counseling biweekly alternating with phone call updates—supplemented by education/practice with meditation and stress management techniques in group therapy programs. Case manager collaborates closely with the primary care physician in developing a drug treatment program plan and encouraging adherence*
c. Option 2: *Patient referred to a psychologist for CBT with informational support for meditation and stress management approaches*
d. *In both arms patients are provided educational materials informing them that opioids are only one component of a pain treatment program that requires other nondrug approaches to improve function.*
e*. Similar to outcomes above but focus on empowerment, satisfaction, mental health conditions (e.g., PHQ9)*

Although the panel considered this an important research question, it is unclear how this study would add to research studies currently under way.

Comments included:

- Engaging patients in non-pharmaceutical approaches is a significant barrier.
- Cultural acceptance is a concern with cognitive behavioral therapy.
- Cognitive behavioral therapy requires high-caliber counselors for successful implementation, which may limit adoption due to cost barriers.
- The scope of the research could be broadened to include group therapy focused on patient education.

Question 1.7 What is the benefit of chronic opioid treatment (COT) compared to self-care management for patients with chronic pain for whom primary care providers are considering initiating COT? Using a 2x2 factorial design would allow one to examine both of these as individual modalities a well as their combination with usual care.

Overall, the panel was unclear what the comparators would be for this research question as components of self-care management are an aspect of usual care.

Comments included:

- Self-care management needs to be defined as some components are included as standard of care.

- Education interventions (e.g., app, cognitive therapy) should be included as a comparator.
- Physician education regarding pain management should also be included.

Question 1.8 For patients with chronic pain already established on opioid therapy, are more intensive specialty-based interdisciplinary services superior for reducing patients' reliance on opioids and facilitating improvements in functioning/QOL when compared with evidence-based multimodal services that can be feasibly delivered in closer connection with primary care clinics/clinicians?

The panel questioned whether this was feasible to expand across the country due to a potential workforce shortage of pain specialists and lack of relevant payment mechanisms.

Comments included:

- This research question is not feasible due to the potential lack of patient access to specialty-based services. Additionally, there is a potential shortage of pain specialists.
- One panelist suggested considering web-based approaches to help overcome access barriers.
- Technology-based, non-pharmaceutical approaches (e.g., spinal cord stimulation) should also be considered.

Category 2: Risk Assessment and Risk Mitigation Strategies – High-level question: In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of various instruments in predicting the risk for opioid overdose, addiction, abuse, or misuse?

Question 2.1 What are the benefits and risks of assessing adults with chronic pain syndromes for coexisting behavioral health disorders and substance abuse disorders before initiating long-term opioid treatment versus not assessing for those disorders?

Overall, it was unclear to the panel whether this research question has already been addressed in previous research. Additionally, there was disagreement among the participants as to the established efficacy of risk assessment tools.

Comments included:

- Assessment for coexisting behavioral health disorders and substance use disorders before initiating long-term opioid treatment is becoming the standard of care in most states. Additionally, publications in the *Journal of Pain* address this research question.
- It may be beneficial to consider genetic risk factors as well.
- Risk seems to be defined in this question as risk of overdose, addiction, abuse, and misuse. The scope of the research should be broadened to include depression, stigmatization, alcohol abuse, and side effects (e.g., neuropathy, fertility).
- It is unclear whether effective assessment tools are available.

Question 2.2 For patients with chronic non-cancer pain who have been on long-term opioid therapy, what is the comparative effectiveness on outcomes related to overdose, addiction, abuse, or misuse for the following risk mitigation strategies: (1) opioid management plans; (2) patient education; (3) urine drug testing; (4) prescription drug monitoring; (5) monitoring instruments; (6) more frequent monitoring intervals; (7) pill counts; and (8) use of abuse-deterrent formulations?

The panel largely agreed that this question was highly relevant to state and federal legislatures and other regulators and policy makers, and could serve as the basis for a broad risk mitigation strategy question. There were strong cautions

from patient representatives indicating that these strategies can, and often do, go poorly for patients who try to adhere to their care plans.

Comments included:

- Pharmacy lock-in programs (i.e., programs requiring patients on long-term opioid therapy to fill opioid prescriptions at one pharmacy) should be considered.
- It is important to consider the patient perspective when considering risk mitigation strategies as some may be offensive and stigmatizing to patients. It is also important to consider the feasibility of the strategies outlined in this research question.
- Although there is a lack of data on abuse-deterrent formulations, payers are interested in this risk mitigation strategy.

The panel concluded that this research question should be the basis for a more inclusive subtopic on risk management and mitigation approaches.

Question 2.3 Compared with other medications for various illnesses, through DNA testing can people be identified as those who will or will not respond to opioid pain relievers? The intended outcome: Identify patients who will benefit from opioid therapies, which will diminish the possibility of prescribing these drugs for people who will not benefit, decrease addiction and overdose complications, and protect healthcare providers who treat chronic pain patients.

The panel agreed that the National Institute on Drug Abuse (NIDA) has active research in this area in its portfolio. It was also determined that the state of the science may be too developmental for definitive CER studies at this time.

Question 2.4 What are the comparative benefits and risks of pain versus no pain contracts for individuals with chronic pain who are utilizing chronic opioids?

The panel considered this to be a potentially important question; however, many states already mandate the use of patient-provider agreements. Although pain agreements are currently in use, more data is needed to demonstrate effectiveness. Therefore, comparison between existing approaches is likely to be of some benefit to policy makers, clinicians, and patients. The panel also agreed that agreements must be truly bidirectional, with physicians demonstrating what they will do when a patient presents with pain exacerbation.

Category 3: Other – High-level question: What is the comparative effectiveness of treatment strategies for managing patients with an addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and QOL?

Question 3.1 How effective is the use of technology in community-based transition programs for youths and young adults (ages 15–25) in managing chronic pain and mitigating the risk of opioid dependence compared with traditional transition programs?

The panel was unclear if the definition of transitions in this research question referred to pediatrics-to-adult medicine transition or a residential setting-to-home transition. The panel agreed that a health systems component was missing from this research question.

Comments included:

- It is unclear whether residential treatment centers are effective.

- The research question should include an educational component and a health systems aspect.

Stakeholders were encouraged to comment on the feasibility and implications of each research question, and the research question language evolved accordingly.

Afternoon Session

During the workshop's afternoon session, results from the morning prioritization session were shared. For each priority question, participants were asked to refine the research question and identify the (1) patient population; (2) intervention; (3) comparators; (4) outcomes of interest; (5) time frame; (6) setting; and (7) study design. Only the top three ranked questions were discussed:

Priority Question 1 (modified after discussion): In patients with chronic pain, what is the comparative effectiveness and risks of opioids with patient monitoring and education versus opioids plus non-opioid therapy (including pharmacologic and non-pharmacologic options) versus non-opioids alone on outcomes related to pain, function, quality of life, and doses of opioids used?

> **Patient population:** Patients with pain lasting longer than three months or past the time of normal healing
> **Intervention:** Opioid therapy with patient monitoring and education; non-opioid therapy including pharmacologic and non-pharmacologic options
> **Comparators:** Opioid therapy with patient monitoring and education versus opioid plus non-opioid therapy (including pharmacologic and non-pharmacologic options) versus non-opioid therapy alone
> **Outcomes of interest:** Reduction in opioid dose; six-minute walk test; sleep quality; quality of life; healthcare utilization; mood; daily function; opioid misuse; patient-reported pain; patient satisfaction; patient self-efficacy; promise measures; patient engagement in treatment
> **Time frame:** Three-year study
> **Setting:** Outpatient; community-based settings (e.g., home, gym, community centers, library, church); assisted living facilities; academic medical centers
> **Study design:** Observational studies; randomized controlled trial; design should include a sustainability component

Priority Question 2 (modified after discussion): For patients with chronic pain who have been on long-term opioid therapy or who are initiating opioid therapy, what is the comparative effectiveness on outcomes related to overdose, addiction, abuse, or misuse for the following risk mitigation strategies: (1) opioid management plans; (2) patient education; (3) monitoring instruments (e.g., opioid screening tools, pill counts, urine drug testing, and state prescription drug monitoring); (4) more frequent monitoring intervals; (5) use of abuse-deterrent formulations; (6) patient agreements; (7) pharmacy lock-in; (8) safe disposal; (9) rescue drugs (e.g., naloxone); and (10) screening for co-morbidities at risk for adverse events?

> **Patient population:** Chronic pain patients (pain lasting longer than three months or past the time of normal healing) currently on or starting opioid therapy; chronic pain syndrome patients
> **Intervention:** Opioid management plans; patient education; monitoring instruments (e.g., opioid screening tools, pill counts, urine drug testing, state prescription drug monitoring); frequent monitoring intervals; abuse-deterrent formulations; patient agreements; pharmacy lock-in; safe disposal; rescue drug (e.g., naloxone); screening for co-morbidities at risk for adverse events; DNA testing
> **Comparators:** Pharmacologic risk mitigation strategies (e.g., abuse-deterrent formulations) versus opioid

compliance risk mitigation strategies
Outcomes of interest: Patient-reported pain; overdose; addiction; abuse; misuse; reduction in opioid dose; six-minute walk test; sleep quality; quality of life; healthcare utilization; mood; daily function; patient satisfaction; patient self-efficacy; promise measures; patient engagement in treatment; stigmatization; utilization of other central nervous system (CNS) depressants; improvement of provider-patient relationship; trust
Time frame: Three-year study
Setting: Outpatient; emergency department; assisted living facilities
Study design: Observational studies; randomized controlled trial; should consider wait-list control

Priority Question 3 (modified after discussion): What are the benefits and risks of assessing and/or treating adults, adolescents, and children with chronic pain syndromes for coexisting behavioral health disorders, mental health disorders, and/or substance use disorders on pain management before initiating or during opioid treatment versus not assessing for those disorders?

Patient population: Adults, adolescents, and children with chronic pain syndromes
Outcomes of interest: Reduction in opioid dose; six-minute walk test; sleep quality; quality of life; healthcare utilization; mood; daily function; opioid misuse; patient-reported pain; patient satisfaction; patient self-efficacy; PROMIS measures; patient engagement in treatment

The panelists concluded that Priority Question 3 should be included as a subgroup analysis for Priority Question 1. Therefore, the potential interventions, comparators, time frame, setting, and study design were not discussed.

Moving Forward

The workshop provided an opportunity for key questions to be discussed and refined by a diverse range of stakeholders. There was a significant amount of deliberation and conversation surrounding each research question presented. Building on these stakeholder efforts, PCORI staff further refined and modified two draft research questions in consultation with the Scientific Oversight Committee members. Results will be presented at the August 18, 2015, Board of Governor's meeting to pursue the development of funding opportunities in this area.