Prioritizing Comparative Effectiveness Research Questions for the Long-Term Use of Opioids for Chronic Pain: A Stakeholder Workshop on Pharmacologic Treatment Options and Dosing Strategies 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 focusing on the use of long-term opioid therapy for chronic pain that would address current gaps in knowledge. Colorado Medicaid’s Chief Medical Officer and Client, Clinical Care Office, Judy Zerzan, MD, MPH, 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 pharmacologic treatment options and dosing strategies.

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: Pharmacologic Treatment Options** – High-level question: In patients with chronic pain, what is the comparative effectiveness of opioids versus non-opioid medications or compared with other opioids on outcomes related to pain, function, quality of life, fractures, endocrine dysfunction, abuse, overdose, and death?

**Question 1.1.** For patients with chronic pain, what are the comparative benefits and harms of the following analgesic combination regimens: (1) non-opioid analgesics (no opioids) versus (2) non-opioid analgesics with limited, as-needed low-dose opioids versus (3) non-opioid analgesics with daily opioid analgesics (up to 100 morphine-equivalent mg per day)? This study design should include flexible drug and dosing options within defined parameters for each arm and treatment-to-response targets (rather than fixed dose/drug targets).

Comments included:
- The panel agreed that this is an important question. There was much discussion within the group about what constitutes “higher-dose” versus “lower-dose” prescribing.
- The panel discussed whether underlying conditions, subpopulations, and type of pain should be defined within the question.
- Some within the group expressed that it’s important to understand the subpopulation being studied, but general consensus was that this should be left up to applicants to define.

**Question 1.2.** What is the long-term benefit/risk profile of opioids (stratified by whether the drug is immediate- or extended-release and by low versus high dose in morphine equivalents) compared with prescription NSAIDS, COX-II inhibitors, and acetaminophen, when used for >90 days to treat chronic non-cancer pain? This would require evaluation of a broad range of outcomes including pain, functional status, quality of life, adverse events relevant to these drugs, abuse, overdose, death, and others pertinent to a full benefit-risk assessment.

There was consensus among the panel that this is an important question, but many in the room felt there was substantial overlap between question 1.1 and question 1.2. The panel recommended that questions 1.1 and 1.2 be merged.

Comments included:
- Multimodal analgesia is widely accepted in the acute pain literature, but it is less studied in chronic pain. It would be beneficial to study this in a structured fashion.
- It was noted that pain is defined specifically as “non-cancer pain” in this question, and that what constitutes “cancer pain” needs to be defined.

**Question 1.3.** For patients with chronic pain, what are the benefits and harms of tramadol versus typical immediate-release opioid analgesics?

There was general consensus among panelists that this question is too narrow and should be dropped.

Comments included:
- Comparison of tramadol versus something stronger was noted as potentially useful.
- One panelist noted that this question is somewhat interesting as there is clinical debate about whether tramadol should be treated more like an opioid or a non-opioid.
- Another panelist added that this is an important question to those interested in addiction as tramadol was
marketed as nonaddictive but is widely abused worldwide. Accordingly, tramadol was recently rescheduled as a Class 4 narcotic (previously Class 5).

- One panelist noted that the more relevant question is opioid versus non-opioid analgesia, not opioid versus opioid.
- A broader multimodal pharmacologic treatment question may be more relevant as multimodal drug therapy also includes other classes of drugs (e.g., antidepressants, muscle relaxants, etc.).

**Question 1.4. What is the comparative effectiveness of opioid analgesics versus transdermal medication therapy for individuals with chronic pain?**

There was consensus among the panel that this question is too narrow and should be dropped, especially as various formulations could be compared within combined question 1.1 and 1.2.

Comments included:
- One panelist noted that transdermal formulations were thought to be more abuse-deterrent. However, there have been cases in which patients who are addicted to narcotics were able to squeeze liquid out of the transdermal patch and smoke it.
- Another panelist noted that patients who are switching from oral opioids to other formulations (e.g., transdermal patches) need to be educated on how these new formulations work.
- The panel suggested that patient education be added as an outcome to combined question 1.1 and 1.2.

**Question 1.5. What are the comparative benefits and risks of using non-pharmacological modalities and non-opioid analgesics versus closely monitored long-term opioid analgesics in chronic pain patients with a history of substance abuse and addiction disorder? Outcome measures include quality-of-life indices (better mobility, sleep, mood, function) and decreased incidence of relapse.**

There was consensus among the panel that this is an important question and subpopulation to study.

Comments included:
- Providers are often hesitant to prescribe opioids to those with a history of substance use disorder. Perceived addiction is also a barrier to prescribing.
- Evaluating multimodal treatment approaches that include both pharmacologic and non-pharmacologic options is extremely important from a patient perspective. If non-pharmacologic options are found to be effective, this may help to inform payment policy as many non-pharmacologic options are currently not covered by payers.

**Category 2: Dosing Strategies** – High-level question: In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?

**Question 2.1. In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?**

Although the panel considered this to be a very important research question that could fill a significant evidence gap, there was concern that it would be quite challenging to study.

Comments included:
The many barriers to the feasibility of studying this question include the ethical and legal issues related to managing withdrawal and the difficulty in getting patients to agree to randomization. In clinical practice, providers tend not to reduce opioid dosing if a patient is doing well. If a study were able to show that tapering yielded beneficial results, this could change clinical practice. The FDA is now requiring post-marketing surveillance studies to assess the effects of long-term opioid use at a steady dose versus tapering. Resulting data may help to answer this question.

**Question 2.2. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids or sustained-release formulations on outcomes related to pain, function, quality of life, risk of overdose, addiction, abuse, misuse, or doses of opioid used?**

There was general consensus among the panel that this is an important question.

Comments included:
- Answering this question has the potential to change clinical practice as providers need to know which opioids work best and for whom.
- One panelist noted that it would be helpful to compare single opioid formulations versus combined opioid/non-opioid formulations (e.g., acetaminophen + opioid drugs) as addiction profiles are different.

**Question 2.3. For patients with chronic non-cancer pain who have been on long-term opioid therapy, what is the comparative effectiveness of rotation to buprenorphine/naloxone and to methadone for outcomes of pain, function, misuse, overdose, and addiction?**

The panel did not reach consensus on whether including methadone as a comparator would be beneficial, but it concurred that studying treatment options for those with substance use disorders is important.

Comments included:
- There was a divergence in opinions within the group about whether a study that includes methadone as a comparator is needed at this time.
- There was a divergence of opinions in group regarding whether this question should be combined with the previous question looking at treatment options for individuals with a history of substance use disorders.
- One panelist noted that specialists receive referrals from primary care clinicians with patients who are having trouble with opioid misuse and often rotate these patients to buprenorphine.

**Question 2.4. For patients with persistent chronic pain who are currently treated with opioids at ≥50 morphine-equivalent mg per day, what are the benefits and harms of opioid rotation with stable or increased dose versus opioid rotation with dose reduction or tapering to discontinuation? To mirror the realities of clinical practice and allow for individual patient differences in medication tolerance and efficacy, this study design should include protocols for co-treatment with non-opioid analgesics and flexibility in drug/dose options within defined parameters for each arm.**

There was general consensus among the panel that when to rotate a patient to a different opioid is an important question, particularly within the primary care setting.

Comments included:
- This is an important question as clinicians must balance potential risks of increasing opioid dose versus rotating to another opioid.
• Defining parameters of question (e.g., among patients who are developing a tolerance at their current dose of opioid) is important.
• There was general consensus that defining a dose of >50 morphine-equivalent mg per day is arbitrary and should be removed.

Question 2.5. Do people with chronic pain require escalation of opioid dosing over time when these medications are taken for a year or longer, compared with short-term use of opioids for less than one year? The intended outcome: If chronic pain patients can utilize opioid medications without escalating dosage amounts over time, then these drugs could be prescribed with less concern and be construed as appropriate medications in the treatment of chronic pain by healthcare professionals.

Consensus was reached within the panel that tolerance is important to consider, but that this question is largely captured within question 2.1.

Comments included:
• Understanding the transition between acute and chronic pain is important.
• The literature currently doesn’t tell us much about which patients are likely to develop tolerance and when. This is an evidence gap.
• Two emerging themes develop within the question: (1) How to handle treatment for those who develop tolerance to opioids; and (2) how to handle the long-term treatment of patients with opioid therapy.

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 quality of life? Potential populations may include those with a history of substance use disorders, pregnant women, those recently incarcerated, etc.

Question 3.1. What is the comparative effectiveness of treatment strategies to reduce the overprescribing of opiates (including Prescription Drug Monitoring Programs) in the Medicaid population?

There was general consensus among the panel that this is an interesting and potentially important question, but that it is relevant to all populations, not just those covered by Medicaid.

Comments included:
• While there is great variation in prescribing within clinical practice and no consensus on what constitutes overprescribing within the clinical community, there is certainly consensus that opioids are overprescribed. In addition, there are definitions of overprescribing set within policy (e.g., Office of Inspector General definition), but the criteria included within these definitions are a bit arbitrary.
• It may be easier to focus on “high-risk” prescribing rather than overprescribing.
• The focus on provider behavior makes this question interesting, but it may be very difficult to study as teasing out what drives prescribing behavior will likely present quite a challenge.
• It would be interesting to look at prescribing patterns across payers (e.g., Medicaid versus private coverage).
• It is important to include both overprescribing and underprescribing. Broaden the question to look at prescribing patterns by patient population.
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. Participants were asked to refine the research questions and identify the (1) patient population; (2) intervention; (3) comparators; (4) outcomes of interest; (5) time frame; (6) setting; and (7) study design for each priority question. Only the top four ranked questions were discussed:

**Priority Question 1 (modified after discussion):** Among people with a history of substance use disorder (SUD) or at risk of developing a SUD, what are the comparative benefits and risks of prescribing an opioid (with or without non-pharmacological co-intervention) versus a nontraditional opioid (e.g., buprenorphine/naloxone) (with or without non-pharmacological co-intervention)?

- **Patient population:** Patients with chronic pain (lasting greater than three months) with a history of substance abuse disorder or at risk of developing opioid use disorder
- **Intervention:** Non-opioid plus non-pharmacological option; opioid with or without non-pharmacological option
- **Comparators:** Opioid (with or without non-opioid and/or non-pharmacological option) versus nontraditional opioid (e.g., buprenorphine/naloxone) with or without non-pharmacological option
- **Outcomes of interest:** Pain; development of substance abuse disorder; time to development of substance abuse disorder; mobility; sleep; mood; function
- **Time frame:** Long-term measures of at least one year
- **Setting:** Primary care; pain clinics; substance abuse clinics
- **Study design:** No discussion

**Priority Question 2 (modified after discussion):** For patients with chronic pain not currently prescribed long-term opioid therapy/patients who are not opioid tolerant, what are the comparative benefits and harms of the following analgesic combinations: (1) non-opioid analgesics; (2) non-opioid analgesics with low-dose opioids; and (3) non-opioid analgesics with higher-dose opioid analgesics?

- **Patient population:** Patients with chronic pain (lasting greater than three months) not currently prescribed long-term opioid therapy (not opioid tolerant); patients should be stratified by neuropathic/non-neuropathic/combination; investigators to specify exact population to be studied; one population of interest is pregnant women/women of reproductive age
- **Intervention:** Many possibilities include high-dose opioid (to be defined by Principal Investigator or as secondary analysis); low-dose opioid; short-acting opioid; long-acting opioid; abuse-deterrent/non-abuse-deterrent opioids; non-opioid analgesic; non-pharmacologic option (e.g., psychosocial intervention); multimodal combinations (including other classes of drugs, e.g., antidepressants, muscle relaxants)
- **Comparators:** Comparisons of two or more of the interventions mentioned above
- **Outcomes of interest:** Ability to work; validated patient-related outcomes to include quality of life, functional status, and clinician-/team-reported metrics; adverse events and side effects
- **Time frame:** Long-term measures of at least one year with built-in interim analyses
- **Setting:** Primary care; pain clinics
- **Study design:** Retrospective observational data analysis may be useful, especially for adverse consequences at a
high level (text analysis); prospective study for patient-related outcomes and more nuanced adverse event data; observational cohort study may be more feasible/cost-efficient than randomized controlled trial (RCT); RCTs needed to show benefits

Priority Question 3: Among patients on long-term opioid therapy whose pain is not currently well controlled, what are the relative benefits and risks of tapering their opioid doses versus continuing patients on their current dose?

**Patient population:** Patients with chronic pain (lasting greater than three months) whose pain is not well controlled; patients who are opioid-tolerant; one population of interest is adolescents

**Intervention:** Continuing on current prescription at current dose; decreasing dose by specified increment (with or without the addition of co-intervention—pharmacologic or non-pharmacologic; switching to a new drug

**Comparators:** Comparison of two or more of interventions described above

**Outcomes of interest:** Risks such as withdrawal symptoms, mental health outcomes including suicidal ideation and suicide attempt; quality of life; functional status; pain control; development of tolerance; time to tolerance; balancing lowest dose with lowest pain

**Time frame:** Short-term and long-term, including time to increase in dose

**Setting:** Primary care; pain clinics; specialty care

**Study design:** Recruitment and retention challenges expected; mixed methods will be important

Priority Question 4: Among patients with chronic pain currently prescribed short-acting opioid therapy, what is the comparative effectiveness of the following analgesics: (1) continuing short-acting opioids; (2) transitioning to long-acting opioids; and (3) transitioning to a combined regimen of short- and long-acting opioids?

**Patient population:** Patients with chronic pain (lasting greater than three months) already on short-acting opioid transitioning to long-acting or vice versa; may need an opioid-naïve arm; populations of interest include pregnant women, women of childbearing age, and children

**Intervention:** Short-acting opioid transitioning to long-acting or vice versa; combined long-/short-acting; combination opioid/NSAID drug; should consider all formulations (oral, transdermal, sublingual, etc.) and scheduled versus unscheduled dosing

**Comparators:** Comparison of two or more of interventions described above

**Outcomes of interest:** Pain; function; quality of life; risk of overdose; addiction; abuse; misuse; doses of opioid used; ability to drive/operate heavy machinery; rates of development of tolerance; cognitive ability

**Time frame:** Long-term measures of at least one year

**Setting:** Primary care; pain clinics; specialty care

**Study design:** Potential to use crossover design for this study

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.