Long-term Use of Opioids for Chronic Pain:
Questions submitted for consideration by workshop participants

Prioritizing Comparative Effectiveness Research Questions:
PCORI Stakeholder Workshops

June 9, 2015
1. For patients with chronic non-cancer pain, who have been on long-term opioid therapy, what are the comparative effectiveness of rotation to buprenorphine/naloxone and to methadone for outcomes of pain, function, misuse, overdose and addiction?

2. For patients with chronic non-cancer pain, what are the comparative effectiveness of long-acting opioids with synthetic cannabinoids / medical marijuana for outcomes of pain, function, sleep, mood and quality of life?

3. For patients with chronic non-cancer pain, who have been on long-term opioid therapy, what are the comparative effectiveness of regular versus random urine drug screenings for outcomes of misuse, overdose and addiction?

4. More research is needed to elucidate physician factors associated with opioid prescribing, especially for chronic non-cancer pain. Variables to be considered include setting, specialty, age, gender, likelihood to access prescription drug monitoring programs, likelihood to assess urine toxicology, time of day when prescribing, resident vs attending, etc. Understanding how health care provider factors influence opioid prescribing will inform future targeted interventions including education and policy.

5. More research is needed to understand how doctors are responding to patients misusing or addicted to prescription opioids. Anecdotally, doctors currently respond in a number of different ways: Doing nothing and continuing to prescribe as usual, firing the patient for breaking the pain contract, referring the patient to a pain or addiction specialist, etc. Identifying how physicians respond to these patients, and examining how their responses affect patient outcomes (does firing a patient lead to heroin use?) is essential for creating best practices.

6. More research is needed on how to support and foster a mutually positive and enduring doctor-patient relationship during opioid taper/discontinuation, which is an emotionally stressful endeavor for both patients and their doctors. Examples of support to be studied might include an interdisciplinary team approach, a weekly phone call with an expert for the prescribing doctor to talk through difficult cases, a group education/psychosocial intervention for patients going through the detoxification process, etc. This research would help us learn which forms of health care delivery lead to better outcomes not just for patients (pain, quality of life, function), but also for doctors (quality of professional life and professional function) and the doctor-patient relationship (trust, affection, loyalty, compliance, patient satisfaction).

7. How effective is long term opioid therapy for chronic back pain? Should quality of life measures be included before and after commencement of long term opioid therapy?

8. Will responsible opioid prescription of opioids for pain decrease the incidence of opioid related mortality in USA? If not, then what other measures need to be undertaken? Should opioid prescriptions (schedule II) be restricted to physicians only?

9. What the other hormonal and endocrine effects of long term opioids therapy and how often should laboratory investigations be carried out to detect and treat them?
10. What are the long-term benefits of using opioids (as part of a treatment plan) for people living with chronic pain?

11. What percentage of low income and people of color are included in these studies?

12. Long term clinical study of chronic pain, diagnosed using standardized assessments for pain and function, utilizing opioid therapy as per guidelines, that is, after treatment failure or inability to tolerate first-line agents. Consider establishing large Registry type study, such as the NIH-sponsored DCCT/EDIC for Diabetes (http://diabetes.niddk.nih.gov/dm/pubs/control/DCCT-EDIC_508.pdf) or the ACC National Cardiovascular Data Registry (http://cvquality.acc.org/NCDR-Home.aspx), which have provided crucial information on therapy and prevention of disease and therapy complications. Different pain conditions and pathophysiology might be examined in sub-registries.

13. Establish valid opioid dose conversion tables and dose escalation and tapering guidelines. Current conversion data is based mostly on cancer or post-operative pain patients in the 1960’s with single dose regimens. In light of the increasing importance of opioid rotation as a strategy to limit dose, recognition of the potential safety implications of dose alterations and of conversion between opioids, and in order to promote trials of opioid withdrawal during therapy, this basic information is clinically relevant.

14. Observational study of efficacy of implementation of “Universal Precautions” practices in opioid prescribing. Recommended prescribing practices, including risk assessment, treatment agreements, accessing the PDMP (Prescription Drug Monitoring Program), dose reduction strategies and routine urine drug testing can seem overwhelming to the busy primary care practitioner. A study demonstrating the effectiveness of these practices in decreasing the known complications of opioid therapy in patients who are candidates for opioid therapy based on clinical presentation and pain pathophysiology (see 1 above) could provide the required evidence.

15. For patients with chronic back pain, what are the comparative benefits and harms of the following analgesic combination regimens: 1) non-opioid analgesics (no opioids) vs. 2) non-opioid analgesics with limited as needed low-dose opioids vs. 3) non-opioid analgesics with daily opioid analgesics (up to 100 morphine-equivalent mg per day)?

16. 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).”

17. For patients with persistent moderate-severe musculoskeletal 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 vs. opioid rotation with dose reduction or tapering to discontinuation?

18. To mirror 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."

19. For patients with chronic back pain, what are the benefits and harms of tramadol vs. typical immediate-release opioid analgesics?
20. There is evidence that cognitive behavioral therapy (CBT) can be efficacious in treating chronic pain. Does a co-administered opioid prescription facilitate, inhibit or have no effect on the effects of CBT for pain.

21. There is evidence that there is a correlation between overdose risk and dosage in chronic opioid treatment of chronic pain. However, it is unknown whether in these patients there is a parallel increase in efficacy (with regard to pain, mood and function) as dosage escalates. Is there a change in the risk/benefit ratio with increasing opioid doses prescribed for chronic pain?

22. Is there a difference in efficacy or safety in opioids prescribed for chronic pain by prescribers who check a state Prescription drug monitoring program BEFORE prescribing?

23. Comparing chronic pain patient opioid treatment protocols with other treatment modalities which groups of patients derive the greatest benefit and least harm from long term use of opioids?

   Intended outcome: A measure of harm vs benefit (functional status, pain, absenteeism/presentism for work for patients) with chronic pain receiving either long-term opioid treatment or other treatment modalities.

24. In the treatment of chronic pain as opposed to acute pain conditions, what are the main objectives and measurements that need to be included in the development of a risk assessment for prescribing opioids for potential drug addiction issues?

   Intended outcome: By utilizing an opioid addiction risk assessment tool developed for chronic pain patients, a measurement of reducing opioid addiction and abuse in the chronic pain patient community would be obtained.

25. Who are the patients with chronic pain who derive the greatest benefit and least harm from long term use of opioids? Patients with chronic pain are the target, outcome would be a measure of functional status, pain, absenteeism/presentism for work. Are there unintended consequences for people with chronic pain being denied opioid prescriptions, including escalating suicidal ideation due to denial of prescriptions by healthcare professionals and/or by pharmacies refusing to fill opioid prescriptions compared to opioid prescribing habits prior to changes in prescribing regulations meant to curb addiction and overdose deaths in the general public?

   Intended outcome: Identify the unintended consequences of chronic pain patients being denied opioid medications which will help healthcare systems and government agencies take responsibility for developing programs that allow chronic pain patients to continue using opioid medications (or lead patients through the correct procedures for addressing withdrawal symptoms) and reduce the possibility of suicidal ideation caused by escalated pain and sickness.

26. What are the comparative benefits and risks of opioid pain management versus non-opioid pain management (i.e. non-opioid medication, multimodal, and/or regional interventional approaches) for adults with chronic pain and serious life-limiting disease (such as stage III or IV cancer, advanced organ failure, or advanced neurologic, HIV or sickle cell disease)?
27. What are the comparative benefits and risks of opioid pain management with specialty-level interdisciplinary palliative care versus opioid management without specialty-level interdisciplinary palliative care for adults with chronic pain and serious life-limiting illness (such as stage III or IV cancer, advanced organ failure, or advanced neurologic, HIV or sickle cell disease)?

28. What are the comparative benefits and risks of sustained release opioid formulations in people with cancer/cancer survivors?

29. What are the comparative benefits and risks (e.g., pain, function, QOL, substance misuse, fractures, endocrine dysfunction) of chronic opioid use (>1 year) in people with cancer/cancer survivors?

30. Which risk assessment instruments are most predictive in determining potential for opioid abuse or misuse in people with cancer?

31. What are the comparative benefits and risks of the use of agreements (also called “opioid contracts”) when managing pain in the person with cancer?

32. What is the long-term benefit:risk profile of opioids (stratified by whether the drug is immediate- or extended-release and by low vs. high dose in morphine equivalents) compared to 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.

33. What is the impact of parallel vs. 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?

34. What is the impact of common medical and psychological comorbidities on treatment success and chronic pain progression (outcomes to include pain score, quality of life measures, hormones, and biomarkers) in chronic non-cancer pain patients taking opioids long-term (>90 days)?

35. Does integrated psychological therapy for chronic pain patients, to effectively cope with the challenges of living with chronic pain, have a positive effect on long term opioid use levels? Positive study results would increase awareness of the need for integrated psychological therapy and reduce the stigma many patients can feel regarding psychological therapy.

36. Can chronic pain patient efficacy and involvement as part of their own chronic pain care team lead to reductions over time of opioid use levels and improvements to quality of life? Positive study results could have an impact for physician impetus to share and effectively communicate chronic pain care details with the patient and make the patient take a more responsible role in their own treatment.

37. Is research current and/or expected regarding use of antagonists (e.g. Naltrexone, Naloxone, and Buprenorphine) for chronic pain therapy to reduce the negative effects that agonist opioids produce? As an example, Suboxone is now used on a very limited basis for chronic pain relief. Follow-up question: Are
there any new non-opioid, off-label medications used for the treatment of chronic pain? Existing example: Neurontin (first released as a psychotropic) is one effective non-opioid medication used in the treatment of chronic neuropathy and pain caused by nerve damage. Benefits to the chronic pain community would be some elimination of opioid use and thereby alleviating known problems associate with long term opioid use.

38. 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 QOL indices (better mobility, sleep, mood, function), and decreased incidence of relapse.

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

40. 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.

41. Are opioid medications effective in the treatment of chronic pain conditions as measured against other chronic pain treatment modalities, including other types of medications and integrative medicine techniques?

   Intended outcome: If findings from a placebo controlled, double blind research study indicate that these drugs are effective in treating chronic pain by decreasing pain symptoms enough to increase productivity and function, decrease employment absenteeism, and allow patients a better quality of life then prescribing these drugs for chronic pain conditions can be prescribed with confidence by healthcare providers."

42. Compared with other medications for various illnesses, through DNA testing can people be identified who will or won’t respond to opioid pain relievers?

   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.

43. Do people with chronic pain require escalation of opioid dosing over time when these medications are taken for a year or longer compared to short term use of opioids for less than one year?
Intended outcome: Indicate 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."

44. What are the comparative risk and benefits of long term opioid use for the treatment of adults with chronic low back pain/fibromyalgia compared to NSAIDS, antidepressants and muscle relaxants?

45. What are the comparative benefits and risks of long term opioid use for the treatment of adults with fibromyalgia compared to antidepressants and muscle relaxants?

46. What are the comparative benefits and risks of long term opioid use for the treatment of adults with neuropathic pain syndromes compared to antidepressants, anticonvulsants and topical agents?

47. 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?

48. In patients with chronic pain, what is the comparative effectiveness of opioids versus non opioid therapies on outcomes related to pain, function and quality of life, abuse, overdose, death, potential patient populations include: chronic low back pain, fibromyalgia, cancer survivors. Nonopioid therapies could include: NSAIDS, Cox-II inhibitors, antidepressants, muscle relaxants, and synthetic cannabinoids / medical marijuana

49. Subgroup Analysis: How do harms vary depending on 1) type of pain, patient demographics, 3) patient comorbidities (including past or current substance abuse 4) Dose of opioids

50. 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

51. 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

52. In patients with chronic pain, what is the comparative effectiveness of opioids plus non-opioid interventions (including nonpharmacological options) versus opioids or non-opioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used? Patient populations may include those with chronic low back pain, musculoskeletal pain, cancer patients, substance abusers etc.

53. In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of various instruments in predicting risk for opioid overdose, addiction, abuse, or misuse

54. Improving long-term function and pain in opioid-using persons with chronic pain
a. Population: Patients with chronic non-cancer musculoskeletal pain. (3+ months) prescribed >1 month opioid therapy (consider a minimum dose such as >20 morphine equivalent)

b. Option 1: Non-pharmacologic, evidence-based interventions (stretching/massage group education) in primary care clinic with case management to facilitate and promote engagement and long-term maintenance of activities at home

c. Option 2: Similar curriculum/support offered by a community-based organizations several times weekly such as the YMCA. This program must be at no or low cost. Peer coach support to encourage engagement and 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 (PHQ9, anxiety), pain (10 pt scale), change in dose of opioid repeated measures at 3,6, 12 mos

e. Study must involve a multidisciplinary team (primary care, pain specialty, PT, kinesiology, psychology/psychiatry) to insure that the interventions offer high levels of motivation and patient self-management education while coordinating closely with the primary care provider.

55. 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 EMR support package and case management to offer support and insure high quality care. The EMR must offer tools to evaluate risk of OAs (ORT) and monitor of total opioid dose/daily dose as well as concurrent treatment with potentially risky drugs such as psychotherapeutics (e.g. benzodiazepines, hypnotics), antidepressants. EMR prompts about consideration of complementary lower risk alternatives (e.g., topical therapies) and generates reminders for urine drug screening at intervals based on ORT. The EMR offers ready connection to state prescription monitoring programs (obtained by staff at each visit) well as monitors the frequency of requests for refills and visits. Patients complete an opioid agreement that includes expectations to pursue agreed upon non-drug therapies and clinician agreement to refill agreed upon opioid treatment based on assessment of patient functional goals. Physicians receive education about use of EMR to monitor/guide opioid and other pain therapies. Case managers educate about stretching and other non-drug alternative management strategies plus educational materials to give patients.

c. Option 2: low opioid dose therapy and referral to a practice-based pain champion – MD, PA, RN – who has received advanced training in an evidence based pain management program. Patient visits the clinic specialist at least every 6 months (to supplement care from a primary care physician). This arm offers basic EMR support (ORT, OA agreement)
d. Both arms offer collaborative care with appropriate specialists (PT, pain experts).

e. Outcomes: Opioid dose, functional measures (6 min speed walk, 50ft speed walk, 5x sit to stand), mental health (PHQ 9) / mental functioning (symbol digit test) measures, pt satisfaction, measures of opioid misuse (early refill requests, dose escalation)

56. Cognitive behavioral therapy

a. Population: Patient with chronic non-cancer pain >3 months without achievement of functional goals

b. Option 1: individual 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 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 require other nondrug approaches to improve function.

e. Similar to outcomes above but focus on empowerment, satisfaction, mental health conditions (e.g. PHQ9)


58. What is the comparative effectiveness of treatment strategies for managing patients with addition to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, quality of life?

59. What are the comparative benefits and risks of non-opioid medication therapy vs opioid medication therapy for individuals with chronic low back pain?

60. What is the comparative effectiveness of systemic oral medication therapy vs. transdermal medication therapy for individuals with chronic low back pain?

61. What are the comparative benefits and risks of pain contacts vs no pain contract for individuals with chronic low back pain utilizing chronic opiate therapy?
62. The common theme running though the comments we received on the reports on Non-invasive treatment for Low back pain and The long term benefits and safety of opioids for chronic pain (not just low back pain), we offer another question:

63. What is benefit of chronic opioid treatment (COT) compared to supported self-care management for patients with chronic LBP or MSD for whom primary care providers are considering initiating COT? Using a 2x2 factorial design would allow one to examine both theses as individual modalities as well as their combination with a usual care comparison.

64. For patients with chronic LBP/MSD already established on COT, are more intensive specialty-based interdisciplinary services superior for reducing patients’ reliance on opioids and facilitating improvements in functioning/QOL when compared to evidence-based multimodal services that can be feasibly delivered in closer connection with primary care clinics/clinicians?

65. Development of strategies to reduce or prevent opioid misuse in patients with chronic pain.

66. Developing new misuse risk assessment tools in patients with pain that incorporate self-report and genetic profiles

67. Evaluating the utility of abuse deterrent opioid formulations in patients with chronic pain

68. What are the comparative benefits and risk of treating pregnant women with chronic pain with long term use of opioids?

69. What are the comparative benefits and risks of identifying potential abusers in patients treated with long term use of opioids for chronic pain?

70. What are the comparative benefits and risks of outpatient management/care for patients on long term use opioids for chronic pain?

71. What are the comparative benefits and risk of changing drug therapy in patients on long term use of opioids for chronic pain?

72. How effective is the use of technology in community based transition programs for youth and young adults (15-25) in managing chronic pain and mitigating risk of opioid dependence compared to traditional transition programs?

73. It may be interesting to at the use of opioids with SOC vs HU and compare the long-term use against the initiation/duration of HU.

74. What are the comparative risks and benefits of chronic opiate use in the populations of low income people with challenging socioeconomic determinants, rural/frontier, people with functional limitations, recently incarcerated, and pregnant women?
75. What is the safety and effectiveness of treating pregnant women with opiates including methadone or other addiction treatment?

76. What are the most effective strategies to reduce the number of newborns with neonatal abstinence syndrome?

77. What is the comparative effectiveness of strategies to treat opiate addiction, including Medication Assisted Treatment for the Medicaid population and the most cost-effective models for opiate replacement?

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