

Evidence-based Practice Center Technical Brief Protocol

Project Title: *Prevention, Diagnosis, and Management of Opioids, Opioid Misuse and Opioid Use Disorder in Older Adults*

I. Background and Objectives for the Technical Brief

There is a national opioid crisis among older adults; however, media coverage and research has focused almost entirely on younger individuals due to their higher prevalence of misuse.¹⁻³ For adults aged 65 and older, opioid-related hospitalizations increased by 34% and emergency department visits increased by 74% between 2010 and 2015.² Some of this increase is driven by opioid misuse, to which older adults as well younger adults are vulnerable, but some is also driven by the unique challenges of pain management in an aging population.

Opioid misuse is defined as opioid use in any way not directed by a prescriber, including (a) use without a prescription of one's own; (b) use in greater amounts, more often, or longer than told to take a medication, including both opioid use disorder (OUD) and problematic use; or (c) use in any other way that was not directed by a prescriber.⁴ The prevalence of opioid misuse is increasing among older adults (variously defined, but commonly ≥ 65 years old), a population rapidly growing in number that requires many special considerations when using (or misusing) opioids.⁵

Aside from misuse, other important risks of opioids are also particularly pronounced among older adults, even at doses considered therapeutic or appropriate.⁶ Studies have demonstrated an increased rate of falls, fractures, and all-cause mortality associated with opioid use in older adults.⁷⁻¹⁰ Some opioid-related hospitalizations among older adults may actually result from appropriate use of opioids as directed by patients' clinicians. Older adults are often more vulnerable to the adverse effects of opioids and other medications due to alterations in metabolism associated with aging. Older adults thus merit specific attention because they commonly require chronic pain treatment (e.g., for diabetic neuropathy, large joint osteoarthritis, cancer) but have a high prevalence of potential risk factors for harm from opioids, including cognitive impairment, altered hepatic or renal drug metabolism, polypharmacy (resulting in drug-drug interactions), compromised respiration, hypogonadism, osteoporosis, falls with resulting hip or spine fractures, and frailty.¹¹⁻¹⁴ In particular, cognitive decline and dementia may go unrecognized, and could increase the risk for unintentional opioid poisoning or overdose through an unintentional deviation from a prescribed opioid regimen. The risks of harm may also be exacerbated by the high frequency at which older adults see multiple providers and specialists who often do not coordinate their care.^{15,16}

Furthermore, older adults may be predisposed to the transition from acute pain to chronic pain (and to persistence of chronic pain) due to dysfunctional nociceptive processing (i.e., dysfunction in the sensory nervous system's response to certain harmful or potentially harmful stimuli), specifically the impairment of descending inhibitory pain modulation, which is common in this population.^{17,18} Older persons also show enhancement of experimental hyperalgesia and temporal summation of repeated stimuli. These processes, in concert with structural and biochemical changes in the aging nervous system, result in a modest age-related decline in pain

sensitivity to mild noxious stimuli, together with increased vulnerability to severe or persistent pain.¹⁹ Psychological factors are another major contributor to age-related effects upon pain perception and report.^{20,21} Psychological attitudes, such as stoicism and reluctance to confirm the presence of pain, raise the pain threshold in older adults, though once pain is experienced, older adults describe the same severity, quality, and psychological disturbance as younger persons.

Pain control in older adults is, thus, commonly difficult to manage as many older adults are unable to tolerate non-opioid analgesics (e.g., non-steroidal anti-inflammatory drugs) due to impaired liver or kidney function, hypertension,²²⁻²⁴ other cardiac risks,²⁵⁻³¹ concomitant anticoagulant therapy in atrial fibrillation or after stroke, risk of gastrointestinal bleeding,³²⁻³⁵ or others.³⁶ For some, opioids may be the best option, especially since untreated pain has been associated with many negative consequences, including depression, anxiety, falls, functional impairment, slower rehabilitation, decreased socialization, sleep and appetite disturbances, and greater healthcare utilization.³⁷ Appropriate use of opioids under clinicians supervision may provide many older adults with necessary pain relief, allowing them to remain active, independent, engaged in necessary therapy (e.g., rehabilitation or physiotherapy), and able to maintain a higher quality of life. However, it is also important to recognize that some older adults may use opioids recreationally without pain or a medical indication, yet such misuse may go unrecognized due to provider perceptions about how older adults behave and the absence of efforts to screen for such misuse in this population.

II. Overview of the Technical Brief

The Technical Brief will comprise a conceptual framework and an evidence map of the current evidence base in order to understand which issues are driving the current rise in opioid-related morbidity and mortality in older adults, and what evidence is needed to support effective interventions. Ultimately, the framework and evidence map will allow AHRQ and other agencies to design an evidence-based research agenda to answer the most important questions regarding prevention, diagnosis, management, and treatment of opioid misuse among older adults. The ultimate goals are to accelerate practice change and improve outcomes in older adults.

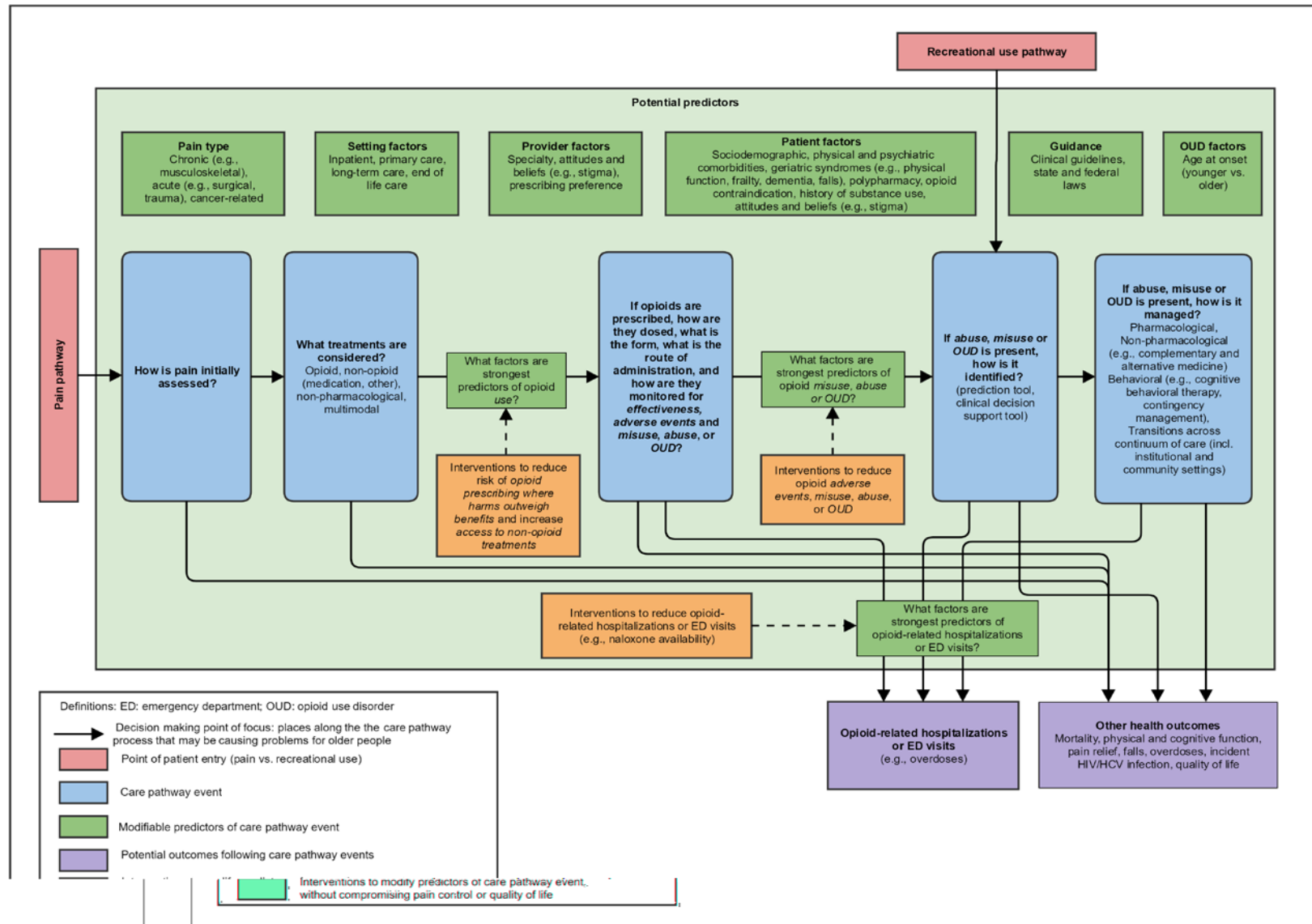
We plan to develop a framework to conceptualize and characterize the multiple factors that interact to impact opioid use and misuse in older adults and opportunities for intervention. This framework will be developed based on current frameworks for opioid use and misuse in the general population, enhanced by evidence and theories about pain management in older adults, and informed by the input of a broad range of federal and nonfederal Key Informants (KIs). Concurrently, we will conduct an evidence map to characterize the existing empirical studies that pertain to the guiding questions (risk, screening, prevention, epidemiology, and treatment of opioid misuse in older adults).

III. Conceptual Framework

Figure 1 shows a global preliminary conceptual framework. It encompasses all Guiding Questions and places a slight emphasis on the interest areas most amenable to an evidence map such as risk factors for opioid-related events among all older adults and risk factors for harm among opioid users. The clinical care pathway events through which an older adults may progress are shown in blue with temporal ordering. The decision-making points that may lead to

the events are depicted by arrows, and factors or predictors that may be contributing to suboptimal opioid management (prescribing and care management that result in net harm) and adverse events in older adults are shown in green. Since older adults may initially engage in opioid use through either pain or recreational pathways, both are included and identified in red. Orange boxes with dashed arrows are used to show where interventions may be particularly appropriate along the care pathway. Finally, the purple box identifies health outcomes.

Figure 1. Draft global conceptual framework



IV. Methods

To address the issues raised by the Guiding Questions, we will develop a conceptual framework and conduct an evidence map of the existing evidence base. The conceptual framework and evidence map will summarize the evidence in a way that allows stakeholders to readily identify the next steps for research on opioid use and misuse in older adults.

We will address the following four Guiding Questions:

Guiding Questions:

1. What are the most important factors driving the increase in opioid-related hospitalizations and ED visits for older adults and what interventions are needed to reduce the risk of opioid-related adverse events, opioid misuse, and opioid use disorder (OUD) in older adults without compromising pain control or quality of life?
 - a. Are there interventions developed for the general population that could be applied to older adults without modification?
 - b. Are there interventions developed for the general population that could be studied in older adults?
 - c. Is there a need for interventions specifically designed or adapted for older adults?
 - d. What outcomes should be captured specifically for older adults (falls, cognitive function, cardiovascular events, etc.)?
2. Among older patients taking opioids, what risk factors are the strongest predictors of harms from opioids (adverse events, misuse, or opioid use disorder)?
 - a. Underlying patient factors, such as fall risk, cognitive impairment, frailty, liver disease, etc.
 - b. Medication factors (opioid dosing and preparation; co-prescribing; etc.)
 - c. Environmental factors (presence of a caregiver, etc.)
3. What interventions have been studied to help providers...
 - a. reduce opioid prescription where harms outweigh benefits in older adults without compromising pain control or quality of life (e.g., shared decision-making)?
 - b. reduce the risk of adverse events, misuse or opioid use disorder in older adults for whom opioids are appropriate?
 - c. identify opioid misuse or opioid use disorder in older adults?
 - d. treat opioid misuse or opioid use disorder in older adults, including facilitating transitions across the continuum of care and across institutional and community settings?

For each sub-question, describe studies by the following populations and settings:

- Different care scenarios (acute, chronic, cancer)
 - Age, sex, race/ethnicity, income, and geography (urban, rural)
 - Settings (inpatient, primary care, long-term care)
 - Early versus late onset OUD
4. What studies are needed to develop evidence based interventions (for providers, patients, or systems) to reduce opioid prescription where harms outweigh benefits, misuse, and opioid use disorder in older adults? What should the design of these studies be?

1. Development of Conceptual Framework

Initial Development

The draft conceptual framework, as presented in *Section III*, above, has been developed in early discussions of the EPC team. It has been developed based on existing prior conceptual frameworks and systems maps. These include ones from Wakeland and colleagues,^{38,39} the U.S. Department of Health and Human Services Pain Management Best Practices Inter-Agency Task Force Report,⁴⁰ and the National Academies of Sciences Engineering and Medicine text Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use.⁴¹ Existing frameworks and systems maps from obesity and other conditions not directly related to pain were considered to help inform alternative structures and formats for the framework.^{42,43}

Our conceptual framework is designed to be an early draft to assist the team with determining the types of sources of information we will seek to inform the final framework and to promote discussion, improvement, and elaboration from the KI panel members. We anticipate that use of a conceptual framework to identify additional elements will be more effective than 1) requesting each KI enumerate a list of relevant risk factors driving the increase in opioid-related hospitalizations and emergency department visits for older adults, and 2) eliciting an enumeration of proposed or potential solutions.

Further Development

The Initial Development phase is expected to yield a comprehensive and complete conceptual framework. Yet, we will iteratively add to and revise the framework through discussions with KI panel members keeping in mind the project timeline. KIs will give input to guide the search process for literature to inform the framework; with each iteration, we will use the updated framework to search for new domains, concepts, and factors. These will be incorporated into the framework to develop a next iteration. Meanwhile, we will also continue to search for potentially relevant existing conceptual frameworks and systems maps. During development, we will consider frameworks and systems maps created for older adults with conditions other than pain or opioid use to ensure no relevant concepts are omitted.

Finalization

The framework will be considered final when 1) no new domains, concepts, or factors arise from discussions with the KI panel members, or 2) new items offer only small incremental gains in information over previously encoded items because they are primarily derivatives of existing concepts or factors. Informational redundancy between the KI input and conceptual framework figure will thus be a key measure of progress toward finalization. KIs contradicting information already encoded in the conceptual framework will not be used to assess progress toward finalization.

2. Evidence Map

To describe the evidence base pertaining to the topic, we will conduct a literature search and create an evidence map. The evidence map will enumerate the number of primary studies (along with systematic reviews and clinical practice guidelines) that directly address relevant questions pertaining to the management of opioid use and misuse in older adults. The evidence map will describe the characteristics of these studies (e.g., their design, basic population descriptors, interventions). It will not summarize the quantitative findings of the studies, nor will it assess

either the quality of the studies or the strength of the evidence. The evidence map will also form a citation list and database for any future systematic review on the topic.

The evidence map will focus primarily on Guiding Questions 1 (patient interventions), (2 (patient risk factors), and 3 (provider interventions).

2.1. Evidence Map Eligibility Criteria

Eligible populations

- Older adults with or without pain prescribed or otherwise using (or having used) opioids (or for whom opioid prescription/use may be warranted)
 - Any timeframe of opioid use in relation to pain (whether past or present)
 - Any cause of pain (including acute, chronic, neuropathic, somatic; any severity), including no pain
 - Any use of opioids, whether prescribed or not, legally obtained or not.
 - Exclude non-opioids (e.g., benzodiazepines, anesthetic narcotics) without concomitant use of opioids
 - The primary definition of older adult is ≥ 65 years of age, but we will include studies and subgroup analyses of populations down to age 50 years.
 - Study conducted in high-income countries (as defined by the World Bank (<https://data.worldbank.org/income-level/high-income>))

Eligible interventions and predictors

- Any intervention, including:
 - Screening questions
 - Prediction tools
 - Clinical decision support tools
 - Quality improvement initiatives / implementation strategies to promote evidence-based care
 - Models of care
 - Non-opioid medications and nonpharmacologic treatments for pain control or for opioid misuse
 - Cognitive behavioral and related interventions for pain control or for opioid misuse
- Any predictor, including:
 - patient demographic features (e.g., age, race/ethnicity, sex)
 - patient social conditions (e.g., housing status, social contacts, employment)
 - patient setting (e.g., outpatient, inpatient, long-term care)
 - patient morbidities (e.g., cause of pain, other clinical conditions)
 - patient cognitive function, quality of life, function
 - patient history of pain, history of opioid use and misuse
 - clinic and clinician descriptors (e.g., primary vs. specialty care, specific specialty)
 - clinical team members (e.g., physician only, nurse outreach, home health aide, pain clinic)

Eligible outcomes

- Any outcome, including:
 - Person-level clinical outcomes (e.g., death, falls, cognitive function, cardiovascular events, respiratory function)
 - Person-level clinical resources (e.g., emergency department visits, clinic visits, hospitalizations)
 - Person-level living status (e.g., residence, work, activities of daily living, social function)
 - Person-level quality of life or function (however measured)
 - Person-level pain and pain control
 - Person-level opioid use, misuse, and OUD
 - Person-level opioid-related adverse events
 - Provider-level outcomes (e.g., barriers/facilitators to/of appropriate opioid prescription, provider knowledge, attitudes and beliefs)
 - System-level outcomes (e.g., likelihood of provider adherence to interventions, changes in the proportion of providers prescribing opioids appropriately)

Eligible study designs

- Any primary study design, including
 - randomized and nonrandomized comparative studies
 - single-group studies
 - case control studies
 - N-of-1 studies
 - prospective or retrospective studies
 - cross-sectional or longitudinal studies
 - surveys or qualitative research analyses
 - data reports (e.g., from FDA or pharmacopeia)
- Systematic review, clinical practice guideline
- Any timing
- Any setting (in high-income countries)
- English language

2.1.1 Rationale for Evidence Map Eligibility Criteria

Eligible populations

Eligible populations are older adults who live with pain, irrespective of when they first experienced pain. Although ≥ 60 or ≥ 65 years of age are more traditional age thresholds for identifying older adults, we will allow subgroup analyses down to 50 years of age for two reasons. First, many studies of opioid misuse and opioid use disorder deviate from traditional age cutoffs and consider individuals aged 50 years or older to be “older adults”. Second, the lower age threshold may allow us to understand how risk factors for opioid use and how opioid use itself changes as individuals transition from middle age to older age. However, our literature search will focus on the population of adults 65 years or older; expanding the literature search to age groups under 65 years would more than double the search yield, which would not allow a feasible search given time and resource constraints for this Technical Brief.

Studies with broader enrollment (e.g., nationally representative studies including individuals of all ages) will be excluded unless they report results for strata of age to enable identification of older adults.

Eligible interventions and predictors

The Technical Brief aims to describe all available interventions, both those developed for a younger or general population that can be adapted to older adults and those that were specifically designed or already adapted for older adults. We aim to be inclusive in terms of interventions and predictors so that we can describe what has been studied (and what there may be evidence for). Therefore, all interventions and predictors are eligible.

Eligible outcomes

The Technical Brief aims to identify what outcomes should (and could) be captured specifically for older adults. Therefore, all patient-level and system-level outcomes will be eligible for the evidence map.

Eligible study designs

To fully describe and map out the evidence base, we will include all primary study designs. However, depending on the number of case reports and case series found, we may fully include them with other studies in the evidence map or we may enumerate and list these without full descriptions. We will include (and briefly summarize) existing systematic reviews and evidence-based clinical practice guidelines to further understand the literature base.

2.2. Literature Search Strategies for Identification of Relevant Articles

We will search PubMed, PsycINFO, and CINAHL. We will coordinate with the social sciences librarian for suggestions of additional databases. We will search for terms related to older age or aging, crossed with terms on opioid use, opioid-related disorders, opioid misuse, and opioid-related adverse events. We will limit results to studies published in English. We will limit the literature search to the years 2000-2019 and the eligibility to the years 1990-present. The rationale underlying the date limits is that opioid prescribing for pain, as it currently occurs in modern clinical practice, began in the 1990s, which is also when opioid prescribing rates dramatically accelerated. To capture articles that may provide insights for the Conceptual Framework, the literature search will include publications that are indexed as non-empirical studies (e.g., editorials, addresses, autobiographies, lectures), but these articles will not be included in the evidence map.

To screen the evidence base, we will use the online software Abstrackr, which uses machine learning algorithms to predict and sort citations based on likely relevance. We will train the team in the study eligibility criteria by going through one or two training cycles where all team members will screen the same citations and we will reconcile conflicts together. Based on our experience with the software (and soon-to-be-completed empirical research), we will stop

screening citations when the software predicts that no further (unscreened) abstracts are likely to be relevant.

We will also search ClinicalTrials.gov and PROSPERO to identify unpublished studies, ongoing studies, and unpublished systematic reviews.

2.3. Data Extraction and Data Management

The evidence map will include extraction of a structured set of elements on the population, the intervention (or predictors), examined outcomes, and study design features (PICOD). The evidence map will be restricted to primary studies, systematic reviews, and clinical practice guidelines.

- a. For populations, we will record information on sample size; period of enrollment, mean age and age range; sex/gender; race/ethnicity groups; care setting (e.g., home, primary care, outpatient clinic, emergency department, inpatient hospitalization, assisted living); pain scenario (e.g., acute, chronic, cancer); and whether the study focused on older adults who belong to one of the following strata: Alzheimer's disease and related dementias, multimorbidity, polypharmacy, co-prescribing of psychotropic medications like benzodiazepines, use of substances like alcohol or marijuana, frailty (robust/pre-frail/frail), depression, caregiver present, and socioeconomic status (low/moderate/high).
- b. For patient interventions, we will record whether they provide medical, behavioral, social, or other support, or a combination thereof. We will categorize interventions based on the care setting(s) in which they are deployed, who they are administered (initiated and used) by, and for how long they are used.
- c. For patient-level predictors, we will capture the predictor categories they fall into, as listed on page 5 under *Eligible interventions and predictors/Any predictor*, including an "other" category.
- d. For clinician and system-level interventions, we will capture the intervention type (e.g., screening tool, model of care, quality improvement initiative) and brief description
- e. We will extract all eligible specific outcome categories (e.g., opioid misuse, fall, cardiovascular event, pain, opioid prescription).

2.4. Assessment of Methodological Risk of Bias of Individual Studies

Not applicable for the purpose of this Technical Brief. Studies will not be assessed for methodological risk of bias.

3. Data Synthesis

We will summarize KI input and use it to inform the design of the conceptual framework, in terms of the data items to be extracted; to identify important evidence gaps; and to prioritize gaps into research needs. For the evidence map, all analyses will be qualitative and descriptive. We will *not* summarize study findings or results.

4. Grading the Strength of Evidence for Major Comparisons and Outcomes

Not applicable for the purpose of this Technical Brief. The study findings will not be summarized; thus Strength of Evidence will not be assessed.

5. Assessing Applicability

The evidence map will characterize the settings and included individuals in studies, but the evidence will not be formally assessed for applicability in this Technical Brief.

V. References

1. Centers for Disease Control and Prevention. Prescription Opioid Data. 2018; <https://www.cdc.gov/drugoverdose/data/overdose.html>. Accessed May 4, 2019.
2. Weiss AJ, Heslin KC, Barrett ML, Izar R, et al. Opioid-Related Inpatient Stays and Emergency Department Visits Among Patients Aged 65 Years and Older, 2010 and 2015: Statistical Brief #244. *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Rockville (MD)2018.
3. Gomes T, Tadrous M, Mamdani MM, Paterson JM, et al. The Burden of Opioid-Related Mortality in the United States. *JAMA Netw Open*. 2018;1(2):e180217.
4. Center for Behavioral Health Statistics and Quality. Behavioral health trends in the United States: results from the 2016 National Survey on Drug Use and Health. 2018; <https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf>. Accessed May 1, 2019.
5. Han B, Compton WM, Blanco C, Crane E, et al. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Annals of internal medicine*. 2017;167(5):293-301.
6. Makris UE, Abrams RC, Gurland B, Reid MC. Management of persistent pain in the older patient: a clinical review. *JAMA : the journal of the American Medical Association*. 2014;312(8):825-836.
7. Miller M, Sturmer T, Azrael D, Levin R, et al. Opioid analgesics and the risk of fractures in older adults with arthritis. *Journal of the American Geriatrics Society*. 2011;59(3):430-438.
8. Buckeridge D, Huang A, Hanley J, Kelome A, et al. Risk of injury associated with opioid use in older adults. *Journal of the American Geriatrics Society*. 2010;58(9):1664-1670.
9. O'Neil CK, Hanlon JT, Marcum ZA. Adverse effects of analgesics commonly used by older adults with osteoarthritis: focus on non-opioid and opioid analgesics. *The American journal of geriatric pharmacotherapy*. 2012;10(6):331-342.
10. Solomon DH, Rassen JA, Glynn RJ, Lee J, et al. The comparative safety of analgesics in older adults with arthritis. *Archives of internal medicine*. 2010;170(22):1968-1976.
11. Horgas AL. Pain Management in Older Adults. *Nurs Clin North Am*. 2017;52(4):e1-e7.
12. Bicket MC, Mao J. Chronic Pain in Older Adults. *Anesthesiol Clin*. 2015;33(3):577-590.
13. Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. *Bmj*. 2015;350:h532.
14. Lautenbacher S, Peters JH, Heesen M, Scheel J, et al. Age changes in pain perception: A systematic-review and meta-analysis of age effects on pain and tolerance thresholds. *Neurosci Biobehav Rev*. 2017;75:104-113.

15. Andersson ML, Bottiger Y, Kockum H, Eiermann B. High Prevalence of Drug-Drug Interactions in Primary Health Care is Caused by Prescriptions from other Healthcare Units. *Basic Clin Pharmacol Toxicol*. 2018;122(5):512-516.
16. Pretorius RW, Gataric G, Swedlund SK, Miller JR. Reducing the risk of adverse drug events in older adults. *American family physician*. 2013;87(5):331-336.
17. Quiton RL, Roys SR, Zhuo J, Keaser ML, et al. Age-related changes in nociceptive processing in the human brain. *Ann N Y Acad Sci*. 2007;1097:175-178.
18. Grashorn W, Sprenger C, Forkmann K, Wrobel N, et al. Age-dependent decline of endogenous pain control: exploring the effect of expectation and depression. *PloS one*. 2013;8(9):e75629.
19. Dostrovsky JO, Carr DB, Koltzenburg M. *Pain and aging: the pain experience over the adult lifespan*. In: *Proceedings of the 10th World Congress on Pain*. Seattle: IASP Press; 2003.
20. Pan F, Tian J, Aitken D, Cicuttini F, et al. Predictors of pain severity trajectory in older adults: a 10.7-year follow-up study. *Osteoarthritis Cartilage*. 2018;26(12):1619-1626.
21. Gibson SJ, Katz B, Corran TM, Farrell MJ, et al. Pain in older persons. *Disabil Rehabil*. 1994;16(3):127-139.
22. Aw TJ, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Archives of internal medicine*. 2005;165(5):490-496.
23. Izhar M, Alausa T, Folker A, Hung E, et al. Effects of COX inhibition on blood pressure and kidney function in ACE inhibitor-treated blacks and hispanics. *Hypertension*. 2004;43(3):573-577.
24. Whelton A, Fort JG, Puma JA, Normandin D, et al. Cyclooxygenase-2--specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *American journal of therapeutics*. 2001;8(2):85-95.
25. Abraham NS, El-Serag HB, Hartman C, Richardson P, et al. Cyclooxygenase-2 selectivity of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction and cerebrovascular accident. *Alimentary pharmacology & therapeutics*. 2007;25(8):913-924.
26. Singh G, Wu O, Langhorne P, Madhok R. Risk of acute myocardial infarction with nonselective non-steroidal anti-inflammatory drugs: a meta-analysis. *Arthritis research & therapy*. 2006;8(5):R153.
27. Caldwell B, Aldington S, Weatherall M, Shirtcliffe P, et al. Risk of cardiovascular events and celecoxib: a systematic review and meta-analysis. *Journal of the Royal Society of Medicine*. 2006;99(3):132-140.
28. Chen LC, Ashcroft DM. Risk of myocardial infarction associated with selective COX-2 inhibitors: meta-analysis of randomised controlled trials. *Pharmacoepidemiology and drug safety*. 2007;16(7):762-772.
29. Scott PA, Kingsley GH, Smith CM, Choy EH, et al. Non-steroidal anti-inflammatory drugs and myocardial infarctions: comparative systematic review of evidence from observational studies and randomised controlled trials. *Annals of the rheumatic diseases*. 2007;66(10):1296-1304.
30. Kearney PM, Baigent C, Godwin J, Halls H, et al. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *Bmj*. 2006;332(7553):1302-1308.

31. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA : the journal of the American Medical Association*. 2006;296(13):1633-1644.
32. Ofman JJ, MacLean CH, Straus WL, Morton SC, et al. A metaanalysis of severe upper gastrointestinal complications of nonsteroidal antiinflammatory drugs. *J Rheumatol*. 2002;29(4):804-812.
33. Boers M, Tangelder MJ, van Ingen H, Fort JG, et al. The rate of NSAID-induced endoscopic ulcers increases linearly but not exponentially with age: a pooled analysis of 12 randomised trials. *Annals of the rheumatic diseases*. 2007;66(3):417-418.
34. Ofman JJ, Maclean CH, Straus WL, Morton SC, et al. Meta-analysis of dyspepsia and nonsteroidal antiinflammatory drugs. *Arthritis and rheumatism*. 2003;49(4):508-518.
35. Richy F, Bruyere O, Ethgen O, Rabenda V, et al. Time dependent risk of gastrointestinal complications induced by non-steroidal anti-inflammatory drug use: a consensus statement using a meta-analytic approach. *Annals of the rheumatic diseases*. 2004;63(7):759-766.
36. Stein CM, Griffin MR, Taylor JA, Pichert JW, et al. Educational program for nursing home physicians and staff to reduce use of non-steroidal anti-inflammatory drugs among nursing home residents: a randomized controlled trial. *Medical care*. 2001;39(5):436-445.
37. Sale JE, Thielke S, Topolovec-Vranic J. Who is addicted to, and dying from, prescription opioids? *Journal of the American Geriatrics Society*. 2010;58(7):1401-1402.
38. Wakeland W, Nielsen A, Geissert P. Dynamic model of nonmedical opioid use trajectories and potential policy interventions. *Am J Drug Alcohol Abuse*. 2015;41(6):508-518.
39. Wakeland W, Schmidt T, Gilson AM, Haddox JD, et al. System dynamics modeling as a potentially useful tool in analyzing mitigation strategies to reduce overdose deaths associated with pharmaceutical opioid treatment of chronic pain. *Pain medicine*. 2011;12 Suppl 2:S49-58.
40. U.S. Department of Health and Human Services. Pain Management Best Practices Inter-Agency Task Force. 2019; <https://www.hhs.gov/ash/advisory-committees/pain/reports/index.html>. Accessed June 29, 2019.
41. National Academies of Sciences Engineering and Medicine (U.S.). Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse., Bonnie RJ, Ford MA, Phillips J. *Pain management and the opioid epidemic : balancing societal and individual benefits and risks of prescription opioid use*. Washington, DC: The National Academies Press; 2017.
42. Solar O, Irwin A. A Conceptual Framework for Action on the Social Determinants of Health. 2010; https://www.who.int/sdhconference/resources/ConceptualframeworkforactiononSDH_eng.pdf. Accessed June 28, 2019.
43. Siokou C, Morgan R, Shiell A. Group model building: a participatory approach to understanding and acting on systems. *Public Health Res Pract*. 2014;25(1).

VI. Definition of Terms

Opioid misuse: Use of opioids in any way not directed by a prescriber, including (a) use without a prescription of one's own; (b) use in greater amounts, more often, or longer than told to take a medication, including both opioid use disorder (OUD) and problematic use; or (c) use in any other way that was not directed by a prescriber.⁴

Older adults: Adults who are aged 50 years or older. While an age cutoff of 60 or 65 years or older is conventional for identifying older adults, the age cutoff of 50 is meant to include literature on opioid use that considers this lower age threshold as indicative of being “older.”

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol, to facilitate tracking. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
The effective date of the change	Where the change would be found in the protocol	Original protocol language	Changed protocol language	Justification for the change, and, as applicable, potential for bias.

VIII. Key Informants (KIs)

KIs are end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the KIs' role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from KIs when developing questions for systematic review or when identifying high priority research gaps and needed new research. KIs are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

KIs must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as KIs and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

IX. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments.

The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

X. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XI. Role of the Funder

This project was funded under Contract No. HHSA290201500002I (Task Order #15) from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The TOO will review contract deliverables for adherence to contract requirements and quality. The authors of this report will be responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.