Evidence-based Practice Center Systematic Review Protocol

Project Title: *Comparative Effectiveness of Pain Management Interventions for Hip Fracture*

I. Background and Objectives for the Systematic Review

Background

Hip fractures are a source of significant morbidity and mortality. Incidence increases substantially with age rising from 22.5 and 23.9 per 100,000 population at age 50, to 630.2 and 1,289.3 per 100,000 population by age 80, for men and women respectively.[1-4] The impact of hip fractures is far reaching. Not only are short-term mortality rates high, but a large proportion of those patients who survive never recover to their prefracture level of function.[5-7] Approximately 25 to 50 percent of elderly patients with hip fractures have not returned home by 1-year postfracture.[8] Up to 25 percent of hip fractures occur in continuing care facilities (long-term residential care for dependent people).[9,10] Because of poor functional recovery, health service utilization associated with recovery after this injury is substantially increased for at least one year, with much of health care cost attributable to subsequent long-term care.[1,11-13]

Pain and limited mobility are the primary issues for patients with hip fractures. Pain has been associated with delirium, depression, sleep disturbance, and decreased response to interventions for other disease states.[14-16] Therefore it is important to treat and manage complaints of pain adequately during acute treatment for hip fracture. Furthermore, poorly managed postoperative pain is associated with delayed ambulation, failure to prevent pulmonary or neurovascular complications after surgery, and subsequent difficulty transitioning from a lower level of care.[17] The established ramifications of poorly managed pain necessitate further interventional research of pain management in this vulnerable patient population.

The patient's self-report of pain is the gold standard for evaluating its character and intensity.[14] However, those with dementia or acute delirium may have difficulty reporting pain levels. The potential for underreporting of pain has direct ramifications for the hip fracture population because many are frail elderly with postoperative confusion and impaired ability to communicate.[18-21]

Objective

The need to improve recovery after hip fracture, particularly among frail elderly persons, is a pressing worldwide problem that will only increase over the foreseeable future with the aging population.[22] Synthesized data are lacking regarding pain management after hip fracture, so our review will be of global interest to patients and families, the medical community and healthcare decision makers. We will seek to provide synthesized evidence to develop recommendations for effective and efficient care delivery and outcomes in this frail senior population. Given the relative lack of evidence regarding most subgroups and most interventions, a comparative effectiveness review of this topic may prove useful for clarifying

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the evidence regarding which treatments are effective and in which circumstances. The review could also elucidate the subgroups and interventions for which further research is most urgently needed.

II. The Key Questions

Following the public posting of the key questions and discussion with the Technical Expert Panel (TEP) members, and members of Eisenberg Center and the Scientific Resource Center, the key questions were modified to reflect the following suggestions:

a. All KQs:
   i. Questions about the minimum age was discussed. Even though there is a consensus that the average age of participants will be over 60 to 65 years old, the inclusion criteria of 50 years was kept so as to be as inclusive as possible.
   ii. The term "comparative" has been removed from the intervention and the statement "or other interventions" has been added to the comparison.

b. KQ1:
   i. The term short and long have been replaced with acute and chronic, respectively.

c. KQ2:
   i. Pain medication use: change in type and quantity has been added as an outcome.
   ii. The outcome 'Ability to pursue rehabilitation' has been modified to 'Ability to participate in rehabilitation'.
   iii. Proxy measures for mental status (not only self report by patients) will be considered, if available.
   iv. Pain and function are linked and it may not be possible to delink them (i.e., we could assume that function will return if pain is relieved; however, the fracture may need repair, regardless of pain, for function to return).

d. KQ3 (p. 4):
   i. Underlying mental health of the patients is important to consider; pain is a perceived concept, not a measured one.
   ii. We will consider post-hospital mortality of women versus men to note if the pattern the same.
   iii. It was noted that we might also consider life philosophies, level of education, earning capacity/financial status, but since information on these confounding factors is not expected to be available, we did not add them to the list of subgroups to investigate.

We have focused the key questions using the PICOTS framework (population, intervention, comparison, outcome, timing, setting) as follows:

KQ 1: In older adults (≥50 years) admitted to hospital following acute hip fracture (population), what is the effectiveness of pharmacologic and/or nonpharmacologic pain management interventions (intervention) for controlling acute and chronic pain (outcomes) up to one year postfracture (timing) compared with usual care or other interventions (comparison) in all settings (setting)?

KQ 2: In older adults (≥50 years) admitted to hospital following acute hip fracture (population), what is the effectiveness of pharmacologic and/or nonpharmacologic pain management interventions (intervention) on other outcomes (outcomes) up to one year postfracture (timing) compared with usual care or other interventions (comparison) in all settings (setting)? Other outcomes include:

a. Mortality (30 day and up to 1-year postfracture)
b. Functional status
c. Pain medication use; change in type and quantity
d. Mental status
e. Health-related quality of life
f. Quality of sleep in the hospital
g. Ability to participate in rehabilitation
h. Return to prefracture living arrangements
i. Health services utilization

KQ 3: In older adults (≥50 years) admitted to hospital following acute hip fracture (population), what is the is the nature and frequency of adverse effects (outcomes) that are directly or indirectly associated with pharmacologic and nonpharmacologic pain management interventions (intervention) up to one year postfracture (timing) compared with usual care or other interventions (comparison) in all settings (setting)?

KQ 4: In older adults (≥50 years) admitted to hospital following acute hip fracture (population), how do the effectiveness and safety (outcomes) of pharmacologic and nonpharmacologic pain management interventions (interventions) vary in differing subpopulations following acute hip fracture up to one year after fracture (timing) compared with usual care or other interventions (comparison) in all settings (setting)?

Important refinement points regarding the key questions:

- **Population(s):**
  Older adults of either sex who are diagnosed as having an acute hip fracture resulting from low energy trauma (e.g., slip and fall) will be included. This includes patients with intracapsular (e.g., intertrochanteric and femoral neck) and extracapsular (e.g., basal, trochanteric and subtrochanteric) fractures regardless of whether surgical repair

was performed. There will be no restrictions on comorbidities or baseline functionality.
Patients with hip fracture due to the following etiologies will not be considered: pathologic hip fractures (e.g., metastatic fractures, Pagets Disease); femoral head fractures; periprosthetic fractures (i.e., post hip replacement fractures/arthroplasty population); fractures resulting from high energy trauma (e.g., motor vehicle crashes, falls from heights, etc.).

- **Interventions:**
  We will consider all interventions, alone or in combination, with various methods of administration and modes of delivery, and at various time points during the care pathway (e.g., preoperative, intraoperative, postoperative, rehabilitation, and following discharge from acute care).
  Interventions will include traditional and nontraditional medications/interventions (e.g., natural health products).
  Interventions that are directly related to surgical/nonsurgical treatment of the hip fracture (e.g., reduction, fixation, hemiarthroplasty, total hip replacement) will not be considered.

- **Comparators:**
  Comparators of interest will be as defined in the primary studies. This includes, but is not limited to, opioid, nonopioid, or nonsteroidal antiinflammatory drugs (NSAIDS).

- **Outcomes for each question:**
  For KQ1, the measurement of pain will be measured using a validated pain measurement tool. It may be patient defined or proxy reported.
  For KQ2, all reported outcomes that are directly or indirectly related to the intervention for pain management will be investigated.
  For KQ3, all reported adverse events (AE) that are directly or indirectly associated to the intervention for pain management (e.g., medication complications such as constipation or gastrointestinal bleeding) will be investigated. AE of interventions directly related to surgical/nonsurgical/medical treatment of the hip fracture (e.g., AEs of anesthesia, wound infection, etc.) will not be investigated.
  For KQ4: Subgroups to be investigated include sex, age, race, marital status, comorbidities, body mass index, prefracture functional status, and family distress.

- **Timing:**

  We will include all followup time points from the time of the trauma leading to the hip fracture and thereafter.

- **Settings:**

  Settings include, but are not limited, to emergency department, hospital, rehabilitation facilities, skilled nursing facility, subacute care facility, and place of residence.

III. Analytic Framework

Figure 1 provides an analytic framework to illustrate the population, interventions, and outcomes that will guide the literature search and synthesis. The figure depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how pharmacologic and nonpharmacologic pain management interventions,

alone or in combination, may result in intermediate outcomes such as control of acute pain, pain medication use, the ability to participate in rehabilitation, the quality of sleep in hospital, and length of stay and/or long-term outcomes such as chronic pain, changes in the mental status, the functional status (e.g., activities of daily living), the ability to return to prefracture place of residence, health-related quality of life, health service utilization, and mortality. Also, adverse events may occur at any point after the treatment is received (e.g., medication adverse effects such as constipation, gastrointestinal irritation, rash).

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

We have developed a preliminary set of criteria for inclusion and exclusion of trials (below). We will include studies published as full-text manuscripts, conference abstracts, or other grey literature. There are no language restrictions. If potentially relevant publications are unclear regarding their inclusion/exclusion criteria, we will contact the corresponding authors of the individual reports for more information to allow for a proper classification. Research published prior to 1990 will not be considered. The rationale is that surgical procedures and medical care (particularly as it relates to aggressive postsurgery mobilization) for this patient population has changed and the earlier research may not be relevant.

Inclusion/exclusion criteria.

Table 1. Inclusion criteria

Study design*	Randomized controlled trials, nonrandomized controlled trials, cohort studies (prospective or retrospective), case-control studies
Participants	Older adults (≥ 50 years old) of either sex admitted to hospital with acute hip fracture due to low energy trauma
Interventions	Pharmacological and/or nonpharmacological pain management monotherapy or combination therapy; regardless of mode of administration or time point during the care pathway
Comparator	Usual care (as defined by study authors) or another intervention(s) for pain management, administered as monotherapy or combination therapy
Outcomes	Primary outcomes: • Acute pain • Chronic pain Secondary outcomes: • Mortality • Functional status • Pain medication use; change in type and quantity Adverse events: • AE related to the pain management intervention • Mental status • Health-related quality of life • Quality of sleep in hospital • Ability to participate in rehabilitation • Return to prefracture place of residence • Length of stay for acute hospitalization, skilled nursing facility, subacute care facility

	• Health service utilization
Timing	From time of trauma leading to acute hip fracture and thereafter
Setting	All settings

* Study designs will be classified according to their methodological hierarchy, with lower levels of evidence included in the report only if there is lack of adequate higher quality evidence. Adequacy of evidence will be determined through discussion between the investigative team and the TEP taking into consideration the number and sample sizes of the included studies for each intervention.

Table 2. Exclusion criteria

Study design	Observational study designs with no comparison group (case reports, case series, cross sectional studies)
Participants	Majority (>80%) of participants <50 years, as stated by the study investigators or evident from the trial characteristics (e.g., mean/SD of patient population); participants with underlying pathological conditions that may directly lead to fracture; acute hip fractures due to high energy trauma
Interventions	Interventions directly related to surgical/nonsurgical treatment of the hip fracture and not a pain management intervention
Comparator	Initial care for patients is substantially different than the current practices in North America (e.g., based on time to discharge from acute care to subacute care)
Outcomes	None of the aforementioned outcomes are available from the trial report or through communication with the trial's corresponding author
Timing	None
Setting	None

Study selection. A two-step process will be used for study selection. First, two reviewers will independently screen the titles and abstracts (when available) to determine if an article meets the broad inclusion/exclusion criteria for study design, population, and intervention. Each article will be rated as: include, exclude or unclear. The full-text of all articles classified as include or unclear will be retrieved for formal review. Next, two reviewers will independently assess each study using a standard form that outlines the pre-determined inclusion and exclusion criteria. Disagreements will be resolved through discussion or third party adjudication as needed.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

The research librarian, in collaboration with the investigative team, will develop and implement search strategies designed to identify evidence relevant to questions of efficacy and effectiveness and safety. Appendix A outlines the most appropriate evidence and sources of evidence searched for these questions.

For the questions on efficacy and effectiveness, we will conduct comprehensive searches in the following electronic databases: BIOSIS Previews (1969 to present), CINAHL Plus with Full Text (via EBSCOhost) (1937 to present), Cochrane Central Register of Controlled Trials (1900 to present), Cochrane Database of Systematic Reviews (2009 Issue 3), Database of Abstracts of Reviews of Effects (2009 Issue 3), EMBASE (1988 to present), Global

Health, Health Source: Nursing/Academic Edition (1975 to present), International Pharmaceutical Abstracts (1970 to present), KoreaMed (1997 to present), Ovid MEDLINE® (1950 to present), Pascal (1987 to present), PEDro (1929 to present), ProQuest® Dissertations and Theses - Full Text (1861 to present), Science Citation Index Expanded® (1900 to present), and Scopus (1823 to present). All searches will be restricted to studies published since 1990. No language or study design restrictions will be applied. The reference lists of reviews and guidelines will be reviewed to help identify potential studies for inclusion. Original studies from the existing reviews identified above that meet the inclusion criteria for this review will be retrieved. We will conduct a forward search of the Scopus™ Citation Tracker for relevant studies.

Appendix B outlines the MEDLINE search terms and strategy that will be adapted to accommodate the controlled vocabulary and search language of each database.

For the questions on safety and adverse effects, in addition to the above databases, we will search the U.S. National Library of Medicine's TOXLINE® (1965 to present), and Canada's Adverse Drug Reaction Database.

We will handsearch the conference proceedings for the following annual conferences for the last 5 years for relevant studies: American College of Rheumatology (ACR), American Geriatrics Society (AGS), American Physical Therapy Association (APTA), American Society of Regional Anesthesia and Pain Medicine (ASRA), Association of Bone and Joint Surgeons (ABJS), European Academy of Anaesthesiology (ESA), International Anesthesia Research Society (IARS), International Association of Gerontology and Geriatrics (IAGG), International Association for the Study of Pain (IASP). Drug manufacturers and authors of relevant studies will be contacted to obtain data from unpublished or ongoing studies. Documents from government and professional associations, theses and dissertations, unpublished studies and studies in progress, will also be searched to identify potentially relevant unpublished studies. We will also search online trial registers (e.g. WHO, ClinicalTrials.gov, ISRCTN, etc.) to identify further unpublished or ongoing trials.

Results from the literature searches will be entered into Reference Manager® 11.0.1, a bibliographic management database from Thomson Reuters.

C. Data Abstraction and Data Management

Data will be extracted and entered into a standard form. Data will be extracted by one reviewer and checked for accuracy and completeness by a second reviewer. In general, data extracted will include details of study design and inclusion/exclusion criteria; details of the population and intervention(s); and results obtained for various outcomes. Reviewers will resolve disagreements in data extraction by consensus or third party adjudication as needed.

D. Assessment of Methodological Quality of Individual Studies

The methodological quality of the included studies will be assessed using the Cochrane Collaboration's Risk of Bias (RoB) tool[23] for randomized and nonrandomized controlled trials and the Newcastle Ottawa scale (NOS)[24] for cohort and case-control studies. Decision rules regarding application of the tools will be developed a priori by the investigative team. We will also report on sources of funding for each included study.

Two reviewers will independently perform quality assessment of the included studies. Disagreements will be resolved through discussion or third party adjudication as needed.

E. Data Synthesis

For all studies comparing effectiveness of treatments, we will extract relevant outcomes. Mean differences (MD) will be calculated for continuous variables. Risk ratios (RR) and odds ratios (OR) will be calculated for dichotomous data. Results will be reported with accompanying 95 percent confidence intervals (95% CI).

If appropriate, meta-analyses will be conducted using the random effects model. Weighted MD (WMD) or standardized MD (SMD) will be calculated for continuous variables with the same or different scales, respectively. The I^2 statistic will be used to assess heterogeneity. Subgroup analyses or meta-regression will be conducted, if possible, to investigate sources of heterogeneity and view differences in outcomes across subgroups of interest. Chi-square tests will be used to test for significant heterogeneity reduction in partitioned subgroups. Sensitivity analyses will be conducted to assess the robustness of the findings across study quality, and random effects vs. fixed effects analyses. Publication bias will be tested visually using the funnel plot, and quantitatively using the Begg adjusted rank correlation test and Egger regression asymmetry test.

All data pooling will be performed using Review Manager 5.0. In the event the studies cannot be pooled, evidence tables will be produced and bivariable statistical comparisons will be used to identify hypotheses for observations.

Additionally, planned subgroup analyses include: sex, age, race, body mass index, marital status, comorbidities, prefracture functional ability, and family distress.

F. Grading the Body of Evidence

Where there are three or more studies, we will grade the body of evidence for primary outcomes using an adaptation of the Grading of Recommendation Assessment, Development & Evaluation (GRADE) system.[25-27] In addition to study design, we will assess the quality of studies, consistency of effect estimates across studies, precision of the effect estimates, and directness. We will classify the bodies of evidence pertaining to each primary outcome into four basic categories: (1) “high” (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change or confidence in the estimate of effect); (2) “moderate” (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate); (3) “low” (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); and (4) “insufficient” (indicating that evidence is either unavailable or does not permit estimation of an effect).

V. Reference List

1. Brainsky A, Glick H, Lydick E, et al. The economic cost of hip fractures in community-dwelling older adults: a prospective study. *J Am Geriatr Soc* 1997;45:281-7.
2. Cooper C, Campion G, Melton LJ 3rd. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285-9.
3. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. *Osteoporos Int* 1997;7:407-13.
4. Maggi S, Kelsey JL, Litvak J, et al. Incidence of hip fractures in the elderly: a cross-national analysis. *Osteoporos Int* 1991;1:232-41.
5. Jette AM, Harris BA, Cleary PD, et al. Functional recovery after hip fracture. *Arch Phys Med Rehabil* 1987;68:735-40.
6. Magaziner J, Simonsick EM, Kashner TM, et al. Predictors of functional recovery one year following hospital discharge for hip fracture: a prospective study. *J Gerontol* 1990;45:M101-7.
7. Mossey JM, Mutran E, Knott K, et al. Determinants of recovery 12 months after hip fracture: the importance of psychosocial factors. *Am J Public Health* 1989;79:279-86.
8. Lyons AR. Clinical outcomes and treatment of hip fractures. *Am J Med* 1997;103:51S-63S.
9. Ronald LA, McGregor MJ, McGrail KM, et al. Hospitalization rates of nursing home residents and community-dwelling seniors in British Columbia. *Can J Aging* 2008;27:109-15.
10. Beaupre LA, Cinats JG, Jones CA, et al. Does functional recovery in elderly hip fracture patients differ between patients admitted from long-term care and the community? *J Gerontol A Biol Sci Med Sci* 2007;62:1127-33.
11. Donald IP, Bulpitt CJ. The prognosis of falls in elderly people living at home. *Age Ageing* 1999;28:121-5.
12. Haentjens P, Autier P, Barette M, et al, for the Belgian Hip Fracture Study Group. The economic cost of hip fractures among elderly women. A one-year, prospective, observational cohort study with matched-pair analysis. *J Bone Joint Surg Am* 2001;83-A:493-500.
13. Wiktorowicz ME, Goeree R, Papaioannou A, et al. Economic implications of hip fracture: health service use, institutional care and cost in Canada. *Osteoporos Int* 2001;12:271-8.
14. American Geriatrics Society. The management of chronic pain in older persons: AGS Panel on Chronic Pain in Older Persons. *J Am Geriatr Soc* 1998;46:635-51.
15. Cleeland CS. Undertreatment of cancer pain in elderly patients. *JAMA* 1998;279:1914-5.
16. Ferrell BA. Pain management in elderly people. *J Am Geriatr Soc* 1991;39:64-73.

17. Nussenzveig TC. Pain management after total joint replacement and its impact on patient outcomes. *AORN J* 1999;70:1060-2.
18. Milisen K, Abraham IL, Broos PL. Postoperative variation in neurocognitive and functional status in elderly hip fracture patients. *J Adv Nurs* 1998;27:59-67.
19. Goldstein FC, Strasser DC, Woodard JL, et al. Functional outcome of cognitively impaired hip fracture patients on a geriatric rehabilitation unit. *J Am Geriatr Soc* 1997;45:35-42.
20. Francis J. Delirium in older patients. *J Am Geriatr Soc* 1992;40:829-38.
21. Williams MA, Campbell EB, Raynor WJ, et al. Reducing acute confusional states in elderly patients with hip fractures. *Res Nurs Health* 1985;8:329-37.
22. Stott DJ, Langhorne P, Knight PV. Multidisciplinary care for elderly people in the community. *Lancet* 20081;371:699-700.
23. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1* [updated September 2008]. London: The Cochrane Collaboration and John Wiley & Sons Ltd; 2008.
24. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed July 14, 2009.
25. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.
26. Atkins D, Briss PA, Eccles M, et al. Systems for grading the quality of evidence and the strength of recommendations II: pilot study of a new system. *BMC Health Serv Res* 2005;5:25.
27. Guyatt G, Vist G, Falck-Ytter Y, et al. An emerging consensus on grading recommendations? *ACP J Club* 2006;144:A8-A9.

VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews,

key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

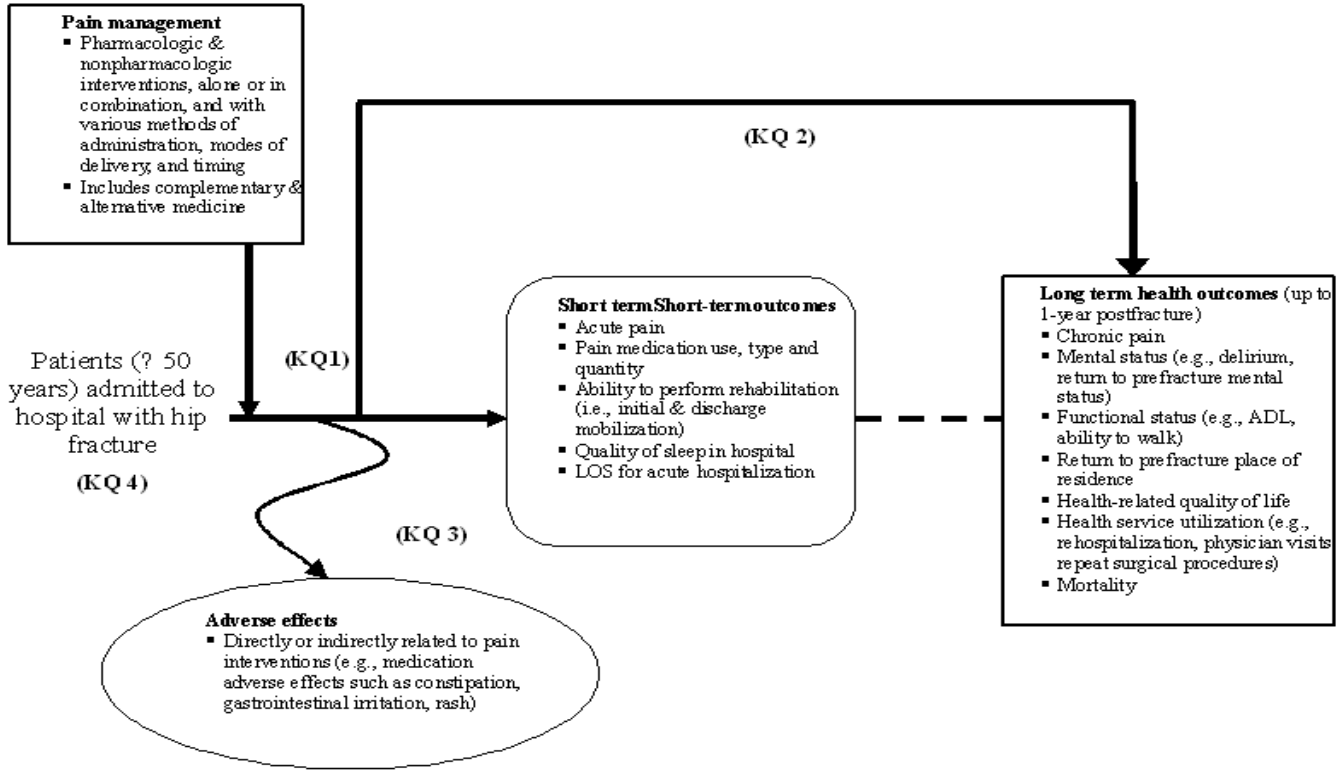
A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.

Figure 1: Analytic Framework



Appendix A – Evidence Search Framework

Topic	Questions	Types of evidence	Electronic databases	Additional searching
I. Evidence for efficacy/effectiveness	K1: In older adults (≥50 years) admitted to hospital following acute hip fracture, what is the effectiveness of pharmacologic and/or nonpharmacologic pain management interventions for controlling short- and long-term pain up to one year postfracture compared with usual care in all settings? K2: In older adults (≥50 years) admitted to hospital following acute hip fracture, what is the effectiveness of pharmacologic and/or nonpharmacologic pain management interventions on other outcomes up to one year postfracture compared with usual care in all settings?	Randomized controlled trials, nonrandomized controlled trials, cohort studies (prospective or retrospective), case-control studies	Academic Search Complete, BIOSIS Previews, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, DARE, Proquest Theses and Dissertations, EMBASE, Global Health, HealthSource, International Pharmaceutical Abstracts, KoreMed, MEDLINE, Pascal, PeDRO, Scopus, Web of Science, ClinicalTrials.gov Current Controlled Trials, ICTRP (International Clinical Trials Registry Platform Search Portal, WHO), CRISP (Computer Retrieval of Information on Scientific Projects).	Selective handsearching of scientific meeting abstracts, contact with authors and experts, relevant grey literature sources, reference lists of relevant studies, contact with manufacturers

II. Evidence for safety of pharmacologic and nonpharmacologic pain management interventions	K3: In older adults (≥50 years) admitted to hospital following acute hip fracture, what is the is the nature and frequency of adverse effects that are directly or indirectly associated with pharmacologic and nonpharmacologic pain management interventions up to one year postfracture compared with usual care in all settings? K4: In older adults (≥50 years) admitted to hospital following acute hip fracture, how do the effectiveness and safety of pharmacologic and nonpharmacologic pain management interventions vary in differing subpopulations following acute hip fracture up to one year postfracture compared with usual care in all settings?	Randomized controlled trials, nonrandomized controlled trials, cohort studies (prospective or retrospective), case-control studies	Same as above as well as TOXNET, Canada's Adverse Drug Reaction Database	Same as above plus: Websites: Australian Adverse Drug Reactions Bulletin, European Agency for the Evaluation of Medicinal Products (EMEA), Health Canada. Advisories Warnings and Recalls, Medicines and Healthcare products Regulatory Agency (MHRA), Prescriber Update, Swiss Medic: Swiss Agency for therapeutic products, US Food and Drug Administration, World Health Organization (WHO) Pharmaceuticals Newsletter

Appendix B – Ovid Medline® Search Strategy

1. exp Pain/
2. exp "anesthesia and analgesia"/or exp analgesia/
3. ((an?esthet$ or an?esthesia) adj4 (regional$ or local$ or general or spinal or epidural)).mp.
4. (block or analges*).mp.
5. or/2-4
6. exp Therapeutics/or exp "Outcome Assessment (Health Care)"/or exp "Length of Stay"/or "Quality of Life"/or "functional outcome".ti,ab.
7. ((pain* or discomfort* or ache* or aching or sore* or suffer*) adj3 (assess* or relief or reliev* or reduc* or treat* or manage* or control* or experience* or medicat* or duration or evaluat* or alleviat* or level or score* or subjective or felt or prevent* or duration or outcome* or heal or healing or therap* or recover* or "quality of life")).mp.
8. exp Pain/rt, th, us, rh, dh, su, pc, dt
9. pain postoperative/pc, th
10. Pain Measurement/
11. or/7-10
12. exp Hip Fractures/rh, nu, th, dt, dh
13. exp Hip Fractures/
14. ((intertrochanter* or petrochanter* or subtrochanter* or extracapsular or petrochant* or trochant* or hip or femoral neck) adj4 (hemiarthroplasty or fracture*)).mp.
15. ("neck of femur" adj4 fractur*).mp.
16. or/13-15
17. 5 and 16
18. 11 and 16
19. 1 and 16
20. 6 and 12
21. or/17-20
22. exp Arthroplasty, Replacement, Hip/
23. THA.mp.
24. total hip*.mp.
25. or/22-24
26. 21 not 25
27. (pediatric* or child or children* or adolesc* or young or youth* or pregnan*).ti,ab,jw,kw,sh.
28. animals/or exp neoplasms/or case reports/or editorials/or exp Emergency Service, Hospital/
29. or/27-28
30. 26 not 29
31. limit 30 to yr="1990 - 2009"