Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness and Safety of Analgesics for Osteoarthritis – An Update to the 2006 Report

I. Background and Objectives for the Systematic Review

This report will serve as an update to the 2006 report Comparative Effectiveness and Safety of Analgesics for Osteoarthritis.[1]

Osteoarthritis is a chronic condition involving degeneration of cartilage within the joints. It is the most common form of arthritis and is associated with pain, substantial disability, and reduced quality of life.[2] About 6 percent of U.S. adults aged 30 years or older have symptomatic osteoarthritis of the knee, and 3 percent have symptomatic osteoarthritis of the hip.[3] Osteoarthritis increases with age: the incidence and prevalence increase two- to tenfold from age 30 to 65 and continue to increase after age 65.[4] The total costs for arthritis, including osteoarthritis, may be greater than 2 percent of the gross domestic product,[3] with more than half of these costs related to work loss.[5]

Common oral medications for osteoarthritis include nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen. Patients with osteoarthritis also use over-the-counter supplements not regulated by the FDA as pharmaceuticals, including glucosamine and chondroitin, as well as topical agents. Opioid medications are also used for selected patients with refractory, chronic pain but are not recommended for first-line treatment of osteoarthritis and therefore will not be included in this review. Each class of medication or supplement is associated with a unique balance of risks and benefits. In addition, efficacy and safety may vary for individual drugs within a class. Nonpharmacologic interventions (such as physical therapy, weight reduction, and exercise) also help improve pain and functional status in patients with osteoarthritis.

A challenge in treating osteoarthritis is deciding which medications will provide the greatest symptom relief with the fewest serious adverse effects. NSAIDs decrease pain, inflammation and fever by blocking cyclo-oxygenase (COX) enzymes. Understanding of the pharmacology of NSAIDs continues to evolve, but it is now thought that most NSAIDs block three different COX isoenzymes, known as COX-1, COX-2, and COX-3. COX-1 protects the lining of the stomach from acid. COX-2 is found in joints and muscles and mediates effects on pain and inflammation; COX-3 is found in the brain cortex. In patients with arthritis,[6] low back pain,[7] minor injuries, and soft tissue rheumatism, NSAIDs reduce pain, when compared with placebo, by blocking COX-2. However, NSAIDs that also block the COX-1 enzyme (also called “nonselective NSAIDs”) can cause gastrointestinal bleeding. In the United States, there are an estimated 16,500 annual deaths due to NSAID-induced gastrointestinal complications,[8] a higher death rate than that for cervical cancer or malignant melanoma. Theoretically, NSAIDs that block only the COX-2 enzyme (also called “coxibs,” “COX-2 selective NSAIDs,” or “selective NSAIDs”) should be safer with regard to gastrointestinal

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bleeding, but they also appear to be associated with increased rates of serious cardiovascular and other adverse effects. Less is known about COX-3, which is found in the cerebral cortex and cardiac tissue and appears to be involved in centrally mediated pain.[9]

This report will update the available evidence comparing the benefits and harms of analgesics in the treatment of osteoarthritis since publication of the original report in 2006.[1] The main conclusions of the original report were:

- Acetaminophen relieves mild pain but is inferior to NSAIDs for reducing moderate or severe pain. Acetaminophen has fewer systemic side effects than NSAIDs.
- All non-aspirin NSAIDs work equally well for pain reduction
- NSAIDs increase the risk of GI bleeding. The risk increases with higher doses and with age. People older than 75 have the highest risk.
- Celecoxib, high dose ibuprofen, and high dose diclofenac increase the risk of myocardial infarction. Naproxen does not increase the risk of myocardial infarction.
- Capsaicin cream relieves chronic osteoarthritic pain, but about half of the people using it will experience local burning sensations. The burning diminishes over time.
- Over the counter topical creams containing salicylates do not reduce osteoarthritic pain.

Since the completion of the original report, three topical NSAIDs have received FDA approval for treating osteoarthritis. There have also been newly published studies of several drugs included in the original report. These newly approved drugs as well as the new publications make an update of the CER necessary at this time.

For this report, we have defined certain terms as follows:

- Selective NSAIDs, or COX-2 selective NSAIDs—drugs in the “coxib” class (celecoxib)
- Partially selective NSAIDs—other drugs shown to have partial in vitro COX-2 selectivity (etodolac, nabumetone, meloxicam)
- Aspirin—differs from other NSAIDs, because it irreversibly inhibits platelet aggregation; salicylic acid derivatives (aspirin and salsalate) are considered a separate subgroup
- All other NSAIDs—nonaspirin, nonselective NSAIDs, or simply nonselective NSAIDs

II. The Key Questions

The purpose of this comparative effectiveness review (CER) is to update the previous report that assessed the comparative efficacy and safety of non-opioid oral medications (selective and non-selective non-aspirin NSAIDs, aspirin, salsalate, and acetaminophen), over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis.

The following key questions will be the focus of our report:

Question 1

a. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?

b. How do these benefits and harms change with dosage and duration of treatment?

c. What is the evidence that standard dosing as labeled or alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?

The only *benefits* considered here are improvements in osteoarthritis symptoms. Evidence of *harms* associated with the use of nonsteroidal antiinflammatory drugs (NSAIDs) includes studies of these drugs for treating osteoarthritis or rheumatoid arthritis and for cancer prevention.

Question 2

Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups of patients?

- Demographic subgroups: age, sex, and race
- Coexisting diseases: cardiovascular conditions, such as hypertension, edema, ischemic heart disease, heart failure; peptic ulcer disease; history of previous gastrointestinal bleeding (any cause); renal disease; hepatic disease; diabetes; obesity
- Concomitant medication use: anti-thrombotics, corticosteroids, antihypertensives, selective serotonin reuptake inhibitors (SSRI)

Question 3

What are the comparative effects of co-prescribing H2 receptor antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?

Question 4

What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations, or of different topical medications compared with one another?

For the update of this comparative effectiveness review, updates have been made to clarify the Key Questions, but these changes do not alter the meaning of each Key Question. Additional coexisting diseases and concomitant medications were included.

Review Scope for Key Questions:

- **Population(s):**
  Adults with osteoarthritis. Note that selection of candidates for therapy is outside the scope of this review. The population included in this review will be the population identified from the existing evidence.
- **Interventions:**
  Table 1. Pharmacokinetics, Indications, and Dosing of drugs to be included.

Oral drugs (trade names provided only for drugs under patent)

Drug (any trade name): acetaminophen

Labeled indications	Dosing	Dose adjustments for special populations
Fever; pain	Pain: 650–1000 mg up to 4 g/day	Pediatric patients (Peds): 10–15 mg/kg/dose up to 5 doses/day

Drug (any trade name): aspirin

Labeled indications	Dosing	Dose adjustments for special populations
Arthritis; cerebrovascular accident; transient ischemia; coronary artery bypass graft; disorder of joint of spine; fever; juvenile rheumatoid arthritis; myocardial infarction; prophylaxis; osteoarthritis; pain; percutaneous coronary intervention;	Osteoarthritis (OA) and rheumatoid arthritis (RA): 3g/day divided into 4 to 6 doses	Peds: 40–130 mg/kg/day, depending upon condition

pleurisy; systemic lupus erythematosus; rheumatoid arthritis; stable angina, chronic; unstable angina		

Drug (any trade name): celecoxib (Celebrex®)

Labeled indications	Dosing	Dose adjustments for special populations
Ankylosing spondylitis; familial adenomatous polyposis; syndrome osteoarthritis; pain; primary dysmenorrhea; rheumatoid arthritis; juvenile rheumatoid arthritis	OA: 200 mg/day; RA: 200–400 mg/day	Renal impairment: reduce dose by 50%; elderly patients weighing < 50 kg: initiate at lowest dose

Drug (any trade name): diclofenac

Labeled indications	Dosing	Dose adjustments for special populations
Ankylosing spondylitis; extraction of cataract; inflammatory disorder of eye; light intolerance; pain in eye; refractive keratoplasty; osteoarthritis; pain; rheumatoid arthritis	OA: delayed release, 100–150 mg/day in 2 to 3 doses; extended release, 100–200 mg/day; RA: delayed release, 100–200 mg/day in 3 to 4 doses; extended release, 75–225 mg/day	Renal impairment: initiate with lowest recommended dose, then monitor closely

Drug (any trade name): diflunisal

Labeled indications	Dosing	Dose adjustments for special populations
Osteoarthritis; pain, mild to moderate; rheumatoid arthritis	OA and RA: 500–1000 mg/day in 2 equally divided doses; maximum dose, 1500 mg/day	Renal impairment and elderly: initiate with lowest dose possible, then monitor closely

Drug (any trade name): etodolac

Labeled indications	Dosing	Dose adjustments for special populations

Juvenile rheumatoid arthritis; osteoarthritis; pain, acute; rheumatoid arthritis	OA and RA initial treatment: immediate release, 300 mg 2–3x/day or 400–500 mg 2x/day; OA and RA maintenance: immediate release, 600–1000 mg/day 2–4x/day with a maximum dose of 1200 mg/day; extended release, 400–1000 mg/day	Juvenile Rheumatoid Arthritis (JRA) weighing 20 to 30 kg: extended release, 400 mg 1x/day; JRA weighing 31 to 45 kg: extended release, 600 mg 1x/day; JRA weighing 46 to 60 kg: extended release, 800 mg 1x/day; JRA, extended release, weighing >60 kg: extended release,1000 mg 1x/day

Drug (any trade name): fenoprofen

Labeled indications	**Dosing**	**Dose adjustments for special populations**
Migraine; osteoarthritis; pain, mild to moderate; rheumatoid arthritis	OA and RA: 300–600 mg, 3 to 4x/day; maximum daily dose, 3200 mg	Elderly: smaller dose recommended, 300 mg 3x/day; renal impairment: no dose adjustment necessary

Drug (any trade name): flurbiprofen

Labeled indications	**Dosing**	**Dose adjustments for special populations**
Constricted pupil, intraoperative prophylaxis; osteoarthritis; rheumatoid arthritis	OA and RA: 200–300 mg/day in 2 to 4 divided doses; maximum dose, 300 mg/day	Renal impairment, liver disease, and geriatric patients: initiate with lowest recommended dose, then monitor closely

Drug (any trade name): ibuprofen

Labeled indications	**Dosing**	**Dose adjustments for special populations**
Fever; juvenile rheumatoid arthritis; osteoarthritis; pain, minor; pain, mild to moderate; primary dysmenorrhea; rheumatoid	OA and RA: 1200–3200 mg/day in 3 to 4 divided doses	Renal impairment: initiate with lowest recommended dose, then monitor closely

arthritis		

Drug (any trade name): indomethacin

Labeled indications	Dosing	Dose adjustments for special populations
Ankylosing spondylitis; bursitis of shoulder–pain, acute; gouty arthritis, acute; osteoarthritis; tendonitis of shoulder—pain, acute; patent ductus arteriosus; rheumatoid arthritis	OA and RA: immediate release, 25–50 mg 2 to 3x/day or a maximum dose of 100 mg 2x/day; sustained release product, 75 mg 1 to 2x/day	Severe renal impairment (creatinine clearance [CrCL] < 15 mL/min), liver disease (Child-Pugh Class III), elderly, and peds: initiate with lowest recommended dose, then monitor closely

Drug (any trade name): ketoprofen

Labeled indications	Dosing	Dose adjustments for special populations
Fever; osteoarthritis; pain, minor; pain, mild to moderate; rheumatoid arthritis	OA and RA: immediate release, 150–300 mg/day in 3 to 4 divided doses; extended release, 100–200 mg 1x/day	Mild renal impairment (CrCL > 25 mL/min): maximum, 150 mg/day; moderate renal impairment (CrCL < 25 mL/min): maximum, 100 mg/day; geriatric (>75 years): initiate with doses of 75-150 mg/day; liver disease and serum albumin < 3.5 g/dL: maximum initial dose, 100 mg/day

Drug (any trade name): ketorolac

Labeled indications	Dosing	Dose adjustments for special populations
Extraction of cataract—inflammatory disorder of eye; light intolerance—pain in eye—refractive keratoplasty; pain, acute—moderate to severe; seasonal allergic conjunctivitis	Pain, acute—moderate to severe (<65 years of age): initiate with 20 mg, followed by 10 mg, every 4 to 6 hours; maximum, 40 mg/day	Peds: lowest effective dose for shortest possible duration; >65 years of age or weight <50 kg or renal impairment: 10 mg every 4 to 6 hours as needed; maximum, 40 mg/day

Drug (any trade name): meclofenamate sodium

Labeled indications	Dosing	Dose adjustments for special populations

Dysmenorrhea; menorrhagia; osteoarthritis; pain; rheumatoid arthritis	OA and RA: 200–400 mg/day in 3 to 4 equally divided doses; maximum, 400 mg/day	Elderly and renal impairment: lowest effective dose for shortest possible duration

Drug (any trade name): mefenamic acid

Labeled indications	Dosing	Dose adjustments for special populations
Dysmenorrhea; pain	Pain (children >14 years and adults): initiate with 500 mg, followed by 250 mg every 6 hours; use beyond 1 week is not recommended	Renal impairment: do not use; peds: use not studied

Drug (any trade name): meloxicam

Labeled indications	Dosing	Dose adjustments for special populations
Juvenile rheumatoid arthritis, polyarticular–pauciarticular juvenile rheumatoid arthritis; osteoarthritis; rheumatoid arthritis	OA and RA: 7.5 mg 1x/day; maximum, 15 mg 1x/day	Elderly, renal impairment, liver disease (Child-Pugh Class III): initiate with lowest recommended dose, then monitor closely

Drug (any trade name): nabumetone

Labeled indications	Dosing	Dose adjustments for special populations
Osteoarthritis; rheumatoid arthritis	OA and RA: initial treatment, 1000 mg/day in a single dose; maintenance, 1000–2000 mg 1x/day or in 2 equally divided doses	Renal impairment and liver disease: monitor closely and reduce dose if necessary

Drug (any trade name): naproxen

Labeled indications	Dosing	Dose adjustments for special populations
Ankylosing spondylitis; bursitis; fever; gout, acute; juvenile rheumatoid arthritis; osteoarthritis; pain; pain, minor; primary dysmenorrhea; rheumatoid arthritis; tendinitis	OA and RA: 250–500 mg 2x/day, maximum, 1500 mg/day ≤ 6 months; over-the-counter, ≤ 10 days	JRA: 10 mg/kg/day in 2 equally divided doses; renal impairment and liver disease: monitor closely and reduce dose if necessary

Drug (any trade name): oxaprozin

Labeled indications	Dosing	Dose adjustments for special populations
Juvenile rheumatoid arthritis; osteoarthritis; rheumatoid arthritis	OA and RA: 1200 mg 1x/day; maximum, 1800 mg/day or 26 mg/kg/day	JRA, 22 to 31 kg: 600 mg 1x/ day; JRA, 32 to 54 kg: 900 mg 1x/day; JRA, >55 kg: 1200 mg 1x/day; renal impairment or weight <50 kg: initiate with 600 mg 1x/day, then monitor closely

Drug (any trade name): piroxicam

Labeled indications	Dosing	Dose adjustments for special populations
Osteoarthritis; rheumatoid arthritis	OA and RA: 20 mg/day 1x/day or 2 equally divided doses	Renal impairment or liver disease: monitor closely and reduce dose if necessary

Drug (any trade name): salsalate

Labeled indications	Dosing	Dose adjustments for special populations
Inflammatory disorder of musculoskeletal system, rheumatic; osteoarthritis; rheumatoid arthritis	OA and RA: 3000 mg/day in 2 to 3 equally divided doses	Elderly: lower doses may be required; peds: safety and efficacy not established

Drug (any trade name): sulindac

Labeled indications	Dosing	Dose adjustments for special populations
Bursitis of shoulder—pain, acute; gouty arthritis, acute; osteoarthritis; tendonitis of shoulder—pain, acute; rheumatoid arthritis	OA and RA: 150 mg 2x/day; maximum 400 mg/day	Renal impairment and liver disease: monitor closely and reduce dose if necessary

Drug (any trade name): tolmetin

Labeled indications	Dosing	Dose adjustments for special populations
Juvenile rheumatoid arthritis; osteoarthritis; rheumatoid arthritis	OA and RA: initial treatment, 400 mg 3x/day for 1 to 2 weeks; maintenance, 200–600 mg 3x/day; maximum, 1800 mg/day	Renal impairment: initiate with lowest recommended dose, then monitor closely and reduce dose if necessary; juvenile rheumatoid arthritis, ≥2 years, initial treatment: 20 mg/kg/day divided into 3 to 4 doses; juvenile rheumatoid arthritis, ≥2 years, maintenance: 15–30 mg/kg/day divided into 3 to 4 doses

Topical drugs (trade names provided only for drugs under patent)

Drug (any trade name): diclofenac epolamine (Flector®; one patch equals180 mg in an aqueous base)

Labeled indications	Dosing	Dose adjustments for special populations
Acute pain from minor strains, sprains, and contusions	1 patch to most painful area 2x/day	Patients with fluid retention or heart failure: use with caution

Drug (any trade name): diclofenac sodium (Voltaren®; 1% gel)

Labeled indications	Dosing	Dose adjustments for special populations
Osteoarthritis of joints amenable to topical treatment, such as knees and hands	Maximum, 32 g/day, over all affected joints; maximum, 16 g/day, to any single joint of lower extremities; maximum, 8 g/day to any single joint of upper extremities	Patients with fluid retention or heart failure: use with caution

Drug (any trade name): diclofenac sodium (Pennsaid®)

Labeled indications	Dosing	Dose adjustments for special populations
Osteoarthritis of knee	40 drops on each painful knee, 4x/day	Patients with fluid retention or heart failure: use with caution

Drug (any trade name): capsaicin

Labeled indications	Dosing	Dose adjustments for special populations
Arthritis; diabetic neuropathy; postherpetic neuralgia	Arthritis: apply thin film 3 to 5x/day	Peds (>2 years): apply thin film 3 to 4x/day

Glucosamine and chondroitin are widely used and available over-the-counter as supplements in the United States. No pharmaceutical grade formulation is approved by the FDA. Accordingly, this report will focus on studies of nonpharmaceutical grade preparations available in the United States. Studies of pharmaceutical-grade glucosamine and chondroitin will also be included, however; they will be analyzed separately, because almost all trials have been conducted on such products and they may provide some information about efficacy.

- **Comparators:**
  - Comparators will include placebo or other drugs included in this CER.
- **Outcomes**
  - Primary outcomes for benefits are improvements in osteoarthritis symptoms.
  - Adverse events will be evaluated from studies of the drugs used for osteoarthritis, rheumatoid arthritis, or cancer treatment.
    - Cardiovascular: stroke, MI, CHF, hypertension and angina
    - GI: perforations, symptomatic gastroduodenal ulcers and upper GI bleeding (PUBs), obstructions, dyspepsia
    - Renal toxicity
    - Hepatotoxicity
  - Other outcomes of interest: Quality of Life, Sudden death
- **Timing:**
  - No minimum threshold will be established for duration of intervention. However, study duration will be considered in the assessment of the quality and applicability of the study.
- **Settings:**
  - Primary care and specialty settings will be included.

III. Analytic Framework

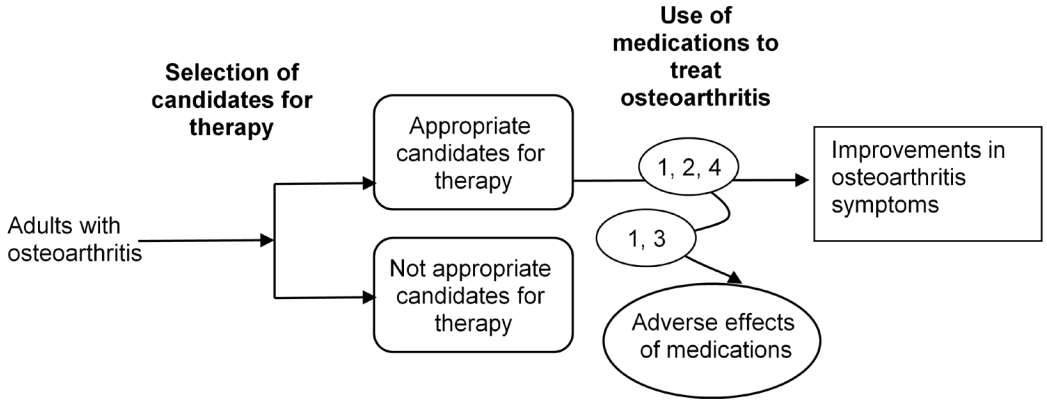

Figure 1: This figure depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how the non-opiod oral medications, over- the –counter supplements, and topical agents may result in outcomes such as improvements in osteoarthritis symptoms. Also, adverse events may occur at any point after the treatment is received.

IV. Methods

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

Systematic reviews and controlled trials pertinent to the key questions will be included. We will retrieve any blinded or open, parallel or crossover randomized controlled trial that compared one included drug to another, or placebo. We will also include cohort and case-control studies with at least 1,000 cases or participants that evaluated serious gastrointestinal and cardiovascular endpoints that were inadequately addressed by randomized controlled trials.

For all studies that meet the criteria above, we will use PICOTS (Population, Intervention, Comparators, Outcomes, Timing and Setting) to evaluate inclusion in the CER Update. We will include studies that evaluate the safety, efficacy or effectiveness of the previously mentioned medications in adults with osteoarthritis. We will also include studies that report safety in patients with rheumatoid arthritis or were taking the drug for cancer or Alzheimer's prevention. Outcomes will include improvements in osteoarthritis symptoms, cardiovascular and gastrointestinal adverse events, renal, and hepatic toxicity, quality of life, and sudden death. There is no minimum threshold for duration of intervention. Studies will be included if they were conducted in primary care or specialty settings.

We will review English language abstracts for non- English studies that otherwise appear to meet eligibility criteria. Non- English studies that appear to meet eligibility criteria will be cited with a brief summary. If a need to include foreign language literature in our analysis arises, we will discuss it with the AHRQ Task Order Officer and the Technical Expert Panel.

If grey literature is identified during the preliminary search for evidence, it will be included as appropriate.

Publications from 2005 to the present will be searched. This date range was selected to provide an overlap with the publication date range used in the original CER.

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

We will replicate the comprehensive search of the scientific literature conducted for the original CER, with an updated date range of 2005- present to identify relevant studies addressing the key questions.

Results from previously conducted meta-analyses and systematic reviews on these topics will be sought and used where appropriate and updated when necessary. To identify systematic reviews, in addition to MEDLINE, we will search the Cochrane Database of Systematic Reviews and the websites of the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Bandolier, and the NHA Health Technology Assessment Programme.

To identify articles relevant to each key question, we will search the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Ovid ®MEDLINE. We will use relatively broad searches, combining terms for drug names with terms for relevant research designs, limiting to those studies that focused on osteoarthritis and rheumatoid arthritis. Other sources may include reference lists of review articles and unpublished materials from the US Food and Drug Administration (FDA). Pharmaceutical manufacturers will be invited to submit scientific information packets, including citations if applicable. All citations from these sources will be imported into an electronic database (EndNote®) and considered for inclusion.

After finalizing our searches, we will systematically review abstracts against our pre-established inclusion/exclusion criteria to determine potential eligibility for inclusion in the evidence synthesis.

Full text literature will be reviewed and key data from each eligible study will be extracted and entered into an electronic database. A file of excluded studies with reasons for exclusion will be maintained.

Our research team will use appropriate procedures to reduce bias and enhance consistency in our study selection process. These procedures include using dual reviewers to review abstracts and full-text articles for inclusion and exclusion for each key question. We will use full text review and a consensus process to resolve conflicting assignments.

Searches will be updated while the report is posted for public comment and peer review to capture any new publications. Literature identified during the update search will go through the same process of dual review as all other literature considered for inclusion in the report. If any pertinent new literature is identified for inclusion in the report, it will be incorporated prior to the final submission of the report.

C. Data Abstraction and Data Management

Once studies have been selected for inclusion based on the key questions and PICOTS, the following data will be extracted and used to assess applicability and quality of the study: study design; population and clinical characteristics (including sex, age, ethnicity, diagnosis, comorbidities, concomitant medications, GI bleeding risk, cardiovascular risk); interventions (dose and duration); method of outcome ascertainment if available, and results for each outcome, focusing on efficacy and safety; setting (primary care or referral); the number of patients randomized relative to the number of patients enrolled, and how similar those patients were to the target population; whether a run in period was used; and the funding source. We will record intention-to-treat results if available.

D. Assessment of Methodological Quality of Individual Studies

We will assess the methodological quality of systematic reviews, randomized trials, and observational studies based on predefined criteria. These criteria are based on the Assessment of Multiple Systematic Reviews (AMSTAR) tool (systematic reviews),[10] methods proposed by Downs and Black (observational studies),[11] and methods developed by the US Preventive Services Task Force.[12] Individual studies will receive quality ratings of "good," "fair," or "poor." Studies could receive one rating for assessment of efficacy and a different rating for assessment of harms. Studies that meet all criteria will be rated good quality and studies that have a serious or "fatal" flaw in one or more categories will be rated poor quality; the remainder will be rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is unlikely to be valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

We will rate the methodological quality of each controlled trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intention-to-treat analysis; and ascertainment of outcomes.[12]

Systematic reviews will be rated based on pre-defined criteria assessing whether they had a clear statement of the questions(s), reported inclusion criteria, used an adequate search strategy, assessed validity, performed dual data abstraction, reported adequate detail of included studies, assessed for publication bias, and used appropriate methods to synthesize the evidence.[10] We will include systematic reviews and meta-analyses that included unpublished data inaccessible to the public, but because the results of such analyses are not verifiable, we will considered this a methodological shortcoming.

For assessing the quality of cohort studies, we will evaluate whether the study authors

used nonbiased selection methods to create an inception cohort; whether rates of loss to follow-up were reported and acceptable; whether they used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether they performed appropriate statistical analyses of potential confounders.[11] For assessing the quality of case-control studies, we will evaluate whether similar inclusion and exclusion criteria were applied to select cases and controls, whether they used accurate methods to identify cases, whether they used accurate methods for ascertaining exposures and potential confounders, and whether they performed appropriate statistical analyses of potential confounders.[11]

The applicability of trials and other studies will be assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, whether differences in outcomes were clinically (as well as statistically) significant, and whether the treatment received by the control group was reasonably representative of standard practice. We will also record the funding source and role of the sponsor.

E. Data Synthesis

We will construct evidence tables showing study characteristics, quality ratings, and results for all included studies. We expect to conduct data synthesis similar to the analyses conducted for the original CER.

In the original CER, we performed two quantitative analyses. An important limitation of observational studies of NSAIDs was that none simultaneously assessed the risk for serious cardiac and GI events. We therefore re-analyzed data from a set of observational studies that reported rates of three different serious adverse events in the same population. We assumed that the adverse events occurred independently and that the logarithm of the rate ratios was distributed normally. After estimating the effect (number of events prevented or caused) for each of the three adverse events, we estimated the net effects on all three serious adverse events using Monte Carlo simulation.

We also pooled clinical success rates and withdrawal due to adverse events from head-to-head trials of topical versus oral NSAIDs using a random effects model (Dersimonian-Laird method, using RevMan® statistical software). We performed standard chi-square tests for heterogeneity. Because only four trials were available for pooling, we did not attempt meta-regression analyses to evaluate potential sources of heterogeneity.

F. Grading the Evidence for Each Key Question

We will assess the overall strength of evidence for a body of literature about a particular key question in accordance with the Grading the Strength of a Body of Evidence when Comparing Medical Interventions chapter of the AHRQ Effective Health Care Program Methods Guide.[13] We will examine the type, number and quality of studies; the risk of bias; the consistency of results within and between study designs; the directness of the

evidence linking the intervention and health outcomes; the precision of the estimate of effect; strength of association (magnitude of effect); and the possibility for publication bias.

We will rate the strength of evidence for each key question using the four categories recommended by Owens, et al.[13]: (1) “high” grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect; (2) “moderate” grade indicates 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” grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; (4) “insufficient” grade indicates evidence either is unavailable or does not permit a conclusion. For example, Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered “high-quality.”) For a body of fair-quality studies, consistent results may indicate that similar biases are operating in all the studies, or results that are likely to be valid. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the overall body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm.

V. References

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VI. Definition of Terms

For this report, we have defined the terms as follows:

- Selective NSAIDs, or COX-2 selective NSAIDs—drugs in the "coxib" class (celecoxib)
- Partially selective NSAIDs—other drugs shown to have partial in vitro COX-2 selectivity (etodolac, nabumetone, meloxicam)
- Aspirin—differs from other NSAIDs, because it irreversibly inhibits platelet aggregation; salicylic acid derivatives (aspirin and salsalate) are considered a separate subgroup
- All other NSAIDs—nonaspirin, nonselective NSAIDs, or simply nonselective NSAIDs

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.

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