

Evidence-based Practice Center Systematic Review Protocol

Comparative Effectiveness of Physical Therapy for Knee Pain Secondary to Osteoarthritis

I. Background and Objectives for the Systematic Review

Osteoarthritis (OA) is a progressive joint disorder caused by gradual loss of cartilage. Cartilage loss results in the development of bony spurs and cysts at the surface and margins of the joints, which leads to inflammation, pain, stiffness, limited movement, and possible deformity of the joint.¹

Osteoarthritis is the most common form of arthritis.² Osteoarthritis of the knee afflicts 28 percent of adults over age 45³ and 37 percent of adults over age 65 in the United States.⁴ OA of the knee may disproportionately affect African Americans and women.³⁻⁶

Osteoarthritis is a leading cause of disability among noninstitutionalized adults.⁴ The Third National Health and Nutrition Examination Survey showed that adults with symptomatic knee osteoarthritis used more assistive walking devices, had slower measured gait velocities, and used more nonsteroidal anti-inflammatory drugs and narcotics than those without knee OA.⁴ The Centers for Disease Control and Prevention asserts that the prevalence, health impact, and economic consequences of OA will increase dramatically during the next few decades due to an aging population and the longer lifespan of patients with chronic diseases.⁷ When conservative therapy fails, patients with knee osteoarthritis undergo surgical treatments, including realignment osteotomy and knee replacements.⁸ In the United States, about 556,400 knee replacement surgeries take place each year.⁸ The number of knee replacements increased nearly three times from 1990 to 2004.⁷⁻⁹ The annual number of revision total knee arthroplasties performed in the United States is projected to increase 600% by 2030.⁹

OA treatments aim to reduce or control pain, improve physical function, prevent disability, and enhance quality of life.¹⁰ Morphological criteria for the diagnosis of knee OA are not reversible with treatment. Therefore, functional status of the patients and quality of life constitute clinical outcomes of treatments for knee OA.¹¹ Treatment options include pain relievers, anti-inflammatory drugs, weight loss, general physical exercise, physical therapy, and, finally, knee replacement surgery.^{11,12} The Osteoarthritis Research Society International (OARSI) asserts that, in general, optimal OA management combines nonpharmacologic and pharmacologic modalities.¹³ Evidence-based guidelines from OARSI also emphasize the role of nonpharmacologic treatments.^{11,12,14} However, scant evidence exists for the efficacy of adjunct therapies for knee OA other than exercise, and some evidence suggests overall underuse of nonpharmacologic knee OA therapies.^{15,16}

The most comprehensive, up-to-date guidelines from OARSI and the American Academy of Orthopaedic Surgeons that are based on a systematic review^{11,17} recommend a variety of physical therapy interventions including low-impact aerobic fitness exercises, range of motion/flexibility exercises, quadriceps strengthening, and patellar taping for short-term pain relief. The OASRI and the Academy were unable to recommend for or against acupuncture as an adjunctive therapy for pain relief. The National Institute for Health and Clinical Excellence guidelines¹² agree that exercise (including local muscle strengthening and general aerobic fitness) should be a core

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treatment for people with osteoarthritis, irrespective of age, comorbidity, pain severity, or disability. The National Institute for Health and Clinical Excellence suggests other nonpharmacologic physical therapy interventions, such as thermal, manipulation, transcutaneous electrical nerve stimulation, bracing, and assistive devices as adjunct therapy to core treatment.

Many systematic reviews, including three Cochrane Collaboration reviews,¹⁸⁻²⁰ synthesized data on physical therapy interventions. However, each review evaluated only one specific physical therapy intervention for knee OA. Published reviews do not examine and compare the efficacy of all physical therapy interventions available for adult patients with knee OA.

Meanwhile, many physical therapies for knee OA have yet to be evaluated, and research is ongoing. Most studies evaluate some form of exercise therapy; however, a variety of physical therapy interventions are being studied, including realignment therapy, insole treatment, knee bracing, wedged orthoses, walking aids, manual therapy, weight loss, home-based exercises, strength training, knee stability training, sling exercises, community-based programs, low-level light, electrical stimulation, ultrasound, and vibration therapy with passive motion. Publication of substantial new research evidence may alter the calculated risk-benefit ratio for some physical therapy treatments for OA and thus necessitate regular updating of research evidence.^{13,21}

Researchers should be able to estimate the benefits and harms of physical therapy by using validated measurements of pain, function, and quality of life.^{22,23} Some consensus exists that clinical trials for knee OA should examine pain, physical function, patient global assessment, and joint imaging.²⁴ However, published studies have interpreted improvement and defined treatment success inconsistently.^{18,19,25,26} Instead of measuring consistently defined clinical outcomes, studies have used various assessment tools to evaluate a range of intermediate outcomes. No systematic reviews or primary studies have specifically examined the relationship between changes in intermediate outcomes and meaningful changes in patient-centered functional outcomes, including disability in activities of daily living, quality of life, or loss of work time. Quality of care for adults with knee OA could be improved by evaluating how clinical effects are measured and documented, as well as by reviewing outcomes information for research.

A comprehensive efficacy review of physical therapy for knee OA is necessary. Our review could contribute to evidence-based physical therapy recommendations for adults with knee OA by synthesizing published efficacy evidence for physical therapy for knee pain secondary to OA in adults. We will conduct a systematic review of studies that examined physical therapy interventions and assessment of intermediate and patient-centered outcomes.

II. Key Questions

Key questions (KQs) were posted for public comment on the AHRQ Effective Health Care Program Web site from October 12, 2010, through November 9, 2010. We revised the questions to reflect the importance of comparing treatments rather than modalities. We also expanded and clarified patient population characteristics that may modify treatment effects on patient outcomes to include obesity and specifics of concomitant/prior treatments. We modified the list of eligible interventions by explicitly defining the word “monotherapy.” Finally, we expanded the analytical plan provided in the Methods section below to better address the complexity of the interventions.

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Question 1

What are the effectiveness and comparative effectiveness of available physical therapy interventions (without drug treatment) for adult patients with chronic knee pain due to OA on intermediate and patient-centered outcomes when compared to no active treatment or another active physical therapy modality?

- a. Which patient characteristics are associated with the benefits of examined interventions of physical therapy on intermediate and patient-centered outcomes?
- b. Do changes in intermediate and patient-centered outcomes differ by the dose, duration, intensity, and frequency of examined interventions of physical therapy?
- c. Do changes in intermediate and patient-centered outcomes differ by duration of examined interventions of physical therapy and the time of followup?

• Population

- Adults with knee pain secondary to knee osteoarthritis in outpatient settings, including home-based therapy.
- Chronic OA is defined as meeting diagnostic criteria and having symptoms of OA for >2 months.

Excluded:

- Adults with knee OA who had knee arthroplasty on the “study limb” within 6 months before the study
- Adults with osteonecrosis
- Adults with acute knee injuries
- Adults with inflammatory arthritis
- Adults with arthritis secondary to systemic disease
- Adults with physical therapy treatment combined with drug treatment

Relevant population characteristics that may modify treatment effects:

- Age
- Gender
- Race
- Baseline activities of daily living (ADL)/instrumental activities of daily living (IADL)
- Disability
- Comorbidity
- Obesity
- Concomitant/prior treatments including history of prior knee surgery or injury
- Presence of significant skeletal abnormality

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- Activity level
- Occupation
- **Intervention**

Physical therapy (monotherapy with one physical therapy intervention or combined physical therapy interventions). Studies examining the marginal effects of drugs combined with physical therapy will be excluded.

Physical therapy interventions eligible for review

General Modality	Specific Intervention	Definition
Patient/client-related instruction		
Instruction, education, and training of patients/clients and caregivers	Current condition Enhancement of performance Health, wellness, and fitness Plan of care Risk factors for pathology/ pathophysiology, impairments, functional limitations, or disabilities	
Therapeutic exercise		
	Aerobic capacity/endurance conditioning or reconditioning	Increased workload over time Walking programs Aquatic therapy
	Flexibility exercises	Muscle lengthening Range of motion Stretching
	Gait and locomotion training	Gait training Implement and device training
	Strength, power, and endurance training for limb muscles	Active assistive, active, and resistive exercises Quadriceps strengthening Aquatic programs Standardized, programmatic, complementary exercise approaches Task-specific performance training Body mechanics and postural stabilization Body mechanics training
	Balance, coordination, and agility training	Neuromuscular education or re-education Posture awareness training
	Muscle relaxation technique for pain management	
Functional training in self-care, home management, work, community, and leisure integration or reintegration (including ADL, IADL, work hardening, and work conditioning)		
	ADL training	
	Devices and equipment use and training	Assistive and adaptive device or equipment training during ADL and IADL Orthotic, protective, or supportive device or equipment training during ADL and IADL
	Functional training programs	Simulated environments and tasks Task adaptation
	IADL training	
	Injury prevention or reduction	Injury prevention education during self-care, home management, work, community, and leisure integration or reintegration Injury prevention or reduction with use of devices and equipment Safety awareness training during self-care, home management, work, community, and leisure integration and reintegration
Manual therapy techniques (Including mobilization/manipulation)		
	Detailed examination to reveal impaired movements	
	Manual techniques with reinforcing exercise to improve movement	

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General Modality	Specific Intervention	Definition
	Manual traction	
	Massage	Connective tissue massage Therapeutic massage
	Mobilization/manipulation	Soft tissue Knee joint, other joints
	Passive range of motion	
Prescription, application of devices and equipment	Adaptive devices	Raised toilet seats
	Assistive devices	Canes
		Crutches
		Walkers
		Long-handled reachers
		Power devices
		Static and dynamic splints Grab bars and tub chairs
Orthotic devices	Braces Shoe inserts Splints	
Protective devices	Braces Protective patellar taping	
Supportive devices	Supportive taping	
Electrotherapeutic interventions	Electrotherapeutic delivery of medications	Iontophoresis
	Electrical stimulation	Electrical muscle stimulation Functional electrical stimulation High-voltage pulsed current Neuromuscular electrical stimulation Transcutaneous electrical nerve stimulation
Physical agents and mechanical interventions	Nonthermal agents	Pulsed electromagnetic fields
	Aquatic therapy	Pools
	Sound agents	Ultrasound
	Thermotherapy	Dry heat
		Hot packs
		Diathermy
Cold modalities		
Cryotherapy	Cold packs	
	Ice massage	

Abbreviations: ADL = activities of daily living; IADL = instrumental activities of daily living.

- **Comparator**

Analysis of efficacy:

- No active treatment (sham stimulation)

Analysis of comparative effectiveness:

- Active control as above
- Monotherapy with one physical therapy intervention compared to combined therapy of more than physical therapy interventions

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- **Outcomes**

Patient-centered outcomes:

- Pain
- Independence in ADL and IADL, with or without devices and equipment
- Ability to assume or resume required self-care, home management, work, community, and leisure roles
- Walking, general physical activity
- Patient satisfaction global assessment
- Time to return to work/activities
- Quality of life

Intermediate outcomes:

- Joint swelling, inflammation, or restriction
- Impaired physical performance
- Tolerance of positions and activities

Question 2

What is the association between changes in intermediate outcomes with changes in patient-centered outcomes after physical therapy interventions?

- a. What is the validity of the tests and measures used to determine intermediate outcomes of physical therapy on OA in association with patient-centered outcomes?
- b. Which intermediate outcomes meet the criteria of surrogates for patient-centered outcomes?
- c. What are minimal clinically important differences of the tests and measures used to determine intermediate outcomes?

- **Population**

Same as KQ1

- **Interventions**

Tests and measurements (intermediate outcomes of physical therapy):

- Muscle performance or strength tests:
 - Manual muscle test
 - Hand-held dynamometer

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- Isokinetic dynamometer
- Knee goniometry
- Lower extremity activity profile
- Measure of balance including single-leg stance test or tandem stance
- Aerobic capacity

- Markers of inflammation:
 - Girth measurements for swelling/edema

- Self-reported patient scales and questionnaires:
 - Knee Pain Screening Tool (KNEST)
 - Extra Short Musculoskeletal Function Assessment questionnaire (XSMFA-D)
 - 12-item Oxford Knee Score
- **Comparator**
 - Normal ranges of the tests and measurements described above
- **Outcomes**

Patient-centered outcomes:

- Independence in activities of daily living (Activities of Daily Living Scale of the Knee Outcome Survey)
 - 6 Minute Walk Test
 - Gait Speed (potential surrogate for clinical outcomes)
 - Functional Status Index
 - Timed Get Up and Go Test
 - Fifty-foot Timed Walk Measure
 - Aggregate Functional Performance Time Measure
 - Lequesne Index for Knee Osteoarthritis
 - Algofunctional Index for Knee Osteoarthritis
 - Lower Extremity Functional Scale (LEFS)

- Time to return to work/activities

- Quality of life measured with:
 - Short Form 36 (SF-36)
 - Mapping the Osteoarthritis Knee and Hip Quality of Life (OAKHQOL)

- Pain measured with:

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- Anterior Knee Pain Questionnaire
- Knee pain osteoarthritis Visual Analogue Scale (VAS)
- Knee Pain Scale (KPS)
- Western Ontario McMaster Osteoarthritis Index (WOMAC) Pain subscale
- Patient Global Assessment
- Arthritis Impact Measurement Scales
- Outcome Measures in Rheumatology
- OMERACT outcome measures including:
 - Pain
 - Physical function
 - Patient global assessment
 - Joint imaging (for studies of 1 year or longer)
 - Health-related quality of life measure
 - Physician global assessment
- Patient Specific Functional Scale (PSFS)
- Knee Injury and Osteoarthritis Outcome Score (KOOS)
- Outpatient Physical Therapy Improvement in Movement Assessment Log (OPTIMAL)

Question 3

What are the harms from physical therapy interventions available for adult patients with chronic knee pain due to osteoarthritis when compared to no active treatment or active controls?

- a. Which patient characteristics are associated with the harms of examined physical therapy interventions?
- b. Do harms differ by the duration of the treatment and time of followup?

- **Population**

Same as KQ 1

- **Interventions**

Same as KQ 1

- **Comparators**

Same as KQ 1

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- **Outcomes**

All reported adverse events

Questions 1–3:

- **Timing**

- At the end of the treatment
- Short-term outcomes (2–6 weeks up to 3 months)
- Long-term outcomes (>3 months)

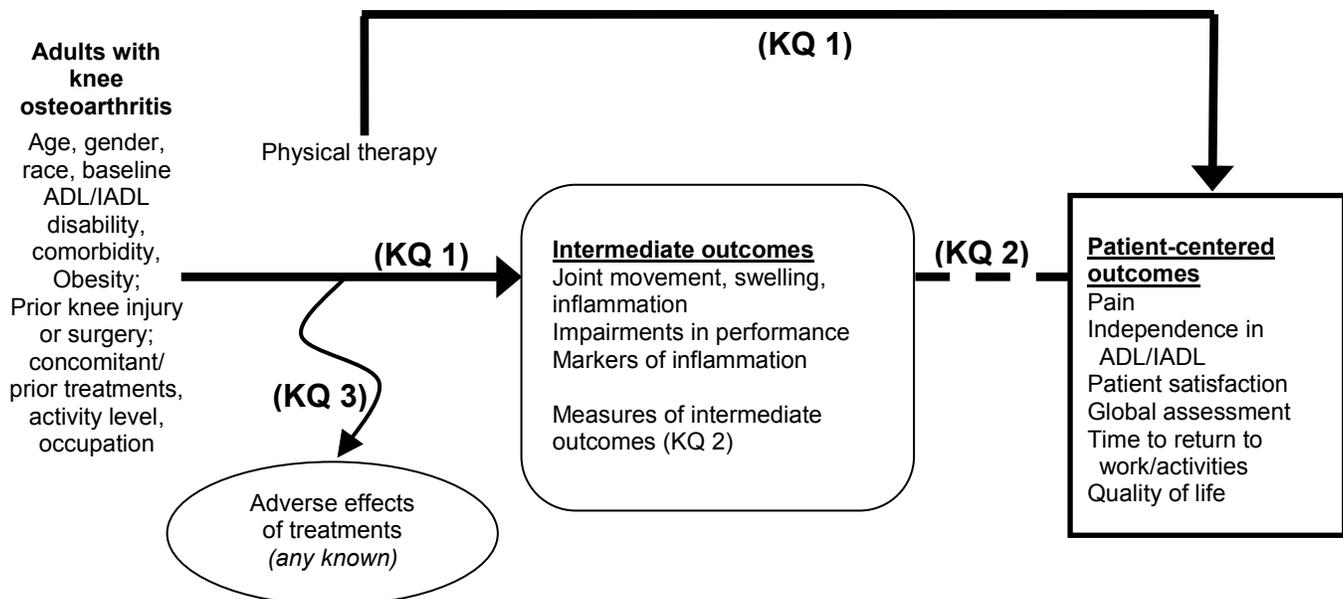
- **Settings**

Outpatient and home-based care settings

- **Safety information from the FDA regarding interventions:**

- The FDA has not released warnings about physical therapy interventions for knee osteoarthritis. We will monitor the FDA Web site for warnings and safety information for all eligible devices.
- The FDA defines physical medicine devices as nonsignificant risk devices.²⁷ We will monitor all databases for adverse effects from physical medicine devices.

III. Analytic Framework (developed by following the AHRQ *Methods Guide for Comparative Effectiveness Reviews* and the methods of the U.S. Preventive Services Task Force²⁸⁻³⁰)



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Abbreviations: ADL = activities of daily living; IADL = instrumental activities of daily living; KQ = key question.

IV. Methods

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

We will follow the *Methods Guide for Comparative Effectiveness Reviews* to select evidence from controlled trials and observational studies.³¹ Three investigators will independently determine study eligibility according to recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions*.³² We will apply the best-available-evidence approach to include poor-quality observational studies when evidence is not available from the randomized controlled trials (RCTs) or high-quality observational studies.³¹

We will review the evidence of the efficacy and comparative effectiveness of physical therapy for knee pain secondary to OA. We will classify interventions and methods to assess the outcomes according to the classifications set in the practice pattern Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Localized Inflammation from the *Guide to Physical Therapist Practice*.

Inclusion Criteria:

1. Original epidemiologic studies, including randomized controlled clinical trials, nonrandomized multicenter clinical trials, and observational studies that used the strategies to reduce bias (adjustment, stratification, matching, propensity scores).
2. Publication in English after 1970.
3. Target population of community dwelling adult with knee osteoarthritis.
4. Eligible intermediate and patient-centered outcomes as listed above.
5. Eligible interventions as listed above.

For KQ 2, we also plan to include the studies that examined the association between intermediate and patient-centered outcomes after physical therapy interventions.

We may include any observational studies that reported the association between intermediate and patient-centered outcomes.

We will include observational studies when trial data are insufficient to estimate the benefits and harms of physical therapy interventions.³¹ We will include unpublished RCTs presented at peer-reviewed scientific meetings only if they provided data on clinical outcomes after eligible treatments that are not available in published articles.

We plan to include RCTs that included adults with OA of knee and hip joints (both in the same patients). For KQ 2, we will include the studies of tests and measures in adults with knee OA.

Exclusion Criteria:

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1. Studies that involved children, adolescents, hospitalized patients, or patients in long-term care facilities.
2. Studies that included patients with knee or hip OA and did not report the outcomes among the patients with knee OA.
3. Studies that involved surgical treatments or pharmacological treatments for knee OA.
4. Studies of adults with knee OA who had knee arthroplasty within 6 months before the study.
5. Studies that validated tests and measures in populations with other diseases.
6. Studies that reported absolute values of the diagnostic tests in adults with knee OA.
7. Studies that did not test the associative hypotheses and did not provide adequate information on tested hypotheses (e.g., least square means, relative risk).
8. Case series when the evidence was available from RCTs or controlled observational studies.
9. Secondary data analysis, nonsystematic reviews, letters, or comments.

To assess harms of treatments we will follow the recommendations from the *Methods Guide for Comparative Effectiveness Reviews*³⁴ and include published and unpublished evidence of the adverse effects of eligible physical therapy interventions including:

- RCTs.
- Published nonrandomized controlled trials.
- Observational studies.
- Observational studies based on patient registries or analyses of large databases.
- Case reports and postmarketing surveillance.

We define harms as a totality of all possible adverse consequences of an intervention.³⁴ We will analyze harms regardless of how authors perceived causality of treatments.

We do not plan to contact the investigators of the primary studies. The Scientific Resource Center will request Scientific Information Packets from appropriate manufacturers (shown in Appendix A) per usual procedures.

B. Literature Search Strategies

We will search several databases including MEDLINE[®] (via OVID and PubMed[®]), the Cochrane Library, the Physiotherapy Evidence Database (PEDro), SCIRUS, Allied and Complementary Medicine (AMED), and the Health and Psychosocial Instruments bibliography database to find published studies. We will also review grey literature packets from the Scientific Resource Center. This search includes regulatory documents and conducted clinical trials. Clinical trial registries will be searched for completed trials related to the KQs, including ClinicalTrials.gov and WHO Clinical Trials (International).

We will review registered ongoing studies of adults with knee OA in www.Clinicaltrials.gov. We will consult with the librarian at our Evidence-based Practice Center (EPC) to define exact

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search strategies to be guided by the Scientific Review Committee. Our EPC has developed an a priori search strategy based on relevant medical subject headings (MeSH) terms, text words, and weighted word frequency algorithms to identify related articles. Members of our Technical Expert Panel and peer reviewers may suggest additional sources of the evidence. We will document each recommended, included, and excluded study in the master library. We will update the literature search while the draft is under peer and public review.

Searching the evidence will involve several steps: 1) evaluate previously published systematic reviews;³⁵ 2) conduct a comprehensive literature search in the databases listed above to retrieve the references that will be stored in the EndNote reference-management system; 3) screen abstracts against pre-established inclusion/exclusion criteria; and 4) retrieve and review full articles on eligible studies to determine potential inclusion in the evidence synthesis. We will determine the eligibility of studies based on the developed a priori algorithm.

To ensure consistency, all evaluators will attend a training session before beginning the abstract review. Inclusion and exclusion criteria will be presented and discussed. In addition, the project team will meet after reviewing the first 25 abstracts to detect, discuss, and minimize disagreements and to develop a standardized reviewing approach. We will also randomly select a 10 percent sample of excluded randomized studies for a second review by the project director. We will develop a coding scheme to document and account for the reasons for exclusion.

C. Data Abstraction and Data Management

Evaluations of the studies and data extraction will be performed independently by four researchers. We will conduct a double independent data extraction from included RCTs. Errors in data extractions will be assessed by a comparison with established ranges for each variable and the data charts with the original articles. Any discrepancies will be detected and discussed. We will abstract the information relevant to the PICOT framework for each question. We will abstract minimum datasets to reproduce the results that were presented by the authors. For categorical variables we will abstract a number of events among treatment groups to calculate rates, relative risk, and absolute risk differences. Means and standard deviations of continuous variables will be abstracted to calculate mean differences with a 95 percent confidence interval (95% CI).

For RCTs, we will abstract the number randomized to each treatment group as the denominator to calculate estimates by applying intention-to-treat principles. We will abstract the time when the outcomes were assessed as weeks from randomization and the time of followup after treatments. For observational studies we will extract relative measures of the association (relative risk, hazard ratio, odds ratio) with standard error or 95% CI and reported adjustments for patient characteristics.

D. Assessment of Methodological Quality of Individual Studies

We will evaluate the quality of studies according to recommendations from the *Methods Guide for Comparative Effectiveness Reviews*:

Stage 1. Classify the Study Design

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Most studies can be classified as interventional (RCT or nonrandomized controlled clinical trial or nonrandomized uncontrolled clinical trial) or observational (cohort or case-control studies, cross-sectional studies, or case series).

Stage 2. Abstract Predefined Criteria for Quality for Critical Appraisal

We will evaluate risk of bias in the studies by using criteria of internal validity. We will evaluate applicability of the studies by using criteria of external validity.

For interventional studies, we will use criteria from the *Methods Guide for Comparative Effectiveness Reviews* including randomization, adequacy of allocation concealment, masking of the treatment status, and intention-to-treat principles.

For observational studies, we will evaluate strategies to reduce bias in study design and analysis, including adjustment for confounding and valid measurements of the outcomes. For diagnostic studies, we will apply the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria.^{36,37}

We will incorporate quality of individual studies into synthesis of evidence using individual quality criteria rather than global score or ranking category of overall quality.^{31,38}

Applicability of the population will be estimated by evaluating the selection of adults with knee OA in observational studies and clinical trials.³⁹ Studies of community dwelling adults that were treated in physical therapy settings will have high applicability. Large observational cohorts based on national registries, population-based effectiveness trials, and nationally representative administrative and clinical databases will have high applicability.

E. Data Synthesis

We will summarize the results into evidence tables. We will define physical therapy interventions according to the *Guide to Physical Therapist Practice* by the American Physical Therapy Association.³³ Eligible treatments would be those within the scope of physical therapy practice but not necessarily administered by physical therapists in a given study. In real life settings, the physical therapy interventions are performed in combination with other interventions for knee OA. However, comparative effectiveness of isolated physical therapy interventions can be examined in RCTs since randomization adequately distributes all factors including concomitant treatments. Thus, we will focus on RCTs to receive unbiased valid estimates of benefits and harms of isolated physical therapy interventions. We will also review observational studies with multivariate adjustment for concomitant treatments and confounding factors.

In addition, we will address the role of concomitant treatments in association with patient outcomes. We will abstract information about other nonsurgical treatments for knee OA that is reported in the studies. For instance, some trials may exclude patients taking pharmacological agents for knee OA. Then we will compare effects of the examined physical therapy interventions across the studies according to reported concomitant drug treatments. We will conduct sensitivity analysis according to concomitant drug treatments if the available data are suitable for the pooling.

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We will emphasize patient-centered outcomes in a synthesis of evidence. Pain related to knee OA, disability, and quality of life will serve as primary outcomes for the review. We will synthesize the evidence by the population characteristics that may modify treatment effect. Such characteristics include age, gender, race, baseline ADL, IADL, comorbidity, obesity, and a presence of significant skeletal abnormality.

We will review validity and reliability of the tests that are within the scope of physical therapy practice. The evidence of the association between intermediate and patient-centered outcomes after a physical therapy intervention will be synthesized from observational studies that adjusted for treatments and confounding factors.

We will calculate differences in relative risk and absolute risk from the abstracted events by using Meta-analyst⁴⁰ and STATA⁴¹ software at a 95% CI. We will calculate mean differences in continuous variables from the reported means and standard deviations by using Meta-analyst⁴⁰ and STATA⁴¹ software at a 95% CI. We will analyze in logarithmic scale the adjusted regression coefficient with a standard error of association between intermediate and patient-centered outcomes.

Pooling criteria for KQs 1 and 3 will include the same definitions of the physical therapy interventions and the outcomes. Standardized mean differences will be calculated for different measures of the same outcome. We will categorize treatment effects from the studies by the clinical importance of differences in intermediate outcomes.

Consistency in the results will be tested by comparing the direction and strength of the association.⁴² Chi square and I square tests will be used to assess heterogeneity in study results.^{43,44} We plan to explore heterogeneity with meta-regression and sensitivity analysis and will report the results from random effects models only.⁴⁵

The number needed to treat to achieve one event of patient-centered outcome will be calculated as reciprocal to absolute risk differences in rates of outcomes events in the active and control groups^{41,46}:

$$1 / (\text{control group event rate} - \text{treatment group event rate}).$$

The number of avoided or excess events (respectively) per population of 1000 is the difference between the two event rates multiplied by 1000:

$$(\text{control group event rate} - \text{treatment group event rate}) * 1000.$$

F. Grading the Evidence for Each Key Question

We will assess strength of evidence by following the guidelines from the *Methods Guide for Comparative Effectiveness Reviews* and will judge the strength of evidence according to risk of bias, consistency, directness, and precision for each major outcome.⁴² When appropriate, dose-response association, presence of confounders that would diminish an observed effect, strength of association, and publication bias will also be included.

We will grade the quality of evidence for primary outcomes across studies as illustrated in the table below:

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Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit a conclusion.

Applicability. Applicability of the population will be estimated by evaluating subject selection in observational studies and clinical trials.³⁹ Studies of community-dwelling adults with knee OA recruited from the general population would have high applicability. Large observational cohorts based on national registries, population-based effectiveness trials, and nationally representative administrative and clinical databases would have higher applicability. Applicability of the interventions would be higher if conducted by physical therapists. Applicability of the intervention duration will be high for studies with followup of 3 months or longer.

V. References

1. Johnson CA. Approach to the patient with knee pain. In: Imboden J, Hellman D and Stone J, eds. CURRENT diagnosis and treatment in rheumatology. 2nd ed. New York, NY: McGraw-Hill Companies; 2007. p. 123-37.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26-35.
3. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 2007;34:172-80.
4. Dillon CF, Rasch EK, Gu Q, et al. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. J Rheumatol 2006;33:2271-9.
5. Oliveria SA, Felson DT, Reed JI, et al. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum 1995;38:1134-41.
6. Felson DT, Zhang Y, Hannan MT, et al. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 1995;38:1500-5.
7. Bernstein AB, Hing E, Moss AJ, et al. Health care in America: trends in utilization. Hyattsville, MD: National Center for Health Statistics; 2003. DHHS Publication No. 2004-1031.
8. Andersson GBJ, Bouchard J, Bozic KJ, et al. Arthritis and related conditions. In: The burden of musculoskeletal diseases in the United States: prevalence, societal and economic cost. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2008. p. 71-96.

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Published Online: March 02, 2011

9. Andersson GBJ, Bouchard J, Bozic KJ, et al. Health care utilization and economic cost of musculoskeletal diseases. In: The burden of musculoskeletal diseases in the United States: prevalence, societal and economic cost. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2008. p. 195-225.
10. Imboden JB. Approach to the patient with arthritis. In: Imboden J, Hellman D and Stone J, eds. CURRENT diagnosis and treatment in rheumatology. 2nd ed. New York, NY: McGraw-Hill Companies; 2007. p. 32-41.
11. American Academy of Orthopaedic Surgeons. Treatment of osteoarthritis of the knee (non-arthroplasty). Rosemont, IL: American Academy of Orthopaedic Surgeons; 2008.
12. National Collaborating Centre for Chronic Conditions. Osteoarthritis: national clinical guideline for care and management in adults. London: Royal College of Physicians; 2008.
13. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16:137-62.
14. Jordan KM, Arden NK, Doherty M, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62:1145-55.
15. Mazucca SA, Brandt KD, Katz BP, et al. Comparison of general internists, family physicians, and rheumatologists managing patients with symptoms of osteoarthritis of the knee. Arthritis Care Res 1997;10:289-99.
16. Ottawa Panel evidence-based clinical practice guidelines for therapeutic exercises and manual therapy in the management of osteoarthritis. Phys Ther 2005;85:907-71.
17. Richmond J, Hunter D, Irrgang J, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on the treatment of osteoarthritis (OA) of the knee. J Bone Joint Surg Am 2010;92:990-3.
18. Rutjes AW, Nuesch E, Sterchi R, et al. Therapeutic ultrasound for osteoarthritis of the knee or hip. Cochrane Database Syst Rev 2010;20(1):CD003132.
19. Rutjes AW, Nuesch E, Sterchi R, et al. Transcutaneous electrostimulation for osteoarthritis of the knee. Cochrane Database Syst Rev 2009;(4):CD002823.
20. Fransen M, McConnell S. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2008;(4):CD004376.
21. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: Part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage 2010;18:476-99.
22. Michael JW, Schlüter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. Dtsch Arztebl Int 2010;107:152-62.
23. Felson DT. Clinical practice. Osteoarthritis of the knee. N Engl J Med 2006;354:841-8.
24. Bellamy N, Kirwan J, Boers M, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol 1997;24:799-802.

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25. Brouwer RW, Jakma TS, Verhagen AP, et al. Braces and orthoses for treating osteoarthritis of the knee. *Cochrane Database Syst Rev* 2005;(1):004020.
26. Brosseau L, Yonge KA, Robinson V, et al. Thermotherapy for treatment of osteoarthritis. *Cochrane Database Syst Rev* 2003;(4):CD004522.
27. US Food and Drug Administration Web site. Code of Federal Regulations. Title 21—Food and Drugs. Chapter 1—Food and Drug Administration and Department of Health and Human Services. Subchapter H—Medical Devices. Part 890—Physical Medicine Devices. Available at:
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=890>. Last Updated April 1, 2010. Accessed February 21, 2011.
28. Slutsky J, Atkins D, Chang S, et al. AHRQ series paper 1: comparing medical interventions: AHRQ and the Effective Health-Care Program. *J Clin Epidemiol* 2010;63:481-3.
29. Helfand M, Balshem H. AHRQ series paper 2: principles for developing guidance: AHRQ and the Effective Health-Care Program. *J Clin Epidemiol* 2010;63:484-90.
30. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20(3 Suppl):21-35.
31. Norris S, Atkins D, Bruening W, et al. Selecting observational studies for comparing medical interventions. In: Agency for Healthcare Research and Quality. *Methods guide for comparative effectiveness reviews*; Posted June 2010. Available at:
[http://www.effectivehealthcare.ahrq.gov/tasks/sites/ehc/assets/File/MethodsGuideNorris_06042010\(1\).pdf](http://www.effectivehealthcare.ahrq.gov/tasks/sites/ehc/assets/File/MethodsGuideNorris_06042010(1).pdf). Accessed February 21, 2011.
32. Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions*. 5.0.2 ed. London: Cochrane Collaboration; 2009.
33. American Physical Therapy Association. Impaired joint mobility, motor function, muscle performance, and range of motion associated with localized inflammation. In: *Guide to physical therapist practice*. 2nd ed. *Phys Ther* 2001;81:9-746.
34. Chou R, Aronson N, Atkins D, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the Effective Health-Care Program. *J Clin Epidemiol* 2010;63:502-12.
35. White CM, Ip S, McPheeters ML, et al. Using existing systematic reviews to replace de novo processes in conducting comparative effectiveness reviews. In: Agency for Healthcare Research and Quality. *Methods guide for comparative effectiveness reviews*; Posted September 2009. Available at:
<http://www.effectivehealthcare.ahrq.gov/ehc/products/123/329/SystematicReviewsReplaceDeNovo.pdf>. Accessed February 21, 2011.
36. Whiting PF, Weswood ME, Rutjes AW, et al. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. *BMC Med Res Methodol* 2006;6:9.
37. Agency for Healthcare Research and Quality. *Methods guide for medical test reviews*. Draft Posted November 2010. Available at:
<http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=558&pageaction=displayproduct>. Accessed February 21, 2011.

Source: www.effectivehealthcare.ahrq.gov

Published Online: March 02, 2011

38. Herbison P, Hay-Smith J, Gillespie WJ. Adjustment of meta-analyses on the basis of quality scores should be abandoned. *J Clin Epidemiol* 2006;59:1249-56.
39. Aschengrau A, Seage GR. *Essentials of epidemiology in public health*. 1st ed. Sudbury, MA: Jones & Bartlett; 2003.
40. Wallace BC, Schmid CH, Lau J, et al. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. *BMC Med Res Methodol* 2009;9:80.
41. Egger M, Smith GD, Altman DG, eds. *Systematic reviews in health care*. 2nd ed. London: John Wiley & Sons; 2001.
42. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. *J Clin Epidemiol* 2010;63:513-23.
43. Viechtbauer W. Confidence intervals for the amount of heterogeneity in meta-analysis. *Stat Med* 2007;26:37-52.
44. Knapp G, Biggerstaff BJ, Hartung J. Assessing the amount of heterogeneity in random-effects meta-analysis. *Biom J* 2006;48:271-85.
45. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
46. Ebrahim S. The use of numbers needed to treat derived from systematic reviews and meta-analysis. Caveats and pitfalls. *Eval Health Prof* 2001;24:152-64.

VI. Definition of Terms

ADL	Activities of Daily Living
CI	Confidence Interval
EPC	Evidence-based Practice Center
IADL	Instrumental Activities of Daily Living
KNEST	Knee Pain Screening Tool
KOOS	Knee Injury and Osteoarthritis Outcome Score
KPS	Knee Pain Scale
LEFS	Lower Extremity Functional Scale
OA	Osteoarthritis
OAKHQOL	Osteoarthritis Knee and Hip Quality of Life
OARSI	Osteoarthritis Research Society International
OPTIMAL	Outpatient Physical Therapy Improvement in Movement Assessment Log

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PEDro	Physiotherapy Evidence Database
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized Controlled Trial
TEP	Technical Expert Panel
TOO	Task Order Officer
VAS	Visual Analogue Scale
WOMAC	Western Ontario McMaster

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.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the 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 Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants 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.

Key Informants 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 Key Informants 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.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are 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,

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relevant systematic review. Therefore, study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The task order officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest that are identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. 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.

Potential 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.

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