

Future Research Needs Paper

Number 37

Physical Therapy for Knee Pain Secondary to Osteoarthritis: Future Research Needs

Identification of Future Research Needs From Comparative Effectiveness Review No. 77

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Prepared by:

Minnesota Evidence-based Practice Center
Minneapolis, MN

Investigators:

Michelle Brasure, Ph.D., M.L.I.S.
Tatyana A. Shamliyan, M.D., M.S.
Becky Olson-Kellogg, P.T., D.P.T., G.C.S.
Mary E. Butler, Ph.D., M.B.A.
Robert L. Kane, M.D.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that are needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang M.D., M.P.H.
Director, EPC Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Suchitra Iyer, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stakeholders

Roy D. Altman, M.D.
Department of Rheumatology
UCLA Medical Center
Los Angeles, CA

Dale Avers, P.T., D.P.T., Ph.D.
Physical Therapy
College of Health Professions
Syracuse, NY

Greg A. Brown, M.D.
Orthopaedic Surgery
University of Minnesota
Minneapolis, MN

Gail Deyle, P.T., D.Sc., D.P.T., O.C.S.,
FAAOMPT
Army-Baylor University
San Antonio, TX

D. T. Felson, M.D.
Arthritis Center/Rheumatology
Boston University School of Medicine
Boston, MA

Mark Haubner
Arthritis Foundation
Aquebogue, NY

Jennifer Hootman, Ph.D., A.T.C.
Division of Adult and Community Health
Centers for Disease Control and Prevention
Atlanta, GA

James Irrgang, Ph.D., P.T., A.T.C.
University of Pittsburgh
Pittsburgh, PA

Lyndon Joseph, Ph.D.
Division of Geriatrics and Clinical
Gerontology
National Institutes of Health
Bethesda, MD

Robin Katzanek, P.T., M.A., Ph.D.
Liberty Physical Therapy
Wakefield, RI

Tim Kauffman, P.T., Ph.D.
Kauffman Physical Therapy
Lancaster, PA

Alan Linblad, P.T., O.C.S.
Park Nicollet
Minneapolis, MN

Susan M. Miller
Centers for Medicare & Medicaid Services
Baltimore, MD

Carol A. Oatis, P.T., Ph.D.
Department of Physical Therapy
Arcadia College
Glenside, PA

Jim Panagis, M.D., M.P.H.
National Institute of Arthritis and
Musculoskeletal and Skin Disease
Bethesda, MD

Karen Siegel
Food and Drug Administration
Silver Spring, MD

Lynn Snyder-Mackler, P.T., A.T.C., S.C.S.,
Sc.D.
Department of Physical Therapy
University of Delaware
Newark, DE

Rita Wong, Ed.D., P.T.
Department of Physical Therapy
Marymount University
Arlington, VA

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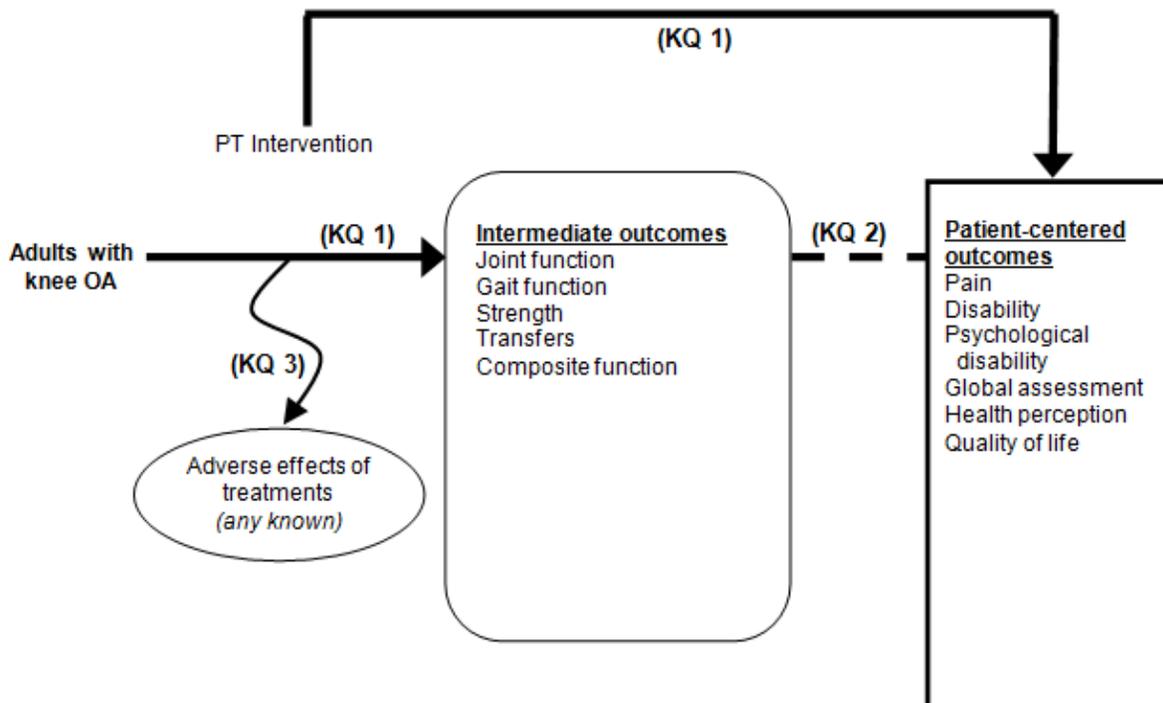
Executive Summary

Background

This Future Research Needs (FRN) project is a followup to the draft Comparative Effectiveness Review (CER) “Physical Therapy Interventions for Knee Pain Secondary to Osteoarthritis.” The review was motivated by uncertainty around the effectiveness and comparative effectiveness of physical therapy (PT) treatments for adult patients with knee pain secondary to osteoarthritis (OA). The purpose of this FRN project is to identify and prioritize specific gaps in the current literature on PT for knee pain due to OA that would aid decisionmakers. We used a deliberative process to identify evidence gaps, translate gaps into researchable questions, and solicit stakeholder opinion on the importance of research questions. This report proposes specific research needs along with research design considerations that may be useful in advancing the field.

The analytic framework adapted from the original draft CER (Figure A) describes the process experienced by adults with knee pain secondary to OA once they are referred for PT. Important Key Questions (KQ) about the efficacy and effectiveness of these treatments (KQ 1), the relationship between intermediate and patient-centered outcomes and use of minimal clinically important differences (MCIDs) (KQ 2), and the potential harms of PT treatments (KQ 3) were addressed in the review.¹

Figure A. Analytic framework



KQ = Key Question; OA = osteoarthritis; PT = physical therapy

The authors of the draft CER found that the evidence for KQ 1 supported the use of various forms of exercise therapy and ultrasound. Exercise therapy was efficacious when supervised by a physical therapist and typically resulted in a clinically meaningful improvement in pain and disability outcomes. The evidence comparing various forms of exercise therapy demonstrated similar benefits in disability measures for aerobic, aquatic, and strengthening exercise. Adherence to exercise therapy was the key to efficacy. Diathermy, orthotics, and magnetic stimulation used as stand-alone treatments demonstrated no benefit. Evidence was insufficient to conclude the best treatment option among effective PT interventions or to conclude differences in effects by patient characteristics. No consistent associations between the duration of examined interventions or followup times and intermediate/patient-centered outcomes were found.

For KQ 2, the intermediate outcomes of gait, mobility restrictions, muscle strength, and range-of-motion measures were associated with patient-centered disability measures in individual studies. However, these intermediate measures could not adequately predict patient-centered outcomes. MCIDs were determined for several outcomes scales, but not used consistently.

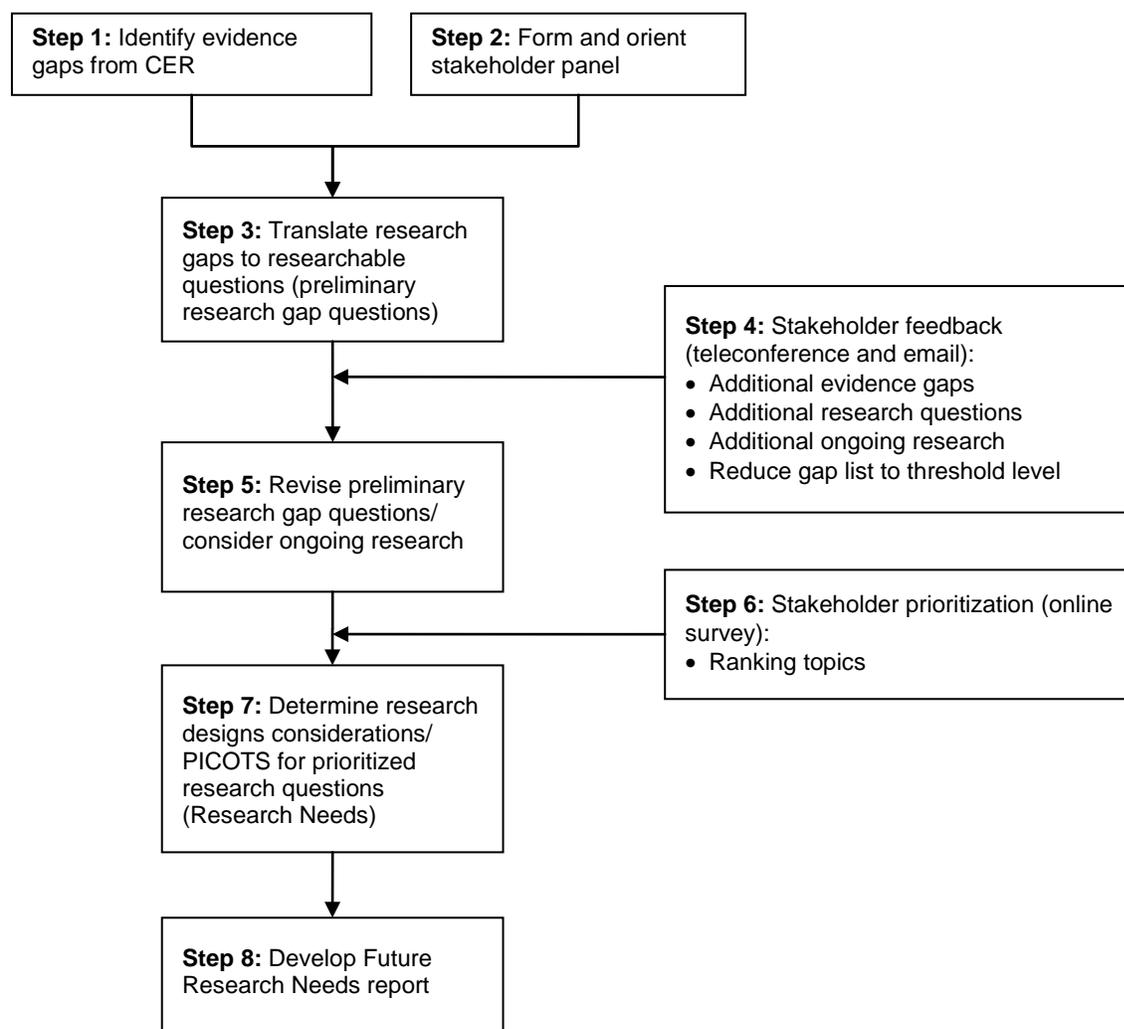
For KQ 3, the authors found that adverse events were uncommon and not severe enough to deter participants from continuing treatment.

Study quality and heterogeneity in populations and treatments, including concomitant treatments, downgraded the strength of evidence to low or moderate in most cases. The authors also identified gaps in evidence limiting their ability to draw definitive conclusions. There were a limited number of comparative effectiveness studies and efficacy studies primarily addressed stand-alone therapies rather than combinations, common in current clinical practice. The CER did not address whether adjunct therapies were effective in regard to their intended goal of enabling patients to more fully participate in primary therapies. Which patients are likely to benefit from exercise therapy alone and who may need a broader treatment approach could not be addressed. Evidence was insufficient to draw conclusions about the most effective activities (aerobic, strength, etc.) or dosage (intensity, frequency, duration) within exercise therapy. Evidence about long-term effectiveness of PT interventions is limited. Another systematic review suggests that long-term effectiveness is enhanced when booster or followup PT sessions are employed.²

Methods

We used a deliberative process to identify and prioritize research questions relevant to the evidence gaps identified in the CER.¹ Figure B illustrates the eight steps used to accomplish the objectives of this project.

Figure B. Project flow



CER = Comparative Effectiveness Review; PICOTS = population, intervention, comparison, outcome, timing, and setting

First, research gaps identified in the CER were translated to research questions. Secondly, a diverse stakeholder panel with representation from various perspectives relevant to the topic was assembled. Research representatives were national experts familiar with evidence-based medicine and the obstacles faced in conducting well-designed research from the fields of rheumatology, orthopedics, and PT. Representatives from organizations supporting or conducting relevant research including the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Aging, the American Physical Therapy Association as well as policy and payer representation from the Centers for Medicare and Medicaid Services and the Centers for Disease Control and Prevention participated on the stakeholder panel. Providers and consumers, including representation from the Arthritis Foundation, were also engaged because the decisional dilemmas faced by these groups are critical to identifying and prioritizing research questions.

We first held conference calls with stakeholders to refine the research gaps identified during the CER process. Based upon these conversations, we refined our initial list of research gap questions and categorized the questions by whether they were methodological, addressing issues

necessary to enhance the usefulness of current research, or topical, addressing issues that have not been sufficiently addressed in the current literature. This list of research questions was sent to a select group of stakeholders for ranking. Stakeholders numerically ranked their top 3 methodological research questions from a total of 7 and their top 4 topical research questions from a total of 11.

Based upon the natural breakpoints in these rankings, we determined high, moderate, and low priority research gap questions. High priority questions were deemed research needs. We then identified and discussed research design considerations for research needs.

Results

Prioritization Results

We analyzed weighted rankings for stakeholders participating in the Web-based prioritization process. From the 14 stakeholders invited to rank research questions, 12 ranked methodological questions and 11 ranked topical questions.

Methodological Research Needs

Natural breakpoints in weighted rankings revealed one high and four moderate priority methodological research questions. Because only one methodological research question appeared as a high priority, we also considered the moderate priority research questions research needs. Addressing methodological research needs will enhance the utility and translation of current and future research on PT interventions for patients with knee pain secondary to OA.

- Which patient-centered outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
- Which intermediate outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
- Should effectiveness research on PT treatments use MCIDs?
- What confounding and effect modifying variables (e.g. OA severity, obesity, comorbidities, and concomitant therapies-including anti-inflammatory and analgesic medication) should be measured and reported in effectiveness research?
- What minimum set of treatment factors (site, treatment components, frequency, duration, intensity, timing) should be reported consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?

Methodological research needs pertain to how effectiveness is measured and the consistency and completeness of research studies and reporting on interventions for knee pain secondary to OA. The draft CER emphasized that relatively few studies utilized MCIDs in evaluating efficacy and effectiveness. However, stakeholder discussions described problems in a reliance on MCIDs. While the concept of MCIDs offers a meaningful interpretation of scale scores, issues surrounding their calculation, reliability, and applicability to specific research populations, and the use of an average score to evaluate effectiveness of all patients deter their validity and utility.

Literature examined for the draft CER rarely provided adequate and consistent measurement and reporting of variables thought to confound or modify the effect of PT treatments for knee OA. Related to the reporting of confounding and effect modifying variables, stakeholders would

like to see a consensus on the identification and measurement of specific intervention characteristics reported in studies.

Considerations for Potential Research Designs

Methodological research needs could be addressed through a consensus development process (i.e., consensus conference). Because knee OA is treated by more than one group of providers, a multidisciplinary approach to consensus development is ideal, including representation from clinical areas (PT, rheumatology, and orthopedics) and researchers with expertise in clinical outcomes, epidemiology, biostatistics, and health services research. Continuing consensus work, facilitated by the Osteoarthritis Research Society International and Outcome Measures in Rheumatology, on improving the reporting and measuring effectiveness in OA trials³ will offer valuable information to address this research need. Specific research needs, such as guidance in the use of MCIDs, may benefit from pre-work prior to the consensus development process. The information needs to facilitate a discussion on MCID could be identified, collected or generated, and distributed before discussion.

Topical Research Needs

A natural breakpoint in weighted rankings of topical research questions revealed four research needs. All topical research needs addressed the PICOTS (population, intervention, comparison, outcome, timing and setting) elements of populations and interventions. Addressing topical research needs will enhance understanding of efficacy and comparative effectiveness, which was limited in the draft CER. Current ongoing studies addressing specific hypothesis will not likely sufficiently answer the research questions. However, related ongoing studies should be watched and their contributions should be considered when future studies are planned.

First Topical Research Need

- Which PT treatments work for which patients?

The draft CER, other reviews on the topic, current efficacy studies, and stakeholder discussions emphasized the need to address efficacy and comparative effectiveness for particular types of patients. While specific subgroups and interventions were not specified in this research need, subgroups can likely be defined by prevalent patient characteristics such as degree of symptoms, severity of disease, age, obesity and other characteristics that appear to have an effect on response to treatment.

Research Design Considerations

Topical research needs are best addressed with experimental designs. However, identifying specific patient subgroups (hypothesis generating research) may first be accomplished with less rigorous research designs. Review of previous systematic reviews, published trials including post hoc subgroup analyses, observational studies, and administrative databases could be used to extract hypothesized relationships between patient characteristics and specific therapies or multimodal treatments. The systematic review found very little evidence testing particular interventions for specific types of patients since very few studies reported the treatment outcomes for specific patient subpopulations. The systematic review focused on randomized controlled trials which can provide valid treatment estimates equally distributing patient characteristics and concomitant treatments among treatment groups. However, the review concluded that the results are applicable to the target population and much less to the

subpopulations by age, gender, baseline OA severity, and response to pharmacological treatments. Therefore, future research is needed for hypotheses by garnering expert opinion about which patient subgroups may respond differently to specific therapies.

Once hypotheses are generated, they should be tested using rigorous experimental design. Randomized controlled trials (RCTs) are the best approach. Conducting RCTs on specific patient subgroups is feasible yet the systematic review found very weak evidence of treatment effects in patient subpopulations. The review concluded that the evidence from individual RCTs did not support robust conclusions about differences in PT effects by patient age, gender, baseline severity of knee OA and multijoint OA, or responses to prior PT and drug treatments. However, a more valuable study design would be a large scale RCT with representative samples of sufficient size (as determined by the appropriate power calculations) from various subgroups of patients identified a priori. In designing these trials, another important concern lies in defining the PT treatments. Treatment definition for the intervention and comparator should be sufficient to explain specific activities used in each PT session or a protocol that explains the sequence of therapies. Treatments compared should capture the full range of PT treatments that would be used in practice. Fidelity checks may be necessary to monitor compliance with protocols. Attention should be paid to other concomitant treats, especially anti-inflammatory drugs and analgesics.

Second Topical Research Need

- How do the duration, intensity, and frequency of examined interventions affect sustained changes in patient-centered outcomes?

The CER found limited evidence to evaluate intervention characteristics. The duration of examined PT interventions was not consistently associated with better intermediate or patient-centered outcomes. Evidence regarding the association between the dose/intensity/frequency of examined interventions and outcomes was not available for the majority of comparisons. The effects of the treatments that significantly improved outcomes, including exercise (aerobic, aquatic, and strengthening) and ultrasound did not differ at shorter versus longer followup times. Moreover, electrical stimulation worsened pain at longer followup. Study risk of bias and heterogeneity in populations and treatments including concomitant treatments hampered strength of evidence to low or moderate in most cases. Stakeholder discussions confirmed that a better understanding of different intervention characteristics (especially dosage) and how they influence effectiveness would better inform decisionmaking.

Research Design Considerations

Processes similar to those mentioned above could be used to identify specific intervention characteristics that contribute to effectiveness. Again, experimental designs are likely the best approach to testing hypothesized relationships, yet very few RCTs examine the role of treatment intensity and duration on patient centered outcomes. The review found no high quality observational studies or administrative databases analyses suggesting significant improvement in patient centered outcomes with longer and more intense PT interventions in adult with knee OA. Design considerations for these experimental studies are also similar to those of this first research need. The approach might be implemented with trials testing the standard evidence-based treatment, exercise therapy. The most valid way to then address this research need would be with RCTs; however it may prove difficult to mount studies of adequate size. In that case quasi-experimental designs may be necessary. Prospective cohort studies with large samples may

be preferred to small RCTs, yet no well designed prospective cohort analyzed the association between PT intensity and duration on pain, function, or disability in older adults with knee OA. In either case, investigators should be careful to appropriately define the PT treatment and document the intensity, duration, and frequency. Special attention should be paid to adherence among study participants. Studies should be sufficiently powered to detect differences between groups as determined by appropriate power calculation. A major concern is in powering the study adequately to test the effects of combinations of treatment variations. The cohort studies should pay additional attention to identifying and adjusting results for potentially confounding variables.

Third Topical Research Need

- What is the comparative effectiveness of comprehensive multimodal PT treatments on patient-centered outcomes when compared with exercise alone?

The two remaining research needs have more focused hypotheses. Few studies comparing multimodal treatments to exercise alone are available, yet this question is particularly important to informing clinical practice. Current guidelines recommend that PT be delivered with a combination of modalities. Published research has focused instead on the marginal effects of individual PT interventions. The systematic review concluded that the studies overall had low applicability to the actual practice of PT because available studies focused on single modalities of PT rather than the combinations typically used in practice. In addition, many of the interventions were physical agents/modalities (i.e., orthotics, ultrasound, taping, etc.). This also contradicts the recommended practice of PT, in which physical agents/modalities are infrequently used in isolation, but rather combined with other more “active” interventions (i.e., exercises). The review found that few studies of combined PT modalities demonstrated no statistically significant benefit on the outcomes when compared with exercise alone.

Research Design Considerations

Given the specific hypothesis of this research need, an RCT is likely the best approach. Randomization eliminates concerns about inherent differences between the groups assigned to each intervention being responsible for differences in outcomes. An RCT will be resource intensive, requiring a large sample size because the marginal difference between the two active treatment arms is likely to be low and subgroups are particularly relevant in this question. Investigators should pay careful attention to defining the multimodal programs; only a limited number of combinations will be feasible.

Fourth Topical Research Need

- In individuals who proceed to joint replacement surgery, do patients who underwent PT treatments prior to surgery fare better postoperatively?

The CER focused on community-dwelling adults with knee pain secondary to OA. While many patients with knee OA eventually undergo joint replacement surgery, postsurgical outcomes were beyond the scope of this review. Stakeholders brought up this question as a research gap. Benefits of pre-surgical PT treatments on patient outcomes after surgery remain unclear and this information would have important clinical implications.

Research Design Considerations

In first addressing this research need, investigators should examine previous literature to determine if studies that address this question are available. Once hypotheses are generated, more rigorous studies can be conducted. Due to the potentially long-term nature of this outcome and the difficulty in identifying group members a priori, an RCT or other prospective design may not be feasible. Therefore, testing the hypothesis that individuals receiving PT treatment fare better after knee replacement surgery might best be approached with case control studies. Large sample sizes and the identification, measurement, and appropriate adjustment for confounding variables with multivariate analysis would strengthen the internal validity of these studies. However, limited causal inference will be a limitation.

Discussion

This FRNs project refined and prioritized research needs relevant to the KQs addressed in the draft CER, Physical Therapy Interventions for Knee Pain Secondary to Osteoarthritis.¹ We conducted a deliberative process to refine and expand research gaps identified in the CER through conversations with stakeholders with various perspectives of expertise on the topic. This process identified 7 methodological and 11 topical research questions thought to address identified evidence gaps. We then had stakeholders rank research questions. The highly ranked questions were deemed research needs. Stakeholders prioritized five methodological and four topical research needs.

Addressing methodological research needs will enhance the utility and comparability of future studies of PT treatments for knee OA. A common set of patient-centered and intermediate outcomes—with guidance on interpreting changes in outcomes scale scores—will provide researchers with concrete approaches to collecting outcomes data and determining effectiveness. Guidance on how PT interventions should be defined in research studies and variables to report in studies as determined by a multidisciplinary panel will, when utilized, enhance the quality of research on the topic.

Topical research needs demonstrate the importance of understanding that all PT interventions may not be ideal for all patients. Advancement in the field needs to address which treatments are effective for which patients. Additionally, a better understanding of how PT treatments are defined is essential to understanding their effectiveness. Complete interventions definitions will enhance the internal validity of studies and allow replicability of effective treatments. Testing specific hypotheses will fill specific evidence gaps identified and prioritized by our stakeholders.

For the specific research design selected to study a particular population and intervention, future studies on PT interventions should pay close attention to reducing bias as much as possible for that particular design and conducting studies with adequate power to test hypothesized relationships, including among subgroups.

While a strength of this project is the multidisciplinary perspective brought by broad stakeholder participation, our inability to collect a representative perspective from a larger sample of stakeholders is also a limitation. The stakeholders participating in this project represented various perspectives on knee OA and PT. However, the prioritized research needs reflect the opinions of these stakeholders and may not be generalizable to the population of stakeholders on this topic.

Conclusions

Addressing research needs identified in this FRN project will help to create a broader and stronger evidence base in which clinical decisions can be made. Future research addressing specific research questions is likely to establish a preliminary research agenda on this topic:

- Which patient-centered outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
- Which intermediate outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
- Should effectiveness research on PT treatments use MCID?
- What confounding and effect modifying variables (e.g., OA severity, obesity, comorbidities, and concomitant therapies-including anti-inflammatory and analgesic medication) should be measured and reported in effectiveness research?
- What minimum set of treatment factors (site, treatment components, frequency, duration, intensity, timing) should be reported consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
- Which PT treatments work for which patients?
- How do the duration, intensity, and frequency of examined interventions affect sustained changes in patient-centered outcomes?
- What is the comparative effectiveness of comprehensive multimodal PT treatments on patient-centered outcomes when compared with exercise alone?
- In individuals who proceed to joint replacement surgery, do patients who underwent PT treatments prior to surgery fare better postoperatively?

References

1. Shamliyan TA, Wang S-Y, Olson-Kellogg B, Kane RL. Physical Therapy Interventions for Knee Pain Secondary to Osteoarthritis. Comparative Effectiveness Review No. 77. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2007-10064-I.) AHRQ Publication No. 12(13)-EHC115-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
2. Pisters MF, Veenhof C, van Meeteren NLU, et al. Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review. *Arthritis & Rheumatism*. 2007 Oct 15;57(7):1245-53. PMID: 17907210.
3. Riddle DL, Stratford PW, Singh JA, et al. Variation in outcome measures in hip and knee arthroplasty clinical trials: a proposed approach to achieving consensus. *Journal of Rheumatology*. 2009 Sep;36(9):2050-6. PMID: 19738212.

Background

Context

This Future Research Needs (FRN) project is a followup to the draft Comparative Effectiveness Review (CER) “Physical Therapy Interventions for Knee Pain Secondary to Osteoarthritis.” The review was motivated by uncertainty around the effectiveness and comparative effectiveness of physical therapy (PT) treatments for adult patients with knee pain secondary to osteoarthritis (OA). FRN projects identify gaps in the current research that limit the conclusions in CERs and inform those who conduct and fund research of these gaps. FRN projects aim to encourage research likely to fill gaps and make the body of evidence more useful to decisionmakers. The report addressed the following Key Questions (KQs):

KQ 1: What are the effectiveness and comparative effectiveness of available PT interventions (without drug treatment) for adult patients with chronic knee pain due to OA on intermediate and patient-centered outcomes when compared with no active treatment or another active PT modality?

- a. Which patient characteristics are associated with the benefits of examined interventions of PT 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 PT?
- c. Do changes in intermediate and patient-centered outcomes differ by the time of followup?

KQ 2: What is the association between changes in intermediate outcomes with changes in patient-centered outcomes after PT interventions?

- a. What is the validity of the tests and measures used to determine intermediate outcomes of PT 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 (MCIDs) of the tests and measures used to determine intermediate outcomes?

KQ 3: What are the harms from PT interventions available for adult patients with chronic knee pain due to OA when compared with no active treatment or active controls?

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

Physical Therapy for Knee Osteoarthritis

OA, the most common form of arthritis,¹ is a progressive disorder characterized by gradual loss of cartilage and the development of bony spurs and cysts at the surface and margins of the joints. Inflammation, pain, stiffness, limited movement, and possible deformity of the joint may result.² In the United States OA of the knee afflicts 28 percent of adults over age 45³ and 37 percent of adults over age 65.³⁻⁶ OA is a leading cause of disability among noninstitutionalized adults;⁴ those affected by it have slower gait velocities and use more assistive walking devices and nonsteroidal anti-inflammatory drugs and narcotics than those not affected. Further, the Centers for Disease Control and Prevention anticipates that the prevalence, health impact, and economic consequences of OA will surge during the next few decades as the population ages.⁷

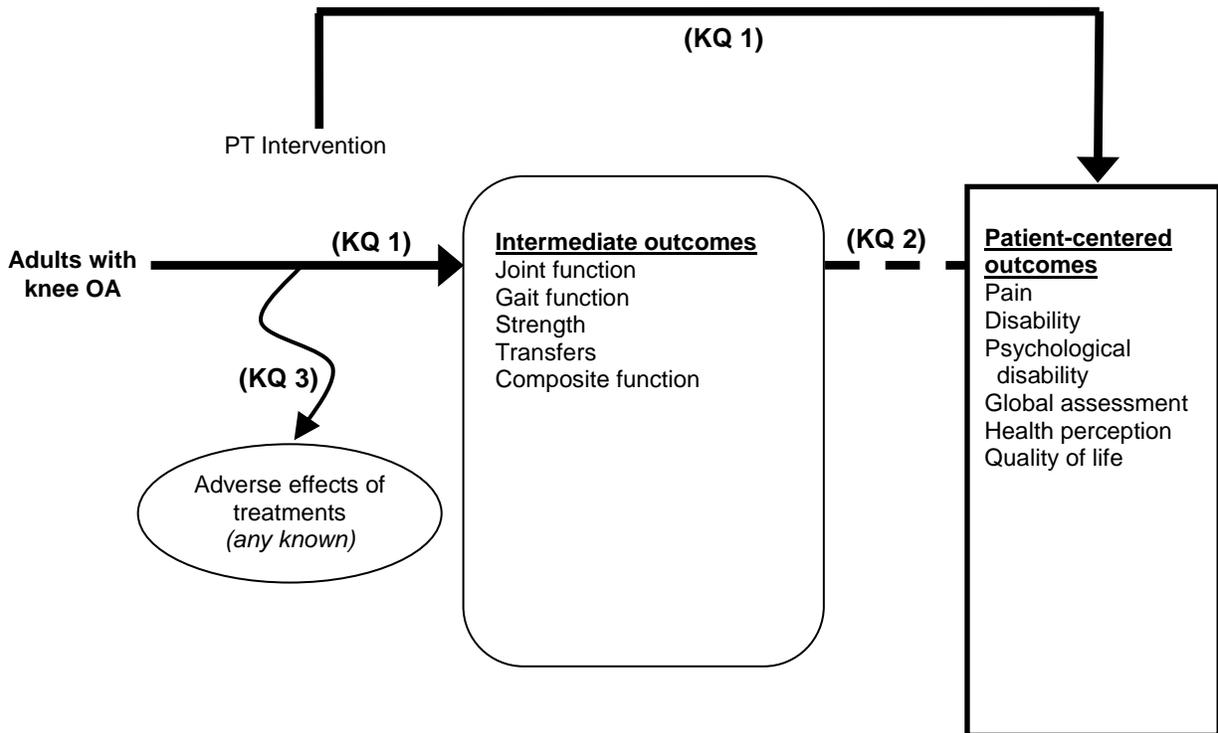
Treatments for OA aim to reduce or control pain, improve physical function, prevent disability, and enhance quality of life—all of which constitute clinical outcomes of importance to patients.^{8,9} Treatment options include pain relievers, anti-inflammatory drugs, weight loss, general physical exercise, PT, and, when conservative treatments fail, surgery.⁹

Comprehensive, up-to-date guidelines are available from the Osteoarthritis Research Society International, the American Academy of Orthopedic surgeons, and the National Institute for Health and Clinical Excellence. These guidelines recommend exercise (including local muscle strengthening and general aerobic fitness) as a core treatment for symptomatic OA, irrespective of patient age, comorbidity, pain severity, or disability.⁹⁻¹¹ Effectiveness has not been clearly established for other nonpharmacologic PT interventions as adjunct to core treatment (e.g. thermal, manipulation, electrical nerve stimulation, and orthotics).⁹

The analytic framework adapted from the original draft CER (Figure 1) simplifies the process experienced by adults with knee pain secondary to OA once they are referred for PT. The actual practice of PT, condensed to a single point in the analytical framework, is a complex process. Traditionally, a patient is seen by a primary care provider or specialist for knee pain. This provider may then diagnose OA and refer the patient for PT. Encounters with the physical therapist are comprehensive. The Guide to Physical Therapy Practice describes five elements of patient management leading to optimal outcomes.¹²

- Examination—Patient history, screening, and specific testing to inform treatment.
- Evaluation—Physical therapist makes clinical judgments based on information gathered during examination.
- Diagnosis—Process and end result of evaluation, organized into categories to help determine prognosis and plan of care.
- Prognosis (including plan of care)—Determination of level of optimal improvement and interventions, duration, timing, and frequency.
- Intervention—Purposeful and skilled interaction of the physical therapist with the patient to produce changes consistent with diagnosis and prognosis. Reexamination to determine changes in patient status and to modify/redirect intervention based upon clinical findings or lack of progress.

Figure 1. Analytic framework



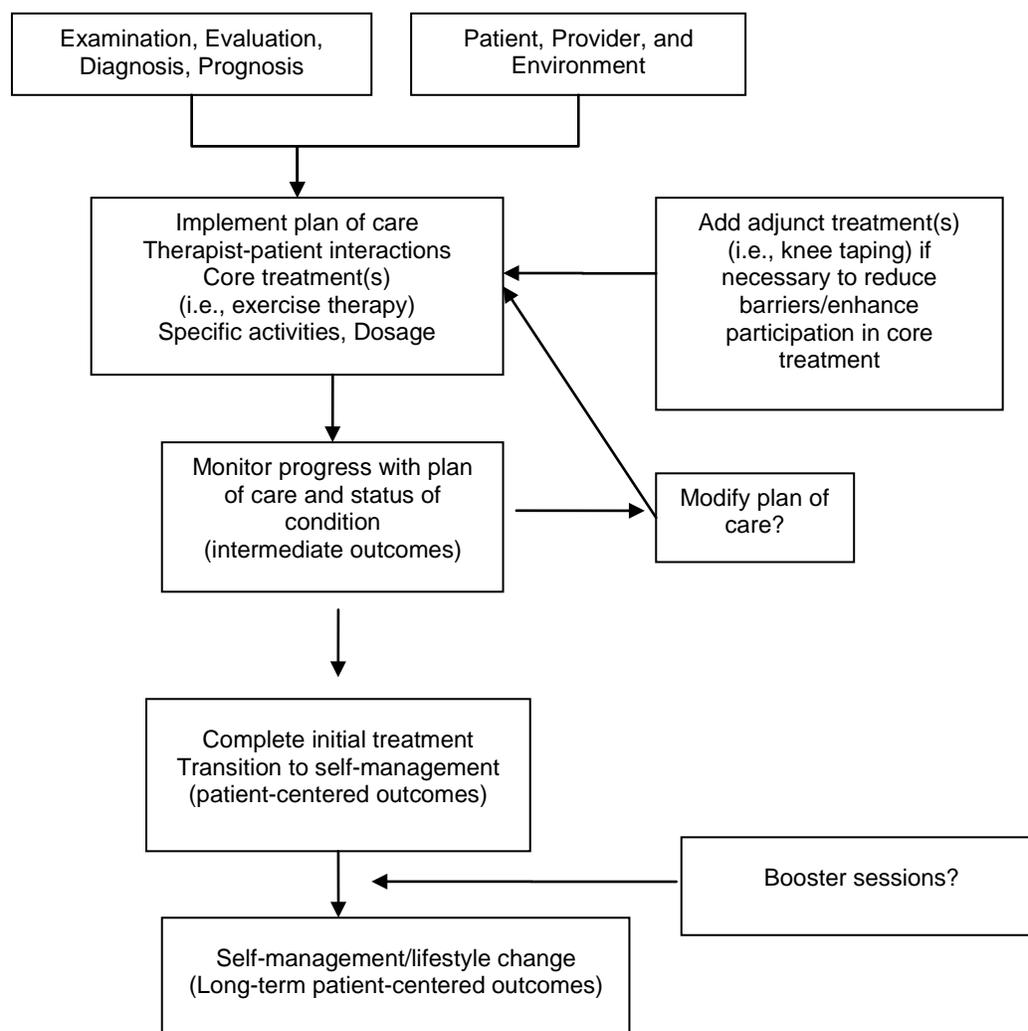
KQ = Key Question; OA = osteoarthritis; PT = physical therapy

The draft CER specifically addressed individual PT interventions; however, in PT practice, the plan of care includes specific interventions or combinations of interventions that are carefully chosen according to patient characteristics and condition status (i.e., symptoms such as pain, functional limitations, inflammation, etc.) (Figure 2). How each intervention fits into the plan of care highlights the relevant outcome by which its effectiveness should be measured.

Plans of care may include primary therapies aimed at decreasing pain and improving function as well as supplemental therapies aimed at removing barriers to or enhancing participation in primary therapies. For instance, exercise therapy is often considered a core therapy for patients with knee pain secondary to OA. However, not all patients can initially tolerate exercise therapy due to pain or limited function. In these cases, adjunct therapies such as manual therapy, taping, or transcutaneous electrical nerve stimulation may be incorporated into the plan of care in order to reduce pain and enable fuller participation in exercise therapy and other physical activity. The same therapies used as adjunct therapies may also be used as stand-alone therapies.

PT practice emphasizes the careful monitoring each patient’s condition status and progress with the plan of care throughout treatment so that the plan of care can be altered as needed to optimize participation and outcomes.

Figure 2. Physical therapy for knee osteoarthritis: intervention algorithm



Findings of the Draft Comparative Effectiveness Review

The authors of the draft review found that the evidence for KQ 1 supported the use of various forms of exercise therapy and ultrasound. Exercise therapy was efficacious when supervised by a physical therapist and typically resulted in a clinically meaningful improvement in pain and disability outcomes. The evidence comparing various forms of exercise therapy demonstrated similar benefits in disability measures for aerobic, aquatic, and strengthening exercise. Adherence to exercise therapy was the key to efficacy. Diathermy, orthotics, and magnetic stimulation used as stand-alone therapies demonstrated no benefit. Evidence was insufficient to conclude the best treatment option among PT interventions or to conclude differences in effects by patient characteristics. No consistent associations between the duration of examined interventions or followup times and intermediate/patient-centered outcomes were found.

For KQ 2, the intermediate outcomes of gait, mobility restrictions, muscle strength, and range-of-motion measures were associated with patient-centered disability measures in individual studies. However, these intermediate measures could not adequately predict patient-centered outcomes. MCIDs in scales were determined for 26 scales, but therapeutic studies did

not consistently evaluate treatments using MCIDs. The Patient Acceptable Symptom State, a threshold for patient satisfaction, was available for three patient-centered outcomes scales.

For KQ 3, the authors found that adverse events were uncommon and not severe enough to deter participants from continuing treatment.

Study quality and heterogeneity in populations and treatments, including concomitant treatments, downgraded the strength of evidence to low or moderate in most cases. The authors also identified gaps in evidence limiting their ability to draw definitive conclusions. There were a limited number of comparative effectiveness studies, and efficacy studies primarily addressed stand-alone therapies rather than combinations, which are more common in current clinical practice. The CER did not address whether adjunct therapies were effective for enabling patients to more fully participate in core therapies as intended. Which patients are likely to benefit from exercise therapy alone and which ones may need a broader treatment approach was not clearly established. Evidence was insufficient to draw conclusions about the most effective activities (aerobic, strength, etc.) or dosage (intensity, frequency, duration) within exercise therapy. Evidence about long-term effectiveness of PT interventions is limited. One systematic review suggests that long-term effectiveness is enhanced by followup booster sessions.¹³

Objective

This FRN project identifies and prioritizes specific gaps in the current literature on PT for knee pain due to OA that would, if addressed, aid decisionmakers. We used a deliberative process to identify specific research needs along with research design considerations meant to advance the field.

Evidence Gaps and Research Question Development

As with much of the research on functional therapies, many studies of PT interventions for patients with knee pain secondary to OA exhibited problems with design and conduct. Our original report included recommendations to improve future research on this topic. We refined and developed the list of evidence gaps listed in the draft report and phrased the gaps as research questions. This preliminary set of research questions (below) are separated into two categories: (1) methodological research questions that need to be addressed to enhance the usefulness of current research and (2) topical research questions that have not been sufficiently addressed within the current literature.

Methodological Research Questions

1. How should combined PT interventions be defined to facilitate hypothesis testing and provide sufficient evidence applicable to current PT practice?
2. How do patient-centered outcomes differ depending on the involvement of a physical therapist or physical therapist assistant, group versus individual exercise, and self-administered versus supervised exercises?
3. What are the valid and reliable instruments used to measure patient-centered outcomes?
 - Pain/Independence in activities of daily life/instrumental activities of daily life
 - Patient satisfaction
 - Time to return to work/activities
 - Quality of life

- Community integration
 - Psychological disability
 - Self-perceived health
- a. What is the minimum clinically important difference (MCID) for each of these valid and reliable instruments?
 - b. What cutpoints should be used to describe clinically meaningful categories in the scale scores created by these instruments?
4. What are the valid and reliable instruments used to measure the following intermediate outcomes when evaluating the effectiveness and comparative effectiveness of PT interventions for knee pain secondary to OA?
 - Joint function
 - Swelling
 - Inflammation
 - Gait function
 - Strength
 - Transfers
 5. Which intermediate outcomes meet the criteria for surrogate patient-centered outcomes?
 6. What confounding variables (e.g., compliance, weight loss, activity levels), and effect modifiers including concomitant therapies should be controlled for?

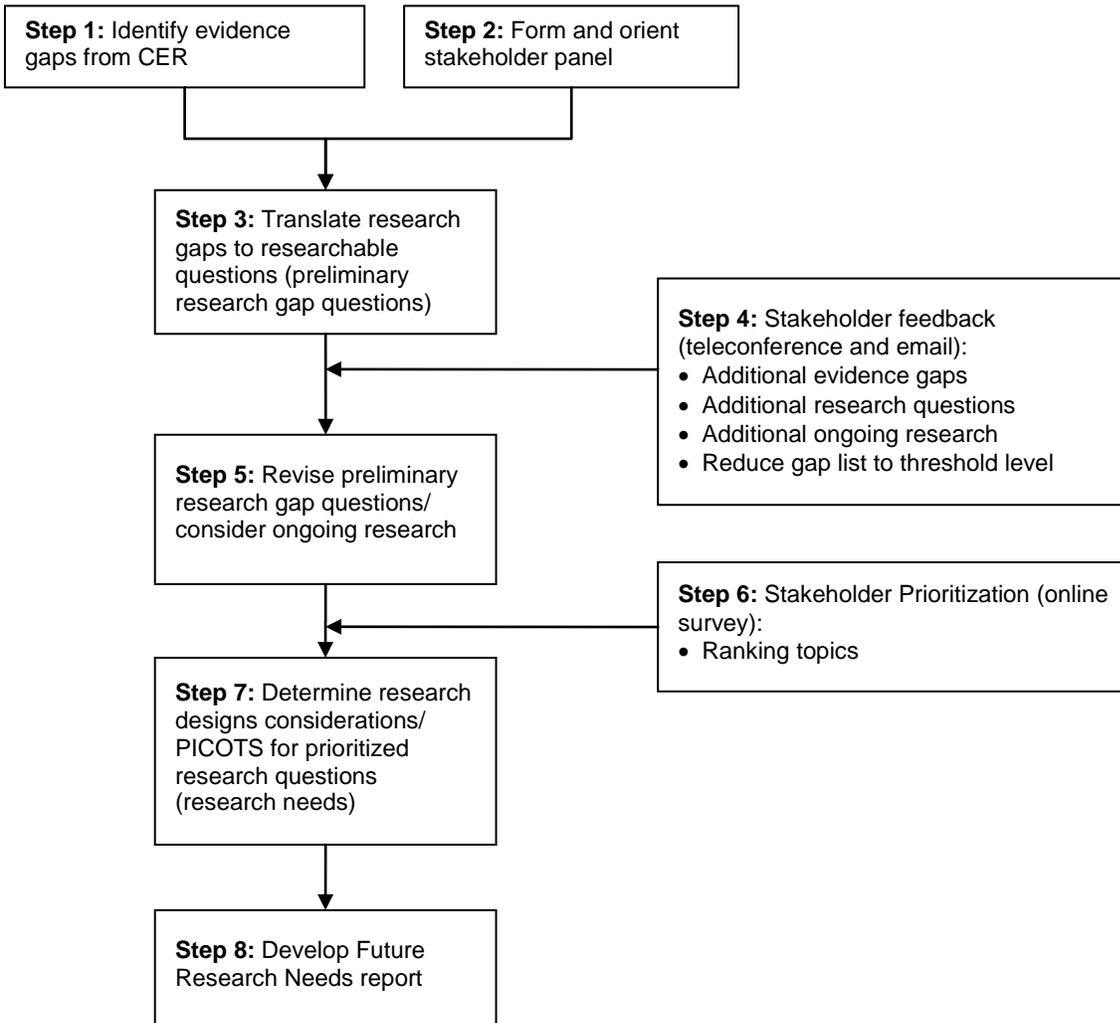
Topical Research Questions

1. What is comparative effectiveness of combined PT interventions for adult patients with chronic knee OA on patient-centered outcomes?
2. What is the marginal benefit from individual treatment modalities (e.g. heat, ice) delivered in the appropriate stage or status of OA?
3. Which patient characteristics are associated with patient-centered outcomes resulting from examined combined or single PT interventions?
 - Age
 - OA severity
 - Multi-joint OA
 - Concomitant treatment
 - Comorbidity
4. Do sustained changes in patient-centered outcomes differ by the duration, intensity, and frequency of examined interventions?
5. What are the harms of PT interventions for knee pain secondary to knee OA?

Methods

We used a deliberative process to identify and prioritize research questions relevant to the evidence gaps identified in the recently completed draft CER on PT for knee pain secondary to OA.¹⁴ Figure 3 illustrates the eight steps used to accomplish the objectives of this project.

Figure 3. Project flow



CER=Comparative Effectiveness Review; PICOTS=population, intervention, comparison, outcome, timing, and setting

Engagement of Stakeholders

We recruited panel of stakeholder’s panel with diverse perspectives relevant to the topic. We followed guidance on stakeholder engagement for recruitment and communication.¹⁵ We sought to recruit stakeholders who were actively interested in PT treatments for patients with knee pain secondary to OA and who wished to help shape future research priorities. We identified potential stakeholders via several means. We sought recommendations from the CER project team, including select Key Informants and Technical Expert Panel members. We also identified stakeholders who were serving on panels from related Agency for Healthcare Research and Quality (AHRQ) FRN projects or who were listed in the Effective Health Care Contacts

Database.¹⁶ Research representatives were national experts familiar with evidence-based medicine and aware of the obstacles faced in conducting well-designed research from rheumatology, orthopedics, and PT. We invited representatives from organizations supporting or conducting relevant research, including the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Aging, the American Physical Therapy Association, and others, as well as policy and payer representation from the Centers for Medicare and Medicaid Services and the Center for Disease Control and Prevention. We engaged providers and consumers, including representation from the Arthritis Foundation, because the decisional dilemmas faced by these groups are critical to identifying and prioritizing research questions. Many stakeholders were also involved in the CER process as Key Informants, Technical Expert Panel members, or peer reviewers. This made engaging them as stakeholders challenging due to the overlap in timing with the FRN project and finalization of the CER.

Handling Conflicts of Interest

We collected disclosures of conflicts of interests from all stakeholders. Disclosed interests did not bar any stakeholders from participation, but allowed the Evidence-based Practice Center (EPC) to evaluate contributions based on possible conflicts. Stakeholders used a Web-based survey to rank specific topical research questions during the prioritization exercise, thus researchers and funders were blind to the others' stated opinions.

Refinement of Research Questions

We provided members of our stakeholder panel with a preliminary set of research questions prior to conference calls. During conference calls, we sought stakeholder input to further refine the research questions (i.e., organization and wording of the questions, identification of additional research questions, and elimination of research questions with limited clinical value). To facilitate this input, we provided stakeholders in advance with background materials, including the draft CER executive summary and the Effective Health Care Program Selection Criteria. We conducted two conference calls with available stakeholders in February and March of 2012. A total of 14 stakeholders participated in the calls. All participants provided input on the calls. We circulated summaries of group calls to all participants, including two additional stakeholders not able to participate in the conference calls. We invited stakeholders to clarify or supplement the call summaries or to suggest additional research questions in response to the call summaries, and several did so via email. We revised the preliminary questions based upon these discussions and email communications. The revised set of questions moving on to the prioritization phase is listed in Appendix A.

Prioritization

We and our stakeholders evaluated the revised set of research questions according to specified criteria. The Effective Health Care Program Selection Criteria provided a starting point (Appendix B), including Appropriateness, Importance, Feasibility, Redundancy, and Potential Impact. The Appropriateness and Importance criteria are de facto met since PT treatments for patients with knee pain secondary to OA was accepted as an AHRQ topic.

We addressed the Redundancy criteria by conducting a search for ongoing and recently completed research using ClinicalTrials.gov. CER authors also updated the bibliographic database search for relevant newly published studies in December 2011 and incorporated these

findings into the final CER. We conducted a precise search of recently published studies addressing aspects of identified research questions through May of 2012. The search strategies appear in Appendix C. We attempted to match identified recent and ongoing studies with revised research questions.

We then asked stakeholders to rank the research questions focusing on their potential impact criteria (i.e., the likelihood that addressing the research gap question would inform clinical practice and policy). We developed a Web-based survey using SurveyMonkey to collect stakeholder prioritization of the research gap questions.¹⁷ A subset of 14 stakeholders (fewer than 10 were non-Federal employees) were invited to rank research questions identified via the stakeholder conference calls. The subset of stakeholders was chosen from the broader set to assure representation from all major viewpoints. These stakeholders numerically ranked their top three of seven methodological research questions, and their top four of 11 topical research questions.

Stakeholder rankings were weighted according to their assigned numerical ranking. If a stakeholder assigned a question the number one priority, that question received four points; number two ranking – three points; number three ranking – two points; and number four ranking – one point. We identified natural breakpoints in the weighted rankings that separated high, moderate, and low priority research questions. Highly prioritized research questions were considered research needs. We disseminated results of the forced ranking procedure to all engaged stakeholders for review and comment prior to preparing the final report.

We then evaluated the feasibility criteria for research needs. We framed feasibility in terms of anticipated research designs. For example, factors that affect the feasibility of conducting randomized controlled trials include the sample size needed for the outcome, the size of the available pool of potential subjects, followup duration, willingness to randomize, and applicability issues. In contrast to randomization and applicability, observational studies face feasibility issues related to measuring study variables using different data sources and unobserved variables that create risk of bias.

Research Design Considerations

We generated research design considerations for identified research needs. For methodological research needs we provided context and described resources and research design considerations potentially useful to researchers, facilitators, and funders of this type of research. For topical research needs we highlighted the relevant PICOTS (population, intervention, comparison, outcome, timing, and setting) element(s), provided context, described related ongoing research, and discussed potential research designs. Because more than one research design can be applied to an individual research need, we discussed the advantages and disadvantages of different options. These discussions were guided by a recent AHRQ report describing frameworks for evaluating research designs in FRNs.¹⁸ We did not consult with stakeholders for input on research design considerations.

Results

Research Needs

Prioritization Results

Stakeholders separately ranked methodological and topical research questions. Of the 14 stakeholders invited to participate in the ranking process, 11 stakeholders ranked methodological research questions and 12 ranked topical research questions. Participating stakeholders primarily identified themselves as physical therapists, but the group also included physicians, an epidemiologist, and a health scientist. We analyzed weighted stakeholder rankings for each research question to identify natural breakpoints (Table 1). High- and moderate-priority methodological research questions and high-priority topical research questions were deemed research needs.

Table 1. Stakeholder prioritization of research gap questions

	Ranking	Total (Points)*	PICOTS Element
Methodological Topics Needing Consensus (n=11)	Tier 1: High Priority		
	Which patient-centered outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?	9 (33)	NA
	Tier 2: Moderate Priority		
	Should effectiveness research on PT treatments use minimal clinically important differences?	7 (21)	NA
	What confounding and effect modifying variables (e.g. OA severity, obesity, comorbidities, and concomitant therapies including anti-inflammatory and analgesic medication) should be measured and reported in effectiveness research?	6 (18)	NA
	Which intermediate outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?	5 (15)	NA
	What minimum set of treatment factors (site, treatment components, frequency, duration, intensity, timing) should be reported consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?	5 (13)	NA
	Tier 3: Low Priority		
	How should multimodal PT treatments be classified?	2 (8)	NA
How should knee OA severity be graded consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?	1 (3)	NA	
Topical Questions Needing Trials (n=10)	Tier 1: High Priority		
	Which PT treatments work for which patients?	7 (22)	P, I
	How do the duration, intensity, and frequency of examined interventions affect sustained changes in patient-centered outcomes?	7 (18)	I
	What is the comparative effectiveness of comprehensive multimodal PT treatments on patient-centered outcomes when compared with exercise alone?	5 (15)	I
In individuals who proceed to joint replacement surgery, do patients who underwent PT treatments prior to surgery fare better postoperatively?	6 (14)	P	

Table 1. Stakeholder prioritization of research gap questions (continued)

	Ranking	Total (Points)*	PICOTS Element	
Topical Questions Needing Trials (n=10) (continued)	Tier 2: Moderate Priority			
	Do periodic followup treatments beyond the initial PT treatments enhance effectiveness?	5 (10)	NA	
	What is the long-term effectiveness of PT treatments on patient centered outcomes?	3 (10)	NA	
	What is the comparative effectiveness over the entire course of different comprehensive multimodal PT programs (from initial PT-directed treatments through self-management and occasional followup treatments)?	3 (8)	NA	
	Tier 3: Low Priority		NA	
	How does the method of delivery (e.g., the involvement of a physical therapist or physical therapist assistant, group versus individual exercise, self-administered versus supervised exercises, etc.) affect patient-centered outcomes?	3 (3)	NA	
	Does PT for knee OA delay time to surgery?	2 (3)	NA	
	Does PT for knee OA reduce medication use?	1 (1)	NA	
Do PT treatments affect structural joint changes?	1 (1)	NA		

NA = Not applicable; OA = osteoarthritis; PICOTS = population, intervention, comparison, outcome, timing, and setting; PT = physical therapy

*Rankings were weighted to create a total point score by assigning questions ranked #1 by stakeholders with 4 points, questions ranked #2 with 3 points, questions ranked #3 by stakeholders with 2 points, and questions ranked #4 by stakeholders with 1 point.

Methodological Research Needs

From among the methodological questions, the identification of a standard set of patient-centered outcomes measures was a clear frontrunner (Tier 1: High Priority), with more than 70 percent of stakeholders ranking it a priority and over half of all stakeholders ranking it the number-one priority. The rankings of four additional methodological research gap questions were clustered together, but distantly less important to stakeholders than the top tier (Tier 2: Moderate Priority). Because only one methodological research gap question appeared to be a high priority according to the natural breakpoint in the rankings, we also considered the moderate priority research gap questions to be research needs. Addressing methodological research needs will enhance the utility and translation of current and future research on PT interventions for patients with knee pain secondary to OA.

- Which patient-centered outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
- Which intermediate outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
- Should effectiveness research on PT treatments use MCIDs?
- What confounding and effect modifying variables (e.g., OA severity, obesity, comorbidities, and concomitant therapies including anti-inflammatory and analgesic medication) should be measured and reported in effectiveness research?
- What minimum set of treatment factors (site, treatment components, frequency, duration, intensity, timing) should be reported consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?

Methodological research needs pertain to how effectiveness is measured and the consistency, completeness, and reporting of intervention studies for knee pain secondary to OA. The first

three research needs reflect the need for consensus on how to best measure effectiveness. Pain and function are considered important patient-centered outcomes for adults with knee OA. PT interventions for knee OA should be evaluated for the degree to which they can improve function and decrease pain. Prior to the stakeholder ranking process, we assumed general agreement about which patient-centered and intermediate outcome measurement instruments should be used in effectiveness research. CER authors and stakeholder discussions appeared to indicate that preferred measures were generally understood. Several stakeholders mentioned the Outcome Measures in Rheumatology recommended set of outcomes measures for future hip, knee, and hand trials.¹⁹ Despite this available guidance, the CER and other OA research demonstrate the use of a wide variety of outcomes measures.^{14,20}

The CER emphasized that relatively few studies used MCIDs in evaluating efficacy and effectiveness. However, stakeholder discussions described problems with relying on MCIDs. Theoretically, MCIDs offer a way to meaningfully interpret scale scores; however, the validity and utility of MCIDs are impeded by issues surrounding their calculation, reliability, and applicability to specific research populations, and by the use of an average score to evaluate effectiveness for all patients.

Literature examined for the draft CER rarely provided adequate and consistent measurement and reporting of variables thought to confound or modify the effect of PT treatments for knee OA. Related to the reporting of confounding and effect modifying variables, stakeholders would like to see consensus on how studies should report specific intervention characteristics.

Considerations for Potential Research Designs

Methodological research needs could be addressed through a consensus development process (i.e. consensus conference). Because knee OA is treated by more than one group of providers, an ideal consensus development process would be multidisciplinary, with representation from clinical areas (PT, rheumatology, and orthopedics) and researchers with expertise in clinical outcomes, epidemiology, biostatistics, and health services research. Continuing consensus work, facilitated by the Osteoarthritis Research Society International and Outcome Measures in Rheumatology, on improving the reporting and measuring effectiveness in OA trials²⁰ will offer valuable information to address this research need. Specific research needs, such as guidance in the use of MCIDs, may benefit from prework prior to the consensus development process. The information necessary for facilitating a discussion on MCIDs could be identified, collected or generated, and distributed before discussion.

Topical Research Needs

We identified four high-priority topical research gap questions as research needs and highlighted the PICOTS element(s) addressed for each need (Table 1). All topical research needs addressed primarily populations and interventions. Addressing topical research needs will enhance understanding of efficacy and comparative effectiveness, which was limited in our recently completed CER. New research addressing topical questions will provide improved information for decisionmakers.

First Topical Research Need

- Which PT treatments work for which patients?

The draft CER, other reviews on the topic, current efficacy studies, and stakeholder discussions emphasized the need to address efficacy and comparative effectiveness for particular types of patients. While specific subgroups and interventions were not specified in this research need, subgroups can likely be defined by prevalent patient characteristics such as age, degree of symptoms, severity of disease, the presence of obesity and other comorbidities that appear to have an effect on response to treatment.

Research Design Considerations

Topical research needs are best addressed with experimental designs. However, identifying specific patient subgroups (hypothesis generating research) may first be accomplished with less rigorous research designs. Review of previous systematic reviews, published trials including post hoc subgroup analyses, observational studies, and administrative databases could be used to extract hypothesized relationships between patient characteristics and specific therapies or multimodal treatments. The systematic review found very little evidence testing particular interventions for specific types of patients since very few studies reported the treatment outcomes for specific patient subpopulations. The systematic review focused on randomized controlled trials which can provide valid treatment estimates equally distributing patient characteristics and concomitant treatments among treatment groups. However, the review concluded that the results are applicable to the target population and much less to the subpopulations by age, gender, baseline OA severity, and response to pharmacological treatments. Therefore, future research is needed for hypotheses by garnering expert opinion about which patient subgroups may respond differently to specific therapies.

Once hypotheses are generated, they should be tested using rigorous experimental design. Randomized controlled trials (RCTs) are the best approach. Conducting RCTs on specific patient subgroups is feasible yet the systematic review found very weak evidence of treatment effects in patient subpopulations. The review concluded that the evidence from individual RCTs did not support robust conclusions about differences in PT effects by patient age, gender, baseline severity of knee OA and multijoint OA, or responses to prior PT and drug treatments. However, a more valuable study design would be a large scale RCT with representative samples of sufficient size (as determined by the appropriate power calculations) from various subgroups of patients identified a priori. In designing these trials, another important concern lies in defining the PT treatments. Treatment definition for the intervention and comparator should be sufficient to explain specific activities used in each PT session or a protocol that explains the sequence of therapies. Treatments compared should capture the full range of PT treatments that would be used in practice. Fidelity checks may be necessary to monitor compliance with protocols. Attention should be paid to other concomitant treats, especially anti-inflammatory drugs and analgesics. Table 2 provides more detailed research design considerations relevant to this research need.

Table 2. First topical research need: research design considerations

Research Question: Which PT treatments work for which patients?	
Considerations	RCT
Design Description	Groups of adults with knee OA randomly assigned to either exercise alone or multimodal program and followed over time to determine improvement in outcomes as response to treatment. Patient and disease characteristics can be tested to examine influence on response to treatment.
Population	A diverse group of patients with knee OA (diverse in terms of patient and disease characteristics). Subgroups defined by patient age, severity of OA, multi-joint OA, prior and concomitant treatments, comorbidities, etc.
Intervention	PT interventions hypothesized to improve response in specific groups of patients.
Comparator	Standard treatment: exercise alone.
Outcomes	Clinically important differences in pain, independence in ADL, patient satisfaction, quality of life, psychological disability, self-perceived health, time to surgery, postsurgical outcomes.
Timing	Followup that extends beyond treatment duration would add value to currently available knowledge.
Setting	PT practices.
Advantages for Producing a Valid Result	Randomization produces the most valid results. Recruitment that includes sufficient numbers of patients in select subgroups allows sample to better reflect real world patients enhancing generalizability. Investigators need to conduct power calculations to recruit sufficient stratified samples.
Resource use, size and duration	Resource use is high. A large sample will be required and follow-up should extend beyond treatment duration.
Ethical, legal, and social issues	Ethical issues are minimal; interventions are non-invasive and harms not life-threatening.
Availability of data/ability to recruit	Not likely to be an issue given the prevalence of knee OA.

ADL = activities of daily living; OA = osteoarthritis; PT = physical therapy; RCT = randomized controlled trial

Second Topical Research Need

- How do the duration, intensity, and frequency of examined interventions affect sustained changes in patient-centered outcomes?

The CER found limited evidence to evaluate intervention characteristics. The duration of examined PT interventions was not consistently associated with better intermediate or patient-centered outcomes. Evidence regarding the association between the dose/intensity/frequency of examined interventions and outcomes was not available for the majority of comparisons. The effects of the treatments that significantly improved outcomes, including exercise (aerobic, aquatic, and strengthening) and ultrasound did not differ at shorter versus longer followup times. Moreover, electrical stimulation worsened pain at longer followup. Study risk of bias and heterogeneity in populations and treatments including concomitant treatments hampered strength of evidence to low or moderate in most cases. Stakeholder discussions confirmed that a better understanding of different intervention characteristics (especially dosage) and how they influence effectiveness would better inform decisionmaking.

Research Design Considerations

Processes similar to those mentioned above could be used to identify specific intervention characteristics that contribute to effectiveness. Again, experimental designs are likely the best approach to testing hypothesized relationships, yet very few RCTs examine the role of treatment intensity and duration on patient centered outcomes. The review found no high quality observational studies or administrative databases analyses suggesting significant improvement in patient centered outcomes with longer and more intense PT interventions in adult with knee OA.

Design considerations for these experimental studies are also similar to those of this first research need. The approach might be implemented with trials testing the standard evidence-based treatment, exercise therapy. The most valid way to then address this research need would be with RCTs; however it may prove difficult to mount studies of adequate size. In that case quasi-experimental designs may be necessary. Prospective cohort studies with large samples may be preferred to small RCTs, yet no well designed prospective cohort analyzed the association between PT intensity and duration on pain, function, or disability in older adults with knee OA. In either case, investigators should be careful to appropriately define the PT treatment and document the intensity, duration, and frequency. Special attention should be paid to adherence among study participants. Studies should be sufficiently powered to detect differences between groups as determined by appropriate power calculation. A major concern is in powering the study adequately to test the effects of combinations of treatment variations. The cohort studies should pay additional attention to identifying and adjusting results for potentially confounding variables. Table 3 provides more detailed research design considerations for this research need.

Table 3. Second topical research need: research design considerations

Research Question: How do the duration, intensity, and frequency of examined interventions affect sustained changes in patient-centered outcomes?		
Considerations	RCT	Prospective Cohort
Design description	Groups of adults with knee OA randomly assigned to exercise therapy at varying levels of intensity, frequency, and duration and followed over time to determine improvement in outcomes as response to treatment. Intervention characteristics can be tested to examine influence on response to treatment.	Prospectively designed cohorts of individuals with knee OA receiving exercise therapy at varying levels of intensity, frequency, and duration and followed over time to determine improvement in outcomes as response to treatment. Intervention characteristics can be tested to examine influence on response to treatment.
Population	Adult patients with knee OA.	Adult patients with knee OA.
Intervention	PT interventions with duration, intensity, and frequency different from standard/average.	PT interventions with duration, intensity, and frequency different from standard/average.
Comparator	PT interventions with standard (average) duration, intensity, frequency.	PT interventions with standard (average) duration, intensity, frequency.
Outcomes	Clinically important differences in pain, independence in ADL, patient satisfaction, quality of life, psychological disability, self-perceived health time to surgery, postsurgical outcomes.	Clinically important differences in pain, independence in ADL, patient satisfaction, quality of life, psychological disability, self-perceived health time to surgery, postsurgical outcomes.
Timing	Follow-up that extends beyond treatment duration would add value to currently available knowledge.	Follow-up that extends beyond treatment duration would add value to currently available knowledge.
Setting	PT practice.	PT practice.
Advantages for producing a valid result	Randomization allows for most valid results. Interventions should be adequately defined. RCTs need to be sufficiently powered to detect differences between groups as determined by appropriate power calculations. Investigators should not impose overly strict inclusion criteria that would hamper generalizability.	Enables recruitment of larger samples. Allows inclusion of real world patients which enhances generalizability. Investigators will need to collect data on known confounders and statistically adjust in analysis.
Resource use, size and duration	Resource use is high. A large sample will be required and follow-up should extend beyond treatment duration.	Resource use is moderate. A large sample will be required and follow-up should extend beyond treatment duration.
Ethical, legal, and social issues	Ethical issues are not a concern because interventions are typical care.	Ethical issues are not a concern because interventions are typical care.
Availability of data/ability to recruit	Not likely to be an issue given the prevalence of Knee OA.	Not likely to be an issue given the prevalence of Knee OA. Prospective approach allows all relevant data to be collected.

ADL = activities of daily living; OA = osteoarthritis; PT = physical therapy; RCT = randomized controlled trial

Third Topical Research Need

- What is the comparative effectiveness of comprehensive multimodal PT treatments on patient-centered outcomes when compared with exercise alone?

The two remaining research needs have more focused hypotheses. Few studies comparing multimodal treatments to exercise alone are available, yet this question is particularly important to informing clinical practice. Current guidelines recommend that PT be delivered with a combination of modalities. Published research has focused instead on the marginal effects of individual PT interventions. The systematic review concluded that the studies overall had low applicability to the actual practice of PT because available studies focused on single modalities of PT rather than the combinations typically used in practice. In addition, many of the interventions were physical agents/modalities (i.e., orthotics, ultrasound, taping, etc.). This also contradicts the recommended practice of PT, in which physical agents/modalities are infrequently used in isolation, but rather combined with other more “active” interventions (i.e., exercises). The review found that few studies of combined PT modalities demonstrated no statistically significant benefit on the outcomes when compared with exercise alone.

Research Design Considerations

Given the specific hypothesis of this research need, an RCT is likely the best approach. Randomization eliminates concerns about inherent differences between the groups assigned to each intervention being responsible for differences in outcomes. An RCT will be resource intensive, requiring a large sample size because the marginal difference between the two active treatment arms is likely to be low and subgroups are particularly relevant in this question. Investigators should pay careful attention to defining the multimodal programs; only a limited number of combinations will be feasible. Table 4 describes research design considerations for this research need in more detail.

Table 4. Third topical research need: research design considerations

Research Question: What is the comparative effectiveness of comprehensive multimodal physical therapy treatments on patient-centered outcomes when compared with exercise alone?	
Considerations	RCT
Design Description	Individual patients randomly assigned to one of two PT treatments, randomization stratified by patient age, baseline OA severity, prior and concomitant treatments, comorbidities (patient subgroups hypothesized to benefit from multimodal therapy).
Population	Patients with knee pain secondary to OA.
Intervention	Multimodal PT program.
Comparator	Exercise therapy alone.
Outcomes	Clinically important changes in pain, independence in ADL, patient satisfaction, quality of life, psychological disability, self-perceived health.
Timing	3-6 months, or consider longer follow-up to address other research gaps.
Setting	PT clinic.
Advantages for Producing a Valid Result	This design is likely to produce the most valid results. However, inclusion criteria should not be overly strict impairing generalizability.
Resource use, size and duration	Likely necessary to recruit large samples because marginal clinically important difference from one approach vs. another is likely to be low and sampling should be stratified to incorporate subgroup analysis.
Ethical, legal, and social issues	Ethical challenges should be minimal; intervention is non-invasive and potential harms are not life-threatening.
Availability of data/ability to recruit	Not likely to be an issue given the prevalence of knee OA.

ADL = activities of daily living; OA = osteoarthritis; PT = physical therapy; RCT = randomized controlled trial

Fourth Topical Research Need

- In individuals who proceed to joint replacement surgery, do patients who underwent PT treatments prior to surgery fare better postoperatively?

The CER focused on community-dwelling adults with knee pain secondary to OA. While many patients with knee OA eventually undergo joint replacement surgery, postsurgical outcomes were beyond the scope of this review. Stakeholders brought up this question as a research gap. Benefits of presurgical PT treatments on patient outcomes after surgery remain unclear and this information would have important clinical implications.

Research Design Considerations

In first addressing this research need, investigators should examine previous literature to determine if studies that address this question are available. Once hypotheses are generated, more rigorous studies can be conducted. Due to the potentially long-term nature of this outcome and the difficulty in identifying group members a priori, an RCT or other prospective design may not be feasible. Therefore, testing the hypothesis that individuals receiving PT treatment fare better after knee replacement surgery might best be approached with case control studies. Large sample sizes and the identification, measurement, and appropriate adjustment for confounding variables with multivariate analysis would strengthen the internal validity of these studies. However, limited causal inference will be a limitation. Table 5 describes more detailed research design considerations for this research needs.

Table 5. Fourth topical research need: research design considerations

Research Question: In individuals who proceed to joint replacement surgery, do patient who underwent PT treatments prior to surgery fare better postoperatively?	
Considerations	Case Control
Design description	Participants recently undergoing knee replacement surgery are selected and categorized by whether they had PT treatments prior to surgery.
Population	Adults recently undergoing knee replacement surgery.
Intervention	PT interventions prior to surgery.
Comparator	No PT interventions prior to surgery.
Outcomes	Time to surgery, surgical outcomes (e.g. pain, mobility, time to return to activities of daily living, rehabilitation progress, etc.).
Timing	Short.
Setting	PT clinics/surgery centers/rehabilitation.
Advantages for producing a valid result	Results will be most valid with a large sample size and the collection of many potentially confounding variables used to statistically adjust multivariate analysis. Causal inference will be limited.
Resource use, size and duration	Significantly less than nested case control study or a prospective design.
Ethical, legal, and social issues	No ethical challenges anticipated.
Availability of data/ability to recruit	Not likely to be an issue given the prevalence of knee OA and knee replacement surgeries. Combining data from different geographic locations should be explored.

OA = osteoarthritis; PT = physical therapy

Ongoing Studies

Recently published or ongoing studies may provide information relevant to these topical research needs. Searches for these studies identified 38 recently published studies and 112 ongoing studies. Screening identified seven relevant newly published studies and 83 recent or ongoing trials with at least one arm relevant to identified research gaps (Appendix D). However, few specifically addressed the topical research needs we have identified. Two trials addressing the comparative effectiveness between manual therapy and exercise therapy were identified in our search for ongoing studies. The first (NCT00988468) was terminated due to an inability to recruit a sufficient number of participants.²¹ The second (NCT01314183) is a four-arm trial comparing supervised exercise alone to exercise plus manual therapy, exercise plus booster sessions after the initial course of treatment, and exercise and manual therapy plus booster sessions after the initial course of treatment.²¹ This RCT will provide valuable evidence to address the manual therapy versus supervised exercise research need. This study also has the potential to address other lower priority research questions (regarding long-term effectiveness and booster sessions). The trial has a planned sample size of 300.

Discussion

This FRN project refined and prioritized research needs relevant to the KQs addressed in the draft CER, “Physical Therapy Interventions for Knee Pain Secondary to Osteoarthritis.”¹⁴ We developed a set of research questions from evidence gaps identified in the CER. Research gaps included methodological issues that limited the utility of the current research and topical questions that limited conclusions about efficacy and comparative effectiveness of PT treatments. We conducted a deliberative process to refine and expand our set of research gap questions through conversations with stakeholders who represented diverse perspectives of expertise on the topic. Our stakeholder group included physical therapists, orthopedists, rheumatologists, patient advocates, academics, third party payers, funders of related research, and patients. Many stakeholders offered two or more perspectives. This process identified seven methodological and 11 topical research questions. Stakeholders then ranked research questions, and the most highly ranked questions were deemed research needs.

Addressing methodological research needs will enhance the utility and comparability of future studies of PT treatments for knee OA. A common set of patient-centered and intermediate outcomes, with guidance on interpreting changes in outcomes scale scores, will provide researchers with concrete approaches to collecting outcomes data and determining effectiveness. The quality of the literature would be further enhanced if a multidisciplinary panel were to create consensus guidance on how research studies should define PT interventions and report specific variables. Research on this topic will advance when guidance from consensus recommendations is utilized and an evidence base of comparable studies becomes available.

Topical research needs demonstrate the importance of understanding that all PT interventions may not be ideal for all patients. To advance the field, research needs to address which treatments are effective for which patients. Identifying these patterns will provide clinically meaningful implications which can be used to design guidelines for treating patients with knee OA. A better understanding of how PT treatments are defined is essential to understanding their effectiveness. We need to know not only the type of therapy used but also the specific activities conducted, the level of supervision, and the exact frequency and duration. Complete definitions of interventions will enhance the internal validity of studies and allow for replicability of effective treatments. Testing specific hypotheses will fill the evidence gaps identified and prioritized by our stakeholders.

Future studies on PT interventions should attend closely to reducing bias as much as possible for the particular research design used. Further, researchers should conduct studies with adequate power to test hypothesized relationships. Attention to reporting standards using the Consolidated Standards of Reporting Trials (CONSORT) statement for nonpharmacologic interventions could guide the data collected and reported in effectiveness research.²² This statement specifically describes elements of interventions that should be included. The Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) statement, designed for public health interventions, also provides a good explanation of the types of information about interventions that should be captured and reported.²³

This FRN project benefited from the multidisciplinary perspective brought by broad stakeholder participation. However, our inability to collect a representative perspective from a larger sample of stakeholders is also our primary limitation. Although the stakeholders participating in this project represented various perspectives on knee OA and PT, the prioritized research needs reflect the opinions of these stakeholders and may not be generalizable to the population of stakeholders on this topic. The sample size was limited by standards and guidelines

for statistical surveys administered by the Office of Management and Budget requiring compliance with the Paperwork Reduction Act and Information Collections Policy (44 USC 3501-3520).²⁴ The Act was designed to minimize the paperwork burden on the public, assure that high quality data are obtained, and minimize costs. However, the approval process to allow greater than nine nongovernment participants exceeded the length of time available to complete this project.

Another limitation stems from the structure of the research questions posed to fill evidence gaps. Topical questions that were ranked highly were broader questions that did not specify specific populations or intervention characteristics that future research should address. Questions that were more specific, such as those that asked about the efficacy and comparative effectiveness with respect to certain outcomes, were not ranked high priority. While this may be an indication about the state of the research in the field (i.e., the identification and measurement of patient-centered outcomes and the measures used has received more attention than identifying and testing efficacy and comparative effectiveness with respect to certain subpopulations or elements of interventions). These lower priority research questions could be addressed in studies designed primarily to address the research needs (e.g., by including the specific outcomes measure or increasing the follow time). While the specificity of the research questions may reflect the current state of research in the field with respect to certain PICOTS elements, they could also reflect stakeholder assumptions that the broader questions could in fact also answer the more specific questions.

Conclusions

We identified specific research needs that may be useful in future efforts to address the efficacy and comparative effectiveness of PT treatments for patients with knee OA. Future research on these topics will create a broader and stronger evidence base for making clinical decisions:

- Which patient-centered outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
- Which intermediate outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
- Should effectiveness research on PT treatments use MCIDs?
- What confounding and effect modifying variables (e.g. OA severity, obesity, comorbidities, and concomitant therapies, including anti-inflammatory and analgesic medication) should be measured and reported in effectiveness research?
- What minimum set of treatment factors (site, treatment components, frequency, duration, intensity, timing) should be reported consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
- Which PT treatments work for which patients?
- How do the duration, intensity, and frequency of examined interventions affect sustained changes in patient-centered outcomes?
- What is the comparative effectiveness of comprehensive multimodal PT treatments on patient-centered outcomes when compared with exercise alone?
- In individuals who proceed to joint replacement surgery, do patients who underwent PT treatments prior to surgery fare better postoperatively?

References

1. 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 & Rheumatism*. 2008 Jan;58(1):26-35. PMID: 18163497.
2. Johnson CA. Chapter 12. Approach to the Patient with Knee Pain. In: Imboden JB, Hellmann DB, Stone JH, eds. *CURRENT Rheumatology Diagnosis & Treatment*, 2e. The McGraw-Hill Companies, Inc.; 2007.
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. *Journal of Rheumatology*. 2007 Jan;34(1):172-80. PMID: 17216685.
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. *Journal of Rheumatology*. 2006 Nov;33(11):2271-9. PMID: 17013996.
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 Aug;38(8):1134-41. PMID: 7639811.
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 Oct;38(10):1500-5. PMID: 7575700.
7. Bernstein AB, Hing E, Moss AJ, et al. Health care in America: Trends in utilization. Hyattsville, Maryland: National Center for Health Statistics; 2003.
8. Imboden J. Chapter 4. Approach to the Patient with Arthritis. In: Imboden JB, Hellmann DB, Stone JH, eds. *CURRENT Rheumatology Diagnosis & Treatment*, 2e. The McGraw-Hill Companies, Inc.; 2007.
9. National Collaborating Centre for Chronic Conditions. Osteoarthritis: national clinical guideline for care and management in adults. Royal College of Physicians. London: 2008.
10. 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. *Journal of Bone & Joint Surgery - American Volume*. 2010 Apr;92(4):990-3. PMID: 20360527.
11. 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 Apr;18(4):476-99. PMID: 20170770.
12. American Physical Therapy Association. Guide to physical therapist practice. 2nd ed. Alexandria, Va.: American Physical Therapy Association; 2001.
13. Pisters MF, Veenhof C, van Meeteren NLU, et al. Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review. *Arthritis & Rheumatism*. 2007 Oct 15;57(7):1245-53. PMID 17907210.
14. Shamliyan TA, Wang S-Y, Olson-Kellogg B, Kane RL. Physical Therapy Interventions for Knee Pain Secondary to Osteoarthritis. Comparative Effectiveness Review No. 77. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2007-10064-I.) AHRQ Publication No. 12(13)-EHC115-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

15. O’Haire C, McPheeters M, Nakamoto EK, et al. Methods for Engaging Stakeholders To Identify and Prioritize Future Research Needs. Methods Future Research Needs Report No. 4. (Prepared by the Oregon Evidence-based Practice Center and the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 11-EHC044-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
16. Effective Health Care Program. Effective Health Care Contacts Database. 2012.
17. SurveyMonkey.com LLC. Palo Alto, California, USA; 2012. www.surveymonkey.com.
18. Carey T, Sanders GD, Viswanathan M, Tet al. Framework for Considering Study Designs for Future Research Needs. Methods Future Research Needs Paper No. 8. (Prepared by the RTI–UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I.) AHRQ Publication No. 12-EHC048-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
19. 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. *Journal of Rheumatology*. 1997 Apr;24(4):799-802. PMID: 9101522.
20. Riddle DL, Stratford PW, Singh JA, et al. Variation in outcome measures in hip and knee arthroplasty clinical trials: a proposed approach to achieving consensus. *Journal of Rheumatology*. 2009 Sep;36(9):2050-6. PMID 19738212.
21. Clinicaltrials.gov. Enhancing the Effectiveness of Physical Therapy for People With Knee Osteoarthritis. clinicaltrials.gov/ct2/results?term=NCT01314183. Accessed on May 8 2012.
22. Boutron I, Moher D, Altman DG, et al. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med*. 2008;148(4):295-309. PMID: 18283207.
23. Des Jarlais DC, Lyles C, Crepaz N, et al. Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. *Am J Public Health*. 2004 Mar;94(3):361-6. PMID: 14998794.
24. Office of Management and Budget. Standards and guidelines for statistical surveys. 2006. www.whitehouse.gov/sites/default/files/omb/inforeg/statpolicy/standards_stat_surveys.pdf. Accessed on May 16 2012.

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CER	Comparative Effectiveness Review
EPC	Evidence-based Practice Center
FRN	Future Research Needs
KQ	Key Question
MCID	Minimum Clinically Important Difference
NIA	National Institute on Aging
OA	Osteoarthritis
PICOTS	Population, intervention, comparison, outcome, timing, and setting
PT	Physical therapy
RCT	Randomized controlled trials

Appendix A. Research Gap Questions for Prioritization

Methods Issues Needing Consensus

1. How should Knee OA severity be graded consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
2. How should multimodal PT treatments be classified?
3. Should effectiveness research on PT treatments use minimal clinically important differences (MCID)?
4. Which patient-centered outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
5. Which intermediate outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?
6. What confounding and effect modifying variables (e.g., OA severity, obesity, comorbidities, and concomitant therapies—including anti-inflammatory and analgesic medication) should be measured and reported in effectiveness research?
7. What minimum set of treatment factors (site, treatment components, frequency, duration, intensity, timing) should be reported consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?

PT for Knee OA Topical Questions

1. Which PT treatments work for which patients?
2. Do periodic followup treatments beyond the initial PT treatments enhance effectiveness?
3. What is the long-term effectiveness of PT treatments on patient centered outcomes?
4. What is the comparative effectiveness of comprehensive multimodal PT treatments on patient-centered outcomes when compared with exercise alone?
5. What is the comparative effectiveness over the entire course of different comprehensive multimodal PT programs (from initial PT-directed treatments through self-management and occasional followup treatments)?
6. Does PT for knee OA delay time to surgery?
7. Does PT for knee OA reduce medication use?
8. Do PT treatments affect structural joint changes?
9. In individuals who proceed to joint replacement surgery, do patients who underwent PT treatments prior to surgery fare better postoperatively?
10. How does the method of delivery (e.g., the involvement of a physical therapist or physical therapist assistant, group versus individual exercise, self-administered versus supervised exercises, etc.) affect patient-centered outcomes?
11. How do the duration, intensity, and frequency of examined interventions affect sustained changes in patient-centered outcomes?

Appendix B. Effective Health Care Program Selection Criteria

Appropriateness:

- Represents a health care drug, intervention, device, technology or health care system/setting available (or soon to be available) in the United States.
- Relevant to 1013 enrollees (Medicare, Medicaid, S-CHIP, other federal health care programs).
- Represents one of the priority conditions designated by the U.S. Department of Health and Human Services (HHS).

Importance:

- Represents a significant disease burden, large proportion, or priority population.
- Is of high public interest; affects health care decisionmaking, outcomes, or costs for a large proportion of the U.S. population or for a priority population in particular.
- Was nominated/strongly supported by one or more stakeholder groups.
- Represents important uncertainty for decisionmakers.
- Incorporates issues around both clinical benefits and potential clinical harms.
- Represents important variation in clinical care, or controversy in what constitutes appropriate clinical care.
- Represent high costs to consumers, patients, health care systems or payers; due to common use, high unit costs, or high associated costs.

Desirability of New Research/Duplication:

- Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high quality systematic review by AHRQ or others).

Feasibility:

- Effectively uses existing research and knowledge by considering adequacy of research for conducting a systematic review, and newly available evidence

Potential Impact:

- Potential for significant health impact, significant economic impact, potential change, potential risk from inaction, addressing inequities and vulnerable populations, and/or addressing a topic with clear implications for resolving important dilemmas in health and health care decisions made by one or more stakeholder groups.

Appendix C. Search Strategy for Recently Published Studies

Ovid Medline Search Strategy

- 1 exp *Physical Therapy Modalities/ (78040)
- 2 physical therap*.ti,ab. (10871)
- 3 1 or 2 (84208)
- 4 exp *Osteoarthritis, Knee/ (6654)
- 5 osteoarthritis.ti,ab. (28073)
- 6 knee.ti,ab. (72016)
- 7 4 or 5 or 6 (90745)
- 8 3 and 7 (3120)
- 9 limit 8 to yr="2012" (38)

Advanced search for Intervention studies on ClinicalTrials.gov

physical therapy or exercise in the intervention field
and (osteoarthritis and knee) in the condition field

Appendix D. Recent and Ongoing Studies

Recently Published Studies

1. Deyle GD, Gill NW, Allison SC, et al. Knee OA: which patients are unlikely to benefit from manual PT and exercise? *Journal of Family Practice*. 2012 Jan;61(1):E1-8. PMID: 22220299.
2. Gundog M, Atamaz F, Kanyilmaz S, et al. Interferential current therapy in patients with knee osteoarthritis: comparison of the effectiveness of different amplitude-modulated frequencies. *American Journal of Physical Medicine & Rehabilitation*. 2012 Feb;91(2):107-13. PMID: 22019968.
3. Hale LA, Waters D, Herbison P. A randomized controlled trial to investigate the effects of water-based exercise to improve falls risk and physical function in older adults with lower-extremity osteoarthritis. *Archives of Physical Medicine & Rehabilitation*. 2012 Jan;93(1):27-34. PMID: 21982325.
4. Hurley MV, Walsh NE, Mitchell H, et al. Long-term outcomes and costs of an integrated rehabilitation program for chronic knee pain: a pragmatic, cluster randomized, controlled trial. *Arthritis Care & Research*. 2012 Feb;64(2):238-47. PMID: 21954131.
5. Loyola-Sanchez A, Richardson J, Beattie KA, et al. Effect of low-intensity pulsed ultrasound on the cartilage repair in people with mild to moderate knee osteoarthritis: a double-blinded, randomized, placebo-controlled pilot study. *Archives of Physical Medicine & Rehabilitation*. 2012 Jan;93(1):35-42. PMID: 22200383.
6. Sayers SP, Gibson K, Cook CR. Effect of high-speed power training on muscle performance, function, and pain in older adults with knee osteoarthritis: a pilot investigation. *Arthritis Care & Research*. 2012 Jan;64(1):46-53. PMID: 22012877.
7. Kettunen JA, Harilainen A, Sandelin J, et al. Knee arthroscopy and exercise versus exercise only for chronic patellofemoral pain syndrome: 5-year follow-up. *British Journal of Sports Medicine*. 2012 Mar;46(4):243-6. PMID: 21357578.

Ongoing Studies

NCT Number	Title	Interventions
NCT00000404	Effects of Comprehensive Care for Knee OA	Behavioral: Patient education in self-care of knee OA
NCT00000406	Effects of Strength Training on Knee Osteoarthritis	Procedure: Progressive resistance exercise
NCT00007241	Muscle Strengthening Device for Knee Osteoarthritis	Device: Isometric exercise
NCT00049816	Aerobic Exercise Intervention for Knee Osteoarthritis	Behavioral: Walking exercise Behavioral: Cycling Exercise
NCT00061490	The Effect of Weight Loss and Exercise on Knee Osteoarthritis	Behavioral: Behavioral weight control and lifestyle exercise
NCT00078624	Knee Stability Training for Knee Osteoarthritis (OA)	Other: Traditional exercise therapy for knee osteoarthritis Other: Knee stability training
NCT00085722	Joint Injections for Osteoarthritic Knee Pain	Procedure: Dextrose Prolotherapy Procedure: Saline Prolotherapy Other: At-home physical therapy exercise group
NCT00104156	Qigong Therapy for Individuals With Knee Osteoarthritis	Procedure: External Qigong therapy
NCT00123994	Tai Chi or Hydrotherapy for People With Osteoarthritis of the Hip(s) or Knee(s)	Behavioral: Tai Chi classes Behavioral: Hydrotherapy classes
NCT00154765	Effect of Sling Suspension Exercises in Proprioception of Patients With Knee Osteoarthritis	Device: sling suspension exercises
NCT00265447	Exercise and Physical Fitness for Persons With Knee Osteoarthritis	Behavioral: self-directed exercise Behavioral: 3 months of aerobic conditioning
NCT00305890	Weight Management and Coping Skills Training For Patients With Knee Osteoarthritis	Behavioral: Lifestyle Behavioral Weight Management Program Behavioral: Pain-Coping Skills Training Other: Standard Care
NCT00362453	Tai Chi Mind-Body Therapy for Knee Osteoarthritis	Behavioral: Tai Chi versus Attention Control
NCT00375544	Study to Evaluate the Safety and Efficacy of a Low Level Light Device in Patients With Knee Osteoarthritis	Device: Low level light therapy
NCT00381290	Intensive Diet and Exercise for Improving Knee Osteoarthritis in Obese and Overweight Older Adults	Behavioral: Diet Behavioral: Exercise
NCT00415259	Effects of Shoes Insoles on Symptoms and Disease Progression in Knee Osteoarthritis	Device: Laterally wedged shoe insoles
NCT00427843	The Influence of Hip Strengthening Exercises on Walking Patterns and Muscle Strength in Persons With Knee Osteoarthritis	Behavioral: home exercise program for the hip abductor muscles
NCT00462319	ARTIST: ARThrose Intervention Standardisée	Behavioral: Education, weight reduction and physical exercise
NCT00465660	Resistive Exercise for Arthritic Cartilage Health (REACH)	Behavioral: Progressive resistance training
NCT00492674	The Effect of Perioperative Neuromuscular Training on the Outcome of Total Knee Arthroplasty	Device: APOS biomechanical gait system Procedure: Physical Therapy
NCT00493142	Pre-operative Rehabilitation Exercise Program for Total Knee Arthroplasty	Behavioral: Exercise
NCT00519922	A Study of the Effectiveness of Different Types of Exercise for People With Knee Osteoarthritis	Other: Kinesthesia, Balance, and Agility (KBA) Exercise Other: Standard LE Strength Training
NCT00522106	The Effectiveness of Behavioral Graded Activity in Patients With Osteoarthritis of the Hip and/or Knee	Behavioral: Behavioral graded activity Other: Exercise therapy
NCT00583245	Improving Walking in Older Adults With Knee Osteoarthritis	Other: Gait Training

NCT Number	Title	Interventions
NCT00586300	Community-Based Programs for Improving Physical Function in People With Early Knee Osteoarthritis	Other: Physical training program Behavioral: Self-management training program Other: Physical training and self-management training programs
NCT00642772	Group Physical Therapy for Knee Osteoarthritis	Other: Group Physical Therapy
NCT00655941	Influence of Weight Loss or Exercise on Cartilage in Obese Knee Osteoarthritis Patients	Behavioral: Dietary instruction Other: Exercise
NCT00687726	Simple Home-Based Exercise for Knee Osteoarthritis	Behavioral: Standing balance exercise Behavioral: Isometric knee extension exercise
NCT00701506	Patterned Electrical Neuromuscular Stimulation and Therapeutic Exercise for Osteoarthritis of the Knee: Pilot Study	Device: Patterned Electrical Neuromuscular Stimulation Device: Placebo PENS
NCT00726492	An Examination of the Value of Shortwave Diathermy and Hydrotherapy for Patients With Osteoarthritis of Their Knees	Other: Continuous short wave diathermy (CSWD) Other: Hydrotherapy
NCT00735098	The Effects of Home-Based Rehabilitation Treatments Among Persons With Symptomatic Knee Osteoarthritis	Other: KBA exercise Other: strength training exercise Other: KBA and strength training Other: Control group
NCT00800254	Early Neuromuscular Electrical Stimulation For Quadriceps Muscle Activation Deficits Following Total Knee Replacement	Procedure: Neuromuscular Electrical Stimulation (NMES) Behavioral: Standard Rehabilitation Protocol
NCT00844558	Mobility Optimization Through Velocity Exercise	Other: Gait Training Other: Power Training Other: Control
NCT00904319	Aquatic Power Training	Other: Aquatic Power Training
NCT00913575	Effect of Pre-surgery Neuromuscular Physiotherapy (PT)	Other: preoperative neuromuscular training Behavioral: knee OA School
NCT00917618	The Effects of Group Cycling (Spinning®) With Knee Osteoarthritis: A Randomized Control Trial	Other: Exercise Other: Control
NCT00950326	A Comparison of Kneipp Hydrotherapy With Conventional Physiotherapy in the Treatment of Osteoarthritis of the Hip or Knee: Protocol of a Prospective Randomised Controlled Clinical Trial	Procedure: Physiotherapy Procedure: Affusion Procedure: Affusion/ Physiotherapy
NCT00976079	The Effect of Transcutaneous Electrical Nerve Stimulation on Quadriceps Central Activation and Gait	Device: Transcutaneous electrical nerve stimulation (TENS) Device: Placebo TENS
NCT00979043	The Arthritis, Diet, and Activity Promotion Trial	Behavioral: Dietary Weight-loss Behavioral: Exercise
NCT00979914	Effect of an Education Programme for Patients With Osteoarthritis in Primary Care - a Randomized Controlled Trial	Other: Patient education programme
NCT00988468	Manual Therapy Versus Exercise on Knee Osteoarthritis	Procedure: Manual Therapy Behavioral: Therapeutic Exercise Behavioral: Video Observation
NCT01003756	Preoperative Exercise in Patients Undergoing Total Hip or Knee Replacement	Other: Preoperative neuromuscular exercise
NCT01003925	Conjoint Analysis of Treatment Preferences for Osteoarthritis	Behavioral: Standard of care for osteoarthritis treatment Behavioral: Conjoint Analysis for Osteoarthritis
NCT01017445	Stick Versus Quadricep Exercise for Knee Osteoarthritis	Other: Boonme stick exercise
NCT01058304	Group Physical Therapy for Knee Osteoarthritis	Other: Group Physical Therapy for Knee OA Other: Individual Physical Therapy for Knee OA
NCT01096524	Effects of Kneehab 12-week Peri-operative Total Knee Arthroplasty	Other: Standard Physiotherapy Device: Kneehab
NCT01099371	Resistance Training in Knee Osteoarthritis	Other: exercise

NCT Number	Title	Interventions
NCT01112319	The Effects of the Electro, Heat and Cold -Therapy During Physiotherapy Treatment in Osteoarthritis(OA) of KNEE	Device: Elf care Other: control group
NCT01210742	The Efficacy of Viscosupplementation for Early Knee Osteoarthritis	Device: Synvisc One
NCT01225133	Complex Āyurvedic Treatment in Osteoarthritis of the Knee Compared to Standard Care.	Other: Complex Ayurvedic Treatment Other: Conventional Care
NCT01239823	Platform Exercise Training	Other: Whole Body Vibration Training Other: Exercise without vibration
NCT01241812	Biomarkers and Knee Osteoarthritis	Behavioral: Lower limb muscle strengthening Behavioral: Usual care
NCT01245283	Resistance Exercise and Knee Osteoarthritis Pain, Functional Impairment and Cartilage Turnover	Other: normal activities and clinical care Other: Concentric Focused Resistance Exercise Other: Eccentric Focused Resistance Exercise
NCT01258985	Tai Chi and Physical Therapy for Knee Osteoarthritis	Behavioral: Tai Chi Behavioral: Physical Therapy
NCT01271218	Effects of Glucosamine and Chondroitin Supplementation in Women With Knee Osteoarthritis Participating in an Exercise and Weight Loss Program	Other: Diet Other: Exercise
NCT01280903	Staying Active With Arthritis	Behavioral: STAR Intervention Behavioral: Attention-Control
NCT01306435	Low Power Laser and Exercise in Osteoarthritis of the Knee: a Randomized Clinical Trial	Other: Laser Other: Placebo Laser
NCT01311206	Low Intensity Resistance Training With Partial Blood Flow Restriction for Quadriceps Strengthening	Other: partial blood flow restriction Other: Low intensity exercise without partial blood flow restriction
NCT01314183	Enhancing the Effectiveness of Physical Therapy for People With Knee Osteoarthritis	Other: Exercise Other: manual therapy
NCT01328340	High-speed Power Training in Older Adults With Knee Osteoarthritis (OA)	Other: weight training
NCT01331174	Pulsed Short Wave in Females With Knee Osteoarthritis	Device: Pulsed short wave
NCT01345825	The Effectiveness of 8-weeks Progressive Strength Training to Patients With Unicompartmental Knee Replacement, Initiated Within the First Postoperative Week	Other: Resistance training
NCT01354860	Moxibustion for Knee Osteoarthritis	Other: Moxibustion treatment plus usual care Other: Usual care alone group
NCT01360281	Neuromuscular Electrical Stimulation and Strength Training in Patients With Knee Osteoarthritis	Other: Neuromuscular Electrical Stimulation Other: ECR
NCT01394874	Can Computer-based Telephone Counseling Improve Long-term Adherence to Strength Training in Elders With Knee OA?	Behavioral: TLC
NCT01410240	Efficacy and Safety of FLOSEAL for Hemostasis in Total Knee Arthroplasty	Other: Standard of Care Drug: FLOSEAL Hemostatic Matrix
NCT01410409	Structured Treatment of Osteoarthritis of the Knee With or Without Total Knee Replacement	Other: Neuromuscular training (NEMEX-TJR) Drug: Paracetamol Drug: Burana Drug: Pantoprazol Behavioral: Dietary counseling Behavioral: Patient education Procedure: TKR Other: Insoles
NCT01427153	A Comparison of Manual Physical Therapy and Corticosteroid Injections for Knee Osteoarthritis	Procedure: Orthopaedic manual physical therapy Procedure: Corticosteroid Injection
NCT01440972	Assessment of Efficacy of Low Intensity Resistance Training in Women at Risk for Symptomatic Knee Osteoarthritis	Other: partial blood flow restriction (PBFRR) Other: low intensity resistance training

NCT Number	Title	Interventions
NCT01483131	Vascular Occlusion in Patients With Osteoarthritis	Other: Exercise training Other: Resistance training with vascular occlusion
NCT01487525	Assessment of Efficacy of Low Intensity Resistance Training in Individuals at Risk for Symptomatic Knee Osteoarthritis	Device: double leg press with partial blood flow restriction Other: double leg press without partial blood flow restriction
NCT01489462	Strength Training for ARthritis Trial	Behavioral: High Intensity Strength Training Behavioral: Low Intensity Strength Training Behavioral: Attention Control
NCT01490606	Knee Osteoarthritis (OA) Project Treatment Versus Conventional Physical Therapy in the Treatment of Knee OA Patients	Other: knee OA project Other: conventional PT
NCT01528566	Effect of Tai Chi on Osteoarthritic Knee Pain in Elders With Mild Dementia	Behavioral: Tai Chi Behavioral: Attention control
NCT01529398	Sensorimotor Training Versus Resistance Training in Patients With Knee Osteoarthritis	Other: Sensorimotor training (SMT) Other: Resistance training (RT) Other: Control group (CG)
NCT01530204	RAPID: Reducing Pain; Preventing Depression	Procedure: Physical Therapy for knee OA Behavioral: Cognitive Behavioral Therapy for Pain CBT-P Other: Enhanced Treatment as Usual
NCT01535001	Structured Non-operative Treatment of Knee Osteoarthritis	Other: Neuromuscular training (NEMEX-TJR) Behavioral: Information Drug: Paracetamol Drug: Burana Drug: Pantoprazole Behavioral: Dietary counseling Behavioral: Patient education Other: Insoles
NCT01538407	Strengthening Exercise and Quadriceps Force During Walking	Other: Strength Training
NCT01544647	Spa Therapy in Knee Osteoarthritis (OA): Nancy-thermal	Other: Usual spa protocol Other: Active spa protocol
NCT01545258	Exercise and Pain Sensitivity in Knee Osteoarthritis	Other: Exercise
NCT01545986	A Comparative Analysis of Two Types of Exercise on Outcomes Following Total Knee Arthroplasty	Behavioral: Exercise
NCT01576159	Serum Cartilage Oligomeric Matrix Protein Accumulation Decreases Significantly After 12 Weeks of Running	Other: Running exercise Other: Cycling exercise Other: Swimming Exercise
NCT01586130	Assessing the Impact of Isokinetic Muscular Strengthening in Eccentric Mode in the Medical Treatment of Knee Osteoarthritis	Other: Exercise in eccentric or concentric mode