Physical Therapy for Knee Pain Secondary to Osteoarthritis: Future Research Needs
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Identification of Future Research Needs From Comparative Effectiveness Review No. 77

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None of the investigators have any affiliation or financial involvement that conflicts with the material presented in this report.

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.

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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.
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 trials 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


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, 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. In the United States OA of the knee afflicts 28 percent of adults over age 45 and 37 percent of adults over age 65. OA is a leading cause of disability among noninstitutionalized adults; 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.
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.\textsuperscript{8,9} Treatment options include pain relievers, anti-inflammatory drugs, weight loss, general physical exercise, PT, and, when conservative treatments fail, surgery.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.
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.
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.\textsuperscript{14} Figure 3 illustrates the eight steps used to accomplish the objectives of this project.

Figure 3. Project flow

<table>
<thead>
<tr>
<th>Step 1: Identify evidence gaps from CER</th>
<th>Step 2: Form and orient stakeholder panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 3: Translate research gaps to researchable questions (preliminary research gap questions)</td>
<td>Step 4: Stakeholder feedback (teleconference and email):</td>
</tr>
<tr>
<td></td>
<td>- Additional evidence gaps</td>
</tr>
<tr>
<td></td>
<td>- Additional research questions</td>
</tr>
<tr>
<td></td>
<td>- Additional ongoing research</td>
</tr>
<tr>
<td></td>
<td>- Reduce gap list to threshold level</td>
</tr>
<tr>
<td>Step 5: Revise preliminary research gap questions/ consider ongoing research</td>
<td>Step 6: Stakeholder Prioritization (online survey):</td>
</tr>
<tr>
<td></td>
<td>- Ranking topics</td>
</tr>
<tr>
<td>Step 7: Determine research designs considerations/ PICOTS for prioritized research questions (research needs)</td>
<td></td>
</tr>
<tr>
<td>Step 8: Develop Future Research Needs report</td>
<td></td>
</tr>
</tbody>
</table>

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

Engagement of Stakeholders

We recruited a panel of stakeholder’s panel with diverse perspectives relevant to the topic. We followed guidance on stakeholder engagement for recruitment and communication.\textsuperscript{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
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. 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. 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>
<thead>
<tr>
<th>Methodological Topics Needing Consensus (n=11)</th>
<th>Total (Points)*</th>
<th>PICOTS Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1: High Priority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Which patient-centered outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?</td>
<td>9 (33)</td>
<td>NA</td>
</tr>
<tr>
<td>Tier 2: Moderate Priority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Should effectiveness research on PT treatments use minimal clinically important differences?</td>
<td>7 (21)</td>
<td>NA</td>
</tr>
<tr>
<td>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?</td>
<td>6 (18)</td>
<td>NA</td>
</tr>
<tr>
<td>Which intermediate outcome measurement instruments should be used consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?</td>
<td>5 (15)</td>
<td>NA</td>
</tr>
<tr>
<td>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)?</td>
<td>5 (13)</td>
<td>NA</td>
</tr>
<tr>
<td>Tier 3: Low Priority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>How should multimodal PT treatments be classified?</td>
<td>2 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>How should knee OA severity be graded consistently by all relevant disciplines (e.g., PT, rheumatology, orthopedics)?</td>
<td>1 (3)</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topical Questions Needing Trials (n=10)</th>
<th>Total (Points)*</th>
<th>PICOTS Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1: High Priority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Which PT treatments work for which patients?</td>
<td>7 (22)</td>
<td>P, I</td>
</tr>
<tr>
<td>How do the duration, intensity, and frequency of examined interventions affect sustained changes in patient-centered outcomes?</td>
<td>7 (18)</td>
<td>I</td>
</tr>
<tr>
<td>What is the comparative effectiveness of comprehensive multimodal PT treatments on patient-centered outcomes when compared with exercise alone?</td>
<td>5 (15)</td>
<td>I</td>
</tr>
<tr>
<td>In individuals who proceed to joint replacement surgery, do patients who underwent PT treatments prior to surgery fare better postoperatively?</td>
<td>6 (14)</td>
<td>P</td>
</tr>
</tbody>
</table>
Table 1. Stakeholder prioritization of research gap questions (continued)

<table>
<thead>
<tr>
<th>Topical Questions Needing Trials (n=10) (continued)</th>
<th>Ranking</th>
<th>Total (Points)*</th>
<th>PICOTS Element</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tier 2: Moderate Priority</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do periodic followup treatments beyond the initial PT treatments enhance effectiveness?</td>
<td>5 (10)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>What is the long-term effectiveness of PT treatments on patient centered outcomes?</td>
<td>3 (10)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>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)?</td>
<td>3 (8)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Tier 3: Low Priority</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td>3 (3)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Does PT for knee OA delay time to surgery?</td>
<td>2 (3)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Does PT for knee OA reduce medication use?</td>
<td>1 (1)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Do PT treatments affect structural joint changes?</td>
<td>1 (1)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

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. Despite this available guidance, the CER and other OA research demonstrate the use of a wide variety of outcomes measures.

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 trials 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

<table>
<thead>
<tr>
<th>Considerations</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design Description</td>
<td>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.</td>
</tr>
<tr>
<td>Population</td>
<td>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.</td>
</tr>
<tr>
<td>Intervention</td>
<td>PT interventions hypothesized to improve response in specific groups of patients.</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard treatment: exercise alone.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinically important differences in pain, independence in ADL, patient satisfaction, quality of life, psychological disability, self-perceived health, time to surgery, postsurgical outcomes.</td>
</tr>
<tr>
<td>Timing</td>
<td>Followup that extends beyond treatment duration would add value to currently available knowledge.</td>
</tr>
<tr>
<td>Setting</td>
<td>PT practices.</td>
</tr>
<tr>
<td>Advantages for Producing a Valid Result</td>
<td>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.</td>
</tr>
<tr>
<td>Resource use, size and duration</td>
<td>Resource use is high. A large sample will be required and follow-up should extend beyond treatment duration.</td>
</tr>
<tr>
<td>Ethical, legal, and social issues</td>
<td>Ethical issues are minimal; interventions are non-invasive and harms not life-threatening.</td>
</tr>
<tr>
<td>Availability of data/ability to recruit</td>
<td>Not likely to be an issue given the prevalence of knee OA.</td>
</tr>
</tbody>
</table>

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 paid, 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>
<thead>
<tr>
<th>Table 3. Second topical research need: research design considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research Question: How do the duration, intensity, and frequency of examined interventions affect sustained changes in patient-centered outcomes?</strong></td>
</tr>
<tr>
<td><strong>Considerations</strong></td>
</tr>
<tr>
<td>Design description</td>
</tr>
<tr>
<td>Population</td>
</tr>
<tr>
<td>Intervention</td>
</tr>
<tr>
<td>Comparator</td>
</tr>
<tr>
<td>Timing</td>
</tr>
<tr>
<td>Setting</td>
</tr>
<tr>
<td>Advantages for producing a valid result</td>
</tr>
<tr>
<td>Resource use, size and duration</td>
</tr>
<tr>
<td>Ethical, legal, and social issues</td>
</tr>
<tr>
<td>Availability of data/ability to recruit</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Considerations</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design Description</td>
<td>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).</td>
</tr>
<tr>
<td>Population</td>
<td>Patients with knee pain secondary to OA.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Multimodal PT program.</td>
</tr>
<tr>
<td>Comparator</td>
<td>Exercise therapy alone.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinically important changes in pain, independence in ADL, patient satisfaction, quality of life, psychological disability, self-perceived health.</td>
</tr>
<tr>
<td>Timing</td>
<td>3-6 months, or consider longer follow-up to address other research gaps.</td>
</tr>
<tr>
<td>Setting</td>
<td>PT clinic.</td>
</tr>
<tr>
<td>Advantages for Producing a Valid Result</td>
<td>This design is likely to produce the most valid results. However, inclusion criteria should not be overly strict impairing generalizability.</td>
</tr>
<tr>
<td>Resource use, size and duration</td>
<td>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.</td>
</tr>
<tr>
<td>Ethical, legal, and social issues</td>
<td>Ethical challenges should be minimal; intervention is non-invasive and potential harms are not life-threatening.</td>
</tr>
<tr>
<td>Availability of data/ability to recruit</td>
<td>Not likely to be an issue given the prevalence of knee OA.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Considerations</th>
<th>Case Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Question</td>
<td>In individuals who proceed to joint replacement surgery, do patients who underwent PT treatments prior to surgery fare better postoperatively?</td>
</tr>
<tr>
<td>Design description</td>
<td>Participants recently undergoing knee replacement surgery are selected and categorized by whether they had PT treatments prior to surgery.</td>
</tr>
<tr>
<td>Population</td>
<td>Adults recently undergoing knee replacement surgery.</td>
</tr>
<tr>
<td>Intervention</td>
<td>PT interventions prior to surgery.</td>
</tr>
<tr>
<td>Comparator</td>
<td>No PT interventions prior to surgery.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Time to surgery, surgical outcomes (e.g. pain, mobility, time to return to activities of daily living, rehabilitation progress, etc.).</td>
</tr>
<tr>
<td>Timing</td>
<td>Short.</td>
</tr>
<tr>
<td>Setting</td>
<td>PT clinics/surgery centers/rehabilitation.</td>
</tr>
<tr>
<td>Advantages for producing a valid result</td>
<td>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.</td>
</tr>
<tr>
<td>Resource use, size and duration</td>
<td>Significantly less than nested case control study or a prospective design.</td>
</tr>
<tr>
<td>Ethical, legal, and social issues</td>
<td>No ethical challenges anticipated.</td>
</tr>
<tr>
<td>Availability of data/ability to recruit</td>
<td>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.</td>
</tr>
</tbody>
</table>

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. 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. 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.” 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. 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.

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). 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


## Abbreviations

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


## Ongoing Studies

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Title</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00000404</td>
<td>Effects of Comprehensive Care for Knee OA</td>
<td>Behavioral: Patient education in self-care of knee OA</td>
</tr>
<tr>
<td>NCT00000406</td>
<td>Effects of Strength Training on Knee Osteoarthritis</td>
<td>Procedure: Progressive resistance exercise</td>
</tr>
<tr>
<td>NCT00007241</td>
<td>Muscle Strengthening Device for Knee Osteoarthritis</td>
<td>Device: Isometric exercise</td>
</tr>
<tr>
<td>NCT00049816</td>
<td>Aerobic Exercise Intervention for Knee Osteoarthritis</td>
<td>Behavioral: Walking exercise; Behavioral: Cycling Exercise</td>
</tr>
<tr>
<td>NCT00061490</td>
<td>The Effect of Weight Loss and Exercise on Knee Osteoarthritis</td>
<td>Behavioral: Behavioral weight control and lifestyle exercise</td>
</tr>
<tr>
<td>NCT00078624</td>
<td>Knee Stability Training for Knee Osteoarthritis (OA)</td>
<td>Other: Traditional exercise therapy for knee osteoarthritis; Other: Knee stability training</td>
</tr>
<tr>
<td>NCT00085722</td>
<td>Joint Injections for Osteoarthritic Knee Pain</td>
<td>Procedure: Dextrose Prolotherapy; Procedure: Saline Prolotherapy; Other: At-home physical therapy exercise group</td>
</tr>
<tr>
<td>NCT00123994</td>
<td>Tai Chi or Hydrotherapy for People With Osteoarthritis of the Hip(s) or Knee(s)</td>
<td>Behavioral: Tai Chi classes; Behavioral: Hydrotherapy classes</td>
</tr>
<tr>
<td>NCT00154765</td>
<td>Effect of Sling Suspension Exercises in Proprioception of Patients With Knee Osteoarthritis</td>
<td>Device: sling suspension exercises</td>
</tr>
<tr>
<td>NCT00265447</td>
<td>Exercise and Physical Fitness for Persons With Knee Osteoarthritis</td>
<td>Behavioral: self-directed exercise; Behavioral: 3 months of aerobic conditioning</td>
</tr>
<tr>
<td>NCT00305890</td>
<td>Weight Management and Coping Skills Training For Patients With Knee Osteoarthritis</td>
<td>Behavioral: Lifestyle Behavioral Weight Management Program; Behavioral: Pain-Coping Skills Training; Other: Standard Care</td>
</tr>
<tr>
<td>NCT00362453</td>
<td>Tai Chi Mind-Body Therapy for Knee Osteoarthritis</td>
<td>Behavioral: Tai Chi versus Attention Control</td>
</tr>
<tr>
<td>NCT00375544</td>
<td>Study to Evaluate the Safety and Efficacy of a Low Level Light Device in Patients With Knee Osteoarthritis</td>
<td>Device: Low level light therapy</td>
</tr>
<tr>
<td>NCT00381290</td>
<td>Intensive Diet and Exercise for Improving Knee Osteoarthritis in Obese and Overweight Older Adults</td>
<td>Behavioral: Diet; Behavioral: Exercise</td>
</tr>
<tr>
<td>NCT00415259</td>
<td>Effects of Shoes Insoles on Symptoms and Disease Progression in Knee Osteoarthritis</td>
<td>Device: Laterally wedged shoe insoles</td>
</tr>
<tr>
<td>NCT00427843</td>
<td>The Influence of Hip Strengthening Exercises on Walking Patterns and Muscle Strength in Persons With Knee Osteoarthritis</td>
<td>Behavioral: home exercise program for the hip abductor muscles</td>
</tr>
<tr>
<td>NCT00462319</td>
<td>ARTIST: ARTthrose Intervention STandardisée</td>
<td>Behavioral: Education, weight reduction and physical exercise</td>
</tr>
<tr>
<td>NCT00465660</td>
<td>Resistive Exercise for Arthritic Cartilage Health (REACH)</td>
<td>Behavioral: Progressive resistance training</td>
</tr>
<tr>
<td>NCT00492674</td>
<td>The Effect of Perioperative Neuromuscular Training on the Outcome of Total Knee Arthroplasty</td>
<td>Device: APOS biomechanical gait system; Procedure: Physical Therapy</td>
</tr>
<tr>
<td>NCT00493142</td>
<td>Pre-operative Rehabilitation Exercise Program for Total Knee Arthroplasty</td>
<td>Behavioral: Exercise</td>
</tr>
<tr>
<td>NCT00519922</td>
<td>A Study of the Effectiveness of Different Types of Exercise for People With Knee Osteoarthritis</td>
<td>Other: Kinesthesia, Balance, and Agility (KBA) Exercise; Other: Standard LE Strength Training</td>
</tr>
<tr>
<td>NCT00522106</td>
<td>The Effectiveness of Behavioral Graded Activity in Patients With Osteoarthritis of the Hip and/or Knee</td>
<td>Behavioral: Behavioral graded activity; Other: Exercise therapy</td>
</tr>
<tr>
<td>NCT00583245</td>
<td>Improving Walking in Older Adults With Knee Osteoarthritis</td>
<td>Other: Gait Training</td>
</tr>
<tr>
<td>NCT Number</td>
<td>Title</td>
<td>Interventions</td>
</tr>
<tr>
<td>------------</td>
<td>-------</td>
<td>---------------</td>
</tr>
<tr>
<td>NCT00586300</td>
<td>Community-Based Programs for Improving Physical Function in People With Early Knee Osteoarthritis</td>
<td>Other: Physical training program</td>
</tr>
<tr>
<td>NCT00642772</td>
<td>Group Physical Therapy for Knee Osteoarthritis</td>
<td>Other: Group Physical Therapy</td>
</tr>
<tr>
<td>NCT00655941</td>
<td>Influence of Weight Loss or Exercise on Cartilage in Obese Knee Osteoarthritis Patients</td>
<td>Behavioral: Dietary instruction</td>
</tr>
<tr>
<td>NCT00687726</td>
<td>Simple Home-Based Exercise for Knee Osteoarthritis</td>
<td>Behavioral: Standing balance exercise</td>
</tr>
<tr>
<td>NCT00701506</td>
<td>Patterned Electrical Neuromuscular Stimulation and Therapeutic Exercise for Osteoarthritis of the Knee: Pilot Study</td>
<td>Device: Patterned Electrical Neuromuscular Stimulation</td>
</tr>
<tr>
<td>NCT00726492</td>
<td>An Examination of the Value of Shortwave Diathermy and Hydrotherapy for Patients With Osteoarthritis of Their Knees</td>
<td>Other: Continuous short wave diathermy (CSWD)</td>
</tr>
<tr>
<td>NCT00735098</td>
<td>The Effects of Home-Based Rehabilitation Treatments Among Persons With Symptomatic Knee Osteoarthritis</td>
<td>Other: KBA exercise</td>
</tr>
<tr>
<td>NCT00800254</td>
<td>Early Neuromuscular Electrical Stimulation For Quadriceps Muscle Activation Deficits Following Total Knee Replacement</td>
<td>Procedure: Neuromuscular Electrical Stimulation (NMES)</td>
</tr>
<tr>
<td>NCT00844558</td>
<td>Mobility Optimization Through Velocity Exercise</td>
<td>Other: Gait Training</td>
</tr>
<tr>
<td>NCT00904319</td>
<td>Aquatic Power Training</td>
<td>Other: Aquatic Power Training</td>
</tr>
<tr>
<td>NCT00913575</td>
<td>Effect of Pre-surgery Neuromuscular Physiotherapy (PT)</td>
<td>Other: preoperative neuromuscular training</td>
</tr>
<tr>
<td>NCT00917618</td>
<td>The Effects of Group Cycling (Spinning®) With Knee Osteoarthritis: A Randomized Control Trial</td>
<td>Other: Exercise</td>
</tr>
<tr>
<td>NCT00976079</td>
<td>The Effect of Transcutaneous Electrical Nerve Stimulation on Quadriceps Central Activation and Gait</td>
<td>Device: Transcutaneous electrical nerve stimulation (TENS)</td>
</tr>
<tr>
<td>NCT00979043</td>
<td>The Arthritis, Diet, and Activity Promotion Trial</td>
<td>Behavioral: Dietary Weight-loss</td>
</tr>
<tr>
<td>NCT00979914</td>
<td>Effect of an Education Programme for Patients With Osteoarthritis in Primary Care - a Randomized Controlled Trial</td>
<td>Other: Patient education programme</td>
</tr>
<tr>
<td>NCT01003756</td>
<td>Preoperative Exercise in Patients Undergoing Total Hip or Knee Replacement</td>
<td>Other: Preoperative neuromuscular exercise</td>
</tr>
<tr>
<td>NCT01003925</td>
<td>Conjoint Analysis of Treatment Preferences for Osteoarthritis</td>
<td>Behavioral: Standard of care for osteoarthritis treatment</td>
</tr>
<tr>
<td>NCT01017445</td>
<td>Stick Versus Quadricep Exercise for Knee Osteoarthritis</td>
<td>Other: Boonme stick exercise</td>
</tr>
<tr>
<td>NCT01058304</td>
<td>Group Physical Therapy for Knee Osteoarthritis</td>
<td>Other: Group Physical Therapy for Knee OA</td>
</tr>
<tr>
<td>NCT01066524</td>
<td>Effects of Kneehab 12-week Peri-operative Total Knee Arthroplasty</td>
<td>Other: Standard Physiotherapy</td>
</tr>
<tr>
<td>NCT01099371</td>
<td>Resistance Training in Knee Osteoarthritis</td>
<td>Other: exercise</td>
</tr>
<tr>
<td>NCT Number</td>
<td>Title</td>
<td>Interventions</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
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</tr>
<tr>
<td>NCT01112319</td>
<td>The Effects of the Electro, Heat and Cold -Therapy During Physiotherapy Treatment in Osteoarthritis(OA) of KNEE</td>
<td>Device: Elf care</td>
</tr>
<tr>
<td>NCT01210742</td>
<td>The Efficacy of Viscosupplementation for Early Knee Osteoarthritis</td>
<td>Device: Synvisc One</td>
</tr>
<tr>
<td>NCT01225133</td>
<td>Complex Ayurvedic Treatment in Osteoarthritis of the Knee Compared to Standard Care.</td>
<td>Other: Complex Ayurvedic Treatment</td>
</tr>
<tr>
<td>NCT01239823</td>
<td>Platform Exercise Training</td>
<td>Other: Whole Body Vibration Training</td>
</tr>
<tr>
<td>NCT01241812</td>
<td>Biomarkers and Knee Osteoarthritis</td>
<td>Behavioral: Lower limb muscle strengthening</td>
</tr>
<tr>
<td>NCT01245283</td>
<td>Resistance Exercise and Knee Osteoarthritis Pain, Functional Impairment and Cartilage Turnover</td>
<td>Other: normal activities and clinical care</td>
</tr>
<tr>
<td>NCT01258985</td>
<td>Tai Chi and Physical Therapy for Knee Osteoarthritis</td>
<td>Behavioral: Tai Chi</td>
</tr>
<tr>
<td>NCT01271218</td>
<td>Effects of Glucosamine and Chondroitin Supplementation in Women With Knee Osteoarthritis Participating in an Exercise and Weight Loss Program</td>
<td>Other: Diet</td>
</tr>
<tr>
<td>NCT01280903</td>
<td>Staying Active With Arthritis</td>
<td>Behavioral: STAR Intervention</td>
</tr>
<tr>
<td>NCT01306435</td>
<td>Low Power Laser and Exercise in Osteoarthritis of the Knee: a Randomized Clinical Trial</td>
<td>Other: Laser</td>
</tr>
<tr>
<td>NCT01311206</td>
<td>Low Intensity Resistance Training With Partial Blood Flow Restriction for Quadriceps Strengthening</td>
<td>Other: partial blood flow restriction</td>
</tr>
<tr>
<td>NCT01314183</td>
<td>Enhancing the Effectiveness of Physical Therapy for People With Knee Osteoarthritis</td>
<td>Other: Exercise</td>
</tr>
<tr>
<td>NCT01328340</td>
<td>High-speed Power Training in Older Adults With Knee Osteoarthritis (OA)</td>
<td>Other: weight training</td>
</tr>
<tr>
<td>NCT01331174</td>
<td>Pulsed Short Wave in Females With Knee Osteoarthritis</td>
<td>Device: Pulsed short wave</td>
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<td>NCT01345825</td>
<td>The Effectiveness of 8-weeks Progressive Strength Training to Patients With Unicompartmental Knee Replacement, Initiated Within the First Postoperative Week</td>
<td>Other: Resistance training</td>
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<td>NCT01354860</td>
<td>Moxibustion for Knee Osteoarthritis</td>
<td>Other: Moxibustion treatment plus usual care</td>
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<td>NCT01360281</td>
<td>Neuromuscular Electrical Stimulation and Strength Training in Patients With Knee Osteoarthritis</td>
<td>Other: Neuromuscular Electrical Stimulation</td>
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<td>NCT01410240</td>
<td>Efficacy and Safety of FLOSEAL for Hemostasis in Total Knee Arthroplasty</td>
<td>Other: Standard of Care</td>
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<td>NCT01440972</td>
<td>Assessment of Efficacy of Low Intensity Resistance Training in Women at Risk for Symptomatic Knee Osteoarthritis</td>
<td>Other: partial blood flow restriction (PBFR)</td>
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<td>Vascular Occlusion in Patients With Osteoarthritis</td>
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<td>NCT01489462</td>
<td>Strength Training for ARthritis Trial</td>
<td>Behavioral: High Intensity Strength Training</td>
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<td>Knee Osteoarthritis (OA) Project Treatment Versus Conventional Physical Therapy in the Treatment of Knee OA Patients</td>
<td>Other: knee OA project</td>
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<td>NCT01528566</td>
<td>Effect of Tai Chi on Osteoarthritic Knee Pain in Elders With Mild Dementia</td>
<td>Behavioral: Tai Chi</td>
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<td>NCT01529398</td>
<td>Sensorimotor Training Versus Resistance Training in Patients With Knee Osteoarthritis</td>
<td>Other: Sensorimotor training (SMT)</td>
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<td>NCT01530204</td>
<td>RAPID: Reducing Pain; Preventing Depression</td>
<td>Procedure: Physical Therapy for knee OA</td>
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<td>Strengthening Exercise and Quadriceps Force During Walking</td>
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<td>NCT01544647</td>
<td>Spa Therapy in Knee Osteoarthritis (OA): Nancy-thermal</td>
<td>Other: Usual spa protocol</td>
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<td>NCT01545258</td>
<td>Exercise and Pain Sensitivity in Knee Osteoarthritis</td>
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<td>NCT01545986</td>
<td>A Comparative Analysis of Two Types of Exercise on Outcomes Following Total Knee Arthroplasty</td>
<td>Behavioral: Exercise</td>
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<tr>
<td>NCT01576159</td>
<td>Serum Cartilage Oligomeric Matrix Protein Accumulation Decreases Significantly After 12 Weeks of Running</td>
<td>Other: Running exercise</td>
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<td>Assessing the Impact of Isokinetic Muscular Strengthening in Eccentric Mode in the Medical Treatment of Knee Osteoarthritis</td>
<td>Other: Exercise in eccentric or concentric mode</td>
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