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Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Treatment of Osteoarthritis of the Knee: An Update Review*

Draft review available for public comment from September 13, 2016 to October 11, 2016.

Research Review Citation: Newberry SJ, FitzGerald J, SooHoo NF, Booth M, Marks J, Motala A, Apaydin E, Chen C, Raaen L, Shanman R, Shekelle PG. Treatment of Osteoarthritis of the Knee: An Update Review. Comparative Effectiveness Review No. 190. (Prepared by the RAND Southern California Evidence-based Practice Center under Contract No. 290-2015-00010-I.) AHRQ Publication No.17-EHC011-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2017.

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Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site or AHRQ Web site in draft form for public comment for a 3-4-week period. Comments can be submitted via the Web site, mail or email. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Quality of Report	Superior	No response needed.
Peer Reviewer #1	Quality of Report	Fair	No response needed.
Peer Reviewer #2	Quality of Report	Superior	No response needed.
TEP Reviewer #2	Quality of Report	Good	No response needed.
TEP Reviewer #3	Quality of Report	Good	No response needed.
Peer Reviewer #4	Quality of Report	Fair	No response needed.
Peer Reviewer #5	Quality of Report	Good	No response needed.
TEP Reviewer #4	Quality of Report	Good	No response needed.
TEP Reviewer #5	Quality of Report	Good	No response needed.
TEP Reviewer #6	Quality of Report	Superior	No response needed.
TEP Reviewer #1	General Comments	The report summarizes the evidence regarding some of the most common conservative therapies offered for knee osteoarthritis pain and physical function complaints. The key questions are appropriate and useful and are clearly stated in the pertinent sections.	Thank you. No further response needed.
TEP Reviewer #1	General Comments	An orthosis is a brace, so distinguishing between braces and orthoses does not	We have clarified the wording throughout the

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		make sense. If the author's meaning is a foot orthosis or medially wedged insole or some other specific device, then they should state that.	report accordingly.
Peer Reviewer #1	General Comments	I believe the manuscript does accomplish what it set out to do; to update the 2007 and 2012 SRs by the EPC. Having said that, I am not really certain the former reviews or this review accomplished another objective; that these reviews will assist healthcare providers, payers, policymakers, patients, and other stakeholders in making informed decisions. The approaches to these systematic reviews seems to water down important information by pooling data from multiple studies on multiple topics. It is not surprising that this approach, in most cases, results in many “unclear” findings. As a provider, these reviews don’t help me much in trying to make clinical decisions. For example, there is nowhere in this manuscript where dosage of interventions is addressed. I am certain that there are likely certain dosages or applications of interventions that may be more effective than others. This type of information would be much more useful to me. It would tell me that if I want to use a particular intervention, what application of the intervention might be worth using, or perhaps that an	Where possible, we have included the doses, e.g., the lengths of sessions and intensities of physical interventions, as well as the durations, compared with followup times in the evidence table and in the text, but we found insufficient numbers of studies to allow us to compare intensities or numbers of sessions across studies, and none of the studies we identified made these comparisons. We have added this point to the limitations, and we also now cite a 2015 Cochrane review that assessed studies that compared high and low intensity exercise for hip and knee OA.

		intervention is not useful at any dose or application. Perhaps the approach to the systematic reviews might be that for any given treatment, which dosages and which applications appear to provide the best outcome. I understand that this was not the purpose of the current or past SRs but I think moving forward, the approach I am suggesting might actually be more useful. Maybe this is something that could be addressed in the Future Research section of this manuscript.	
Peer Reviewer #1	General Comments	The use of the term “Physical Modalities” was confusing to me. Many clinicians think of thermal agents and electrotherapy when this term is used. In the manuscript, it is used as an umbrella term that also includes exercise, agility and balance, manual therapy, etc. Perhaps using the term “Physical Interventions” might be a better term to encompass all of these under one umbrella.	We have revised the term to "physical interventions."
Peer Reviewer #2	General Comments	The report is clinically meaningful and up to date for providers that treat subjects with knee OA. The target population and audience are well defined. Are the key questions appropriate and explicitly stated?- YES, very clearly articulated in the document	Thank you. No further response needed.
TEP Reviewer #2	General Comments	The evidence review is done using the highest standards. The results present	Thank you. No further response needed.

		some surprises such as the modest efficacy seen with PRP and with TENS.	
TEP Reviewer #2	General Comments	The document would benefit from a pictorial representation of the principal findings. The text is necessarily dry and does not bring the work to life.	We have tried to clarify the summary table to make the findings more salient. We welcome suggestions regarding a pictorial representation that would provide a clearer picture of the conclusions.
TEP Reviewer #2	General Comments	Many studies are small and the summaries of these studies does not clearly indicate whether some studies had effect sizes we'd care about but low sample sizes.	We presented the sample sizes in the narrative descriptions of the studies, as well as in the evidence table. And we tried to indicate when a finding was based on small studies. We would welcome suggestions regarding how to emphasize study size more clearly.
TEP Reviewer #2	General Comments	I see no evidence here of bias in the development of this report.	Thank you. No further response needed.
TEP Reviewer #3	General Comments	Overall the report is clinically meaningful. The clinical meaningfulness of the strength training, aerobic, yoga, tai chi etc isn't entirely clear given the approach of the review.	By "clinical meaningfulness," I assume the reviewer is referring to minimum clinically important difference (MCID)? We thought it would be most accurate to indicate whether results met a MCID only if they were pooled results.
TEP Reviewer #3	General Comments	Target populations and audience is explicitly defined. Key questions are	Thank you. No further response needed.

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		explicitly stated and appropriate.	
Peer Reviewer #4	General Comments	The report may be clinically meaningful. I would use "knee osteoarthritis" as the target population. The distinctions between "primary" and "secondary" are not clear and not clinically useful. The important exclusion should be those with an active inflammatory arthropathy. Key questions appear appropriate and are explicitly stated, although those pertaining to effect modification by subgroup were never answered due to paucity of data.	We did not intend to distinguish between primary and secondary OA, as the original report found no evidence of a difference. We have eliminated the distinction between primary and secondary OA.
Peer Reviewer #5	General Comments	This review is a meaningful clinical report, but the target population is not well defined. While this comprehensive non pharmacological review is helpful to researchers in the field of osteoarthritis, I am not sure how much of the report is going to impact the practice of clinical rheumatologist or primary care physicians.	The target population is defined in Table 1 (the PICOTS table). We can't distinguish further whether the report would be more applicable to patients seen in the primary care or specialty care setting.
Peer Reviewer #5	General Comments	The key questions are well stated, based on comments by technical expert team TEP and public	Thank you. No further response needed.
TEP Reviewer #4	General Comments	Page v: The structured abstract could include definitions of short, medium, and long-term follow-up.	We have added the definitions of short-term, medium-term, and long-term to the abstract.
TEP Reviewer #4	General Comments	Table A and ES Acknowledging the use of different instruments, reporting results as beneficial or not could be seen as	We hesitated to indicate whether evidence of benefit meant clinically meaningful benefit unless the finding

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		somewhat problematic. I suspect readers will consider "beneficial" to imply clinically meaningful. I wanted to see something concerning a magnitude of effect (or range) when "benefit" was reported.	was based on pooled results, particularly for interventions with a very small literature and no prior validation of an MCID.
TEP Reviewer #4	General Comments	I would prefer to see Table A structured similarly to the example table in the methods guide strength of evidence (SOE) chapter--including the number of participants and SOE as a separate column which is visually clearer than the present format.	We have tried, through several iterations, to make the table more user friendly by reorganizing the conclusions and making the SoE more salient.
TEP Reviewer #4	General Comments	The Key Questions were appropriate, clear, and mapped to the analytic framework. I felt that the report generally offered balanced and clinically relevant conclusions.	Thank you. No further response needed.
TEP Reviewer #5	General Comments	This report is clinically meaningful in as much as is possible with the dearth of strong clinical trials to provide evidence of efficacy or the lack thereof. Populations and audience are defined explicitly. Key questions are well stated and appropriate for the topic.	Thank you. No further response needed.
TEP Reviewer #5	General Comments	Editorial suggestions: There are two important abbreviations used in the document that are not included in the final page Abbreviations/Acronyms and not defined prior to use. These include SoE (strength of evidence) and PICOT (Patient, Intervention, Comparison, Outcome,	Thank you so much for pointing out these omissions! We have added those terms to the list of Abbreviations.

		Time).	
TEP Reviewer #5	General Comments	There are some confusing sections such as page 59 stating that 45 studies described some assessment of AEs and further down stating that 44 reported AEs.	Thank you. In updating the evidence, we have fixed the numbers.
TEP Reviewer #6	General Comments	The report is clinically meaningful, although the heterogeneity of outcome and effect may not be as prescriptive as some clinicians would like.	No response needed.
Peer Reviewer #6	Abstract	Page 5, line 47: SoE should be spelled out in the abstract and “lack of effect of” should be deleted – Low strength of evidence was also found for manual therapy – if that’s what the authors want to say.	We have revised this text in the abstract.
TEP Reviewer #1	Introduction	The Introduction provides an accurate summary of the problem of treating knee OA patients and common therapeutic approaches. The bulleted list on page 2 is helpful, but it does not mention education in pain coping strategies, activity modification or adaptive equipment to improve patients' environments as therapies for knee OA pain/functional limitations.	Thank you for pointing out this oversight! We have added these to the list, especially as we include PCST in our assessment.
TEP Reviewer #1	Introduction	Also, muscle weakness should be included as a characteristic of knee OA on page 1.	We have added to the ES and main text.
Peer Reviewer #6	Introduction	(ES-1) Page 9, line 13: articular cartilage does not line the knee joints – it is found at the ends of bones that articulate within joints.	Thank you. We have revised the sentence.

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Peer Reviewer #6	Introduction	(ES-1) Page 9, line 16: modern OA scientists do not consider OA to be a “natural consequence of aging” (this is reminiscent of cardiologists saying that coronary heart disease was a natural consequence of gaining in the 1950s). I would eliminate the distinction between primary and secondary knee OA.	We have revised the description of the etiology of primary OA and now note that we do not distinguish between primary and secondary any further in the report.
Peer Reviewer #6	Introduction	(ES-1) Page 9, line 27: instead of “low cutoff scores” and “high cutoff scores” maybe “less severe grades” and “more severe grades”?	We have revised the text as suggested.
Peer Reviewer #6	Introduction	(ES-1) Page 9, line 38: maybe “not yet used in clinical practice”	We have revised the text as suggested.
Peer Reviewer #6	Introduction	(ES-1) Page 9, lines 39 and 51: I would eliminate the references to “slowing of progression” and “disease modification” since we have no means of doing either of these now.	We have revised the text of both sentences as suggested.
Peer Reviewer #6	Introduction	(ES-2) Page 10, line 4: spell out HA	We have spelled out hyaluronic acid (HA).
Peer Reviewer #6	Introduction	(ES-2) Page 10, line 34: spell out SNRIs and TEP	We have spelled out serotonin–norepinephrine reuptake inhibitor (SNRI) and technical expert panel (TEP).
Peer Reviewer #6	Introduction	(ES-5) Page 13, line 28: rated the quality of studies using what methods? You might introduce the study limitations/Risk of Bias idea here.	We have added the methods here.
Peer Reviewer #6	Introduction	(ES-5) Page 13, line 53: spell out RoB	We have spelled out Risk of Bias (RoB).

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Peer Reviewer #6	Introduction	(ES-6) Page 14, line 11: A table summarizing the SoE criteria would be helpful for the naïve reader.	We have added bulleted lists summarizing the criteria and the definitions of the grades to the main text of the report.
Peer Reviewer #6	Introduction	(ES-7) Page 15, line 42: Maybe saying these 4 RCTs had methodologic challenges instead of average RoB: moderate would help the clarity of the text. This occurs many places in the text subsequently.	Unfortunately, we need to report the overall risk of bias of the study literature that addresses a particular conclusion many times, so we have adopted the suggested shorthand. We describe our rating system in the Methods section and refer the reader to the table in the Appendix that lists the detailed risk of bias assessments for each study.
Peer Reviewer #1	Introduction	No comments	Thank you. No further response needed.
Peer Reviewer #2	Introduction	Strong	Thank you. No further response needed.
TEP Reviewer #2	Introduction	Succinct and clear	Thank you. No further response needed.
TEP Reviewer #3	Introduction	The introduction is good. The results of the exercise analyses (strength training, agility, aerobic etc) do not necessarily support other systematic reviews. It would be nice to bring in the previous systematic reviews on exercise since there are several in the introduction or in the discussion of the findings in the context of the literature (more than just ARHQ's).	We have attempted to include relevant higher-quality reviews subsequent to the 2012 EPC review. We have added two more relevant reviews, including one Cochrane reviews, in the Discussion.

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Peer Reviewer #4	Introduction	Aside from the using a very dated definition of "primary osteoarthritis", most modern OA researchers do not think of OA as a "natural consequence of aging" (this is what cardiologists thought of coronary heart disease in the 1950s), this section appears adequate. I would eliminate the distinction between primary and secondary knee OA, given that it did not have any implications in how the review was conducted.	We have clarified that although the distinction was made in the original report, we consider only the one condition. We have changed the report title by removing "primary and secondary knee".
Peer Reviewer #5	Introduction	The introduction is well written as a summary of the osteoarthritis disorder definition and risk factors, with its increased morbidity and mortality and increased cost utilization. treatment strategies is emphasizing non pharmacological approach.	Thank you. No further response needed.
TEP Reviewer #4	Introduction	The introduction was concise and well written.	Thank you. No further response needed.
TEP Reviewer #5	Introduction	This manuscript presents an extensive overview and update on clinical treatments for osteoarthritis of any cause. The list of treatments is inclusive of possible treatments ranging from cell-based to home-based therapies. The review of the literature appears to be very comprehensive and appears to have captured all randomized controlled clinical trials in to 2016. Unfortunately, the strength of evidence for effectiveness of most treatments was	Thank you. No further response needed.

		inconclusive.	
TEP Reviewer #6	Introduction	Appropriate content and definitions.	No response needed.
TEP Reviewer #1	Methods	The PICOT statement is very clear as are the descriptions of the statistical methods used for summarizing or pooling the data. This statement excluded studies that used a participant's less-painful knee as the comparator. Why was this common design excluded?	Based on a prior review we conducted on the effects of HA on function and reviews by other groups, we were concerned that persons with OA in one knee that is severe enough to seek treatment tend to have some degree of OA in the less painful knee that could interfere with a fair assessment of change in function.
TEP Reviewer #1	Methods	The effect of weight loss on reduction in pain and functional limitations is described less profoundly than I recall. Were the FAST, ADAPT, START, CARROT and other large RCT's included?	We do include the CAROT study in our analysis. The FAST and ADAPT studies were included in the 2012 EPC report, so we did not specifically re-review them here The START trial is still in progress; we have added a description of this study to our Discussion section.
Peer Reviewer #1	Methods	For the most part, I believe the methods were sound for the stated purpose of the review. Page ES-4: The scope of the review is unclear. It states the searches commenced with the year 2006 but what was the end date of the reviews? This is	We have added the end date of our searches (most recent date September 2016).

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		important for the reader to know because there are some articles not cited that might be useful in the review, however, perhaps they were beyond the range of dates for the review (see manual therapy comments below).	
Peer Reviewer #1	Methods	Page ES-11: There are a couple of manuscripts missing from the manual therapy review that might be useful. The first is Abbott JH, et al, 2013 and the second is Fitzgerald GK, et al, 2016. The Fitzgerald manuscript may be beyond the range of dates for this review as it was recently released online. However, it does demonstrate a short term effect for manual therapy in a multi-center study, funded by AHRQ, on 300 subjects.	Unfortunately, we reviewed Abbott, 2013 but excluded it because it did not report data separately for individuals with knee (vs. hip) OA. We have updated our original searches and Fitzgerald 2016 is included in the revised version of the report.
Peer Reviewer #2	Methods	Are the inclusion and exclusion criteria justifiable? --YES, well described. Are the search strategies explicitly stated and logical? --YES I agree Are the definitions or diagnostic criteria for the outcome measures appropriate? YES, the definitions and outcome measures are appropriate for knee OA Are the statistical methods used appropriate? YES, statistical methods are appropriate.	Thank you. No further response needed.
TEP Reviewer #2	Methods	Methods are rigorous and explained clearly	Thank you. No further response needed.
TEP Reviewer #2	Methods	You should state more clearly what is meant by self management program. This is a confusing area.	We have clarified the description of self-management programs in the PICOTS table.

TEP Reviewer #3	Methods	Overall yes. I'm not sure why mudbaths are included since this is a rather obscure treatment but explanation if provided how the interventions were selected.	We included mudbaths because they overlap with interventions like balneotherapy and heat in their proposed mechanisms.
TEP Reviewer #3	Methods	The inclusion criteria for exercise--i.e., strength training are not clear. It seems that a large number of articles are missing and the inclusion strategy resulted in odd comparisons (e.g., quadriceps strengthening). Quad strengthening alone without addressing other musculature is not routinely done and better programs are more inclusive of strengthening multiple muscles. In addition, strength training must be done at a dose that results in overload to tissues to foster strengthening. It isn't clear the articles chosen met criteria for strengthening programs.	For this category, we grouped studies that referred to themselves as strength or resistance training programs or for which the focus appeared to be mostly on strength building, based on the criteria used for the 2012 EPC report on physical interventions for knee OA pain. We have included a brief explanation to this effect. We would welcome guidance about studies we should have included (published subsequent to the searches conducted for the 2012 EPC report).
TEP Reviewer #3	Methods	Why was home-based exercise put with self-management since home-based exercise can be done with out without self-management approaches. In many ways home based exercise is just another type of exercise so it could have been strength training. The distinction and rationale is not clear and is not clear in the article.	We combined the two categories, as the intent of both appeared to be on patient-managed interventions. However, we also analyzed the home-based exercise studies along with studies that assessed the same categories of exercise. We have added a

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			note describing why we combined these two types of interventions.
TEP Reviewer #3	Methods	Did the 'manual therapy' category only include massage and acupressure? If so, it might be better to just use the terms "massage and acupressure". Manual therapy is a common technique in physical therapy (I.e., manipulation of the joint for range of motion and joint mobility) that is sometimes done in conjunction with exercise. The term 'manual therapy' can be quite broad and is misleading if it only refers to massage and acupressure.	The studies of manual therapy included the type of manual therapy traditionally used in physical therapy, as well as therapeutic massage and acupressure.
TEP Reviewer #3	Methods	The definitions of outcome criteria are clear. The table describing inclusion and exclusion criteria is helpful. It isn't clear if outcomes assessed were AFTER the study intervention was completed (i.e., 4-12 weeks after the intervention was completed or at 36 months when the intervention was still fully executed.) This is important since adherence to the intervention can have a large effect on outcomes particularly for the exercise interventions. This might help explain some of the discrepancies with other published systematic reviews in this area. Please be clear with the exercise studies in particular if the outcomes are assessed with concurrent intervention. Also, where appropriate and available	We agree that both adherence and the time point at which outcomes were assessed in relation to the end of the intervention is important, and we describe that as a limitation in the Discussion chapter. In most cases, outcomes were assessed at the end of the intervention period. We also showed adherence rates in the evidence tables when this information was reported, but as we discuss in the limitations, adherence to the "homework" portions of interventions was seldom

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		please include information on adherence to exercise protocols since that can impact outcomes.	assessed.
TEP Reviewer #3	Methods	It isn't clear how the exercise studies (strength training, aerobic etc) were selected (terms used). It seems like articles are missing and the articles included are limited in scope (e.g, quad strengthening vs. a more inclusive lower extremity and core strengthening program). Likewise, there is a difference between strengthening exercises that are not progressive in nature and/or not intensive enough to have a therapeutic effect. Were these criteria included to screen articles?	We sought to include all studies that employed an exercise intervention compared to a control (which could be another exercise intervention) and that met our other inclusion criteria (e.g., diagnosed knee OA). We did not exclude studies that failed to use a progressive strengthening protocol or to match the intensity to the needs of individual participants. We classified studies by the type of exercise that was the main focus of the intervention or by how the authors classified them. Again, we would welcome suggestions of additional studies to include in various categories.
Peer Reviewer #4	Methods	Inclusion/exclusion criteria, search strategies, methods to judge quality of studies, and planned pooling strategies all appeared appropriate and well justified. I think creating tables to summarize the risk of bias and the strength of evidence ratings would be helpful for the naive reader.	We have revised the summary table to make it easier to read, although we did not include the RoB ratings for the studies (these are included in the larger SoE table in the Appendix).

Peer Reviewer #5	Methods	The methodology is addressing key questions as a need to update of a systemic review done in 2007. inclusion and exclusion criteria are defined to some extent. The quality of studies was addressed using strength of evidence and risk of bias. Outcome measures were stratified to short-, medium- and long - term effects. such stratification is important for the analyses of each intervention, based on level of pain and physical function. Statistical modeling is appropriate for this review. the minimum clinical improvement differences of clinical outcomes is reported.	Thank you. No further response needed.
TEP Reviewer #4	Methods	Page 11 line 10: It might be reasonable to specify the effect estimate(s) (mean difference) pooled--post-test, change, etc (e.g., from an ANCOVA)--if there was some rule for choosing one over the other or if the approach followed the methods guide. Also, it might be worth stating the SMD calculation (e.g., Hedge's G or whatever) given that many studies were small.	We have added a description of our effect estimates in the Methods section of the main text under Data Synthesis/Analysis.
TEP Reviewer #4	Methods	Page 11 line 15: "...we did not pool studies that used different tools to measure a similar outcome (e.g., VAS and WOMAC pain measures), as two tools used in the same study on the same participant population sometimes resulted in different outcomes."	The reviewer raises a good point. Our priority was to use the WOMAC for pain and function whenever it was reported. We have added this detail to the Methods.

		<p>It is unclear to me how often this occurred, but I wondered about the decision rule and whether there was some precedent for it. I would have some concern that it could introduce a bias in pooled estimates if it occurred commonly. Was consideration given to specifying an a priori hierarchy of instruments to include in a pooled result? I would consider that a preferable approach unless effects on different scales differed qualitatively. In addition, sensitivity analyses could be considered although I suspect would not be warranted.</p>	
TEP Reviewer #4	Methods	<p>Page 11 line 24-25: It might be reasonable to add some further explanation concerning the meaning (and limitations) of comparing a continuous pooled effect to some MCID or MCII. A mean difference less than the MCID or MCII may translate into a substantial number of individuals receiving an important benefit.</p>	<p>We have added the following to the limitations already in the Discussion, to address this point: "Further, in studies with continuous outcomes, even if the mean difference is less than the MCID, a proportion of participants experience outcomes that exceed the MCID. Thus rigorously applying the MCID could prevent patients from obtaining potentially effective treatments."</p>
TEP Reviewer #4	Methods	<p>Page 12 "Assessing Applicability": The explicitness of the section was particularly good and helpful.</p>	<p>Thank you. No further response needed.</p>
TEP Reviewer	Methods	<p>As noted later, it was unclear whether</p>	<p>We re-reviewed all studies</p>

#4		the <50 participant exclusion applied to strength/resistance training.	initially excluded for smaller sample sizes and included all studies that had been excluded only for small sample size, with the exception of studies of glucosamine and chondroitin, as the large number of very large studies would have negated the effect of very small studies.
TEP Reviewer #6	Methods	The inclusion/exclusion criteria are fine, but the devil is in the fact that 22 yo with knee OA are far different than 72 yo with knee OA. This is not a problem isolated to this review. All other methodological approaches are appropriate.	We have acknowledged the comment. Thank you.
TEP Reviewer #5	Results	Inclusion and exclusion criteria are justified and appropriate. Search strategies are well explained and logical. Definitions and diagnostic criteria for outcome measures are appropriate. This reviewer has limited statistical background but found the statistical methods well described and seemingly appropriate.	Thank you. No further response needed.
TEP Reviewer #1	Results	The detail in the results section is appropriate. The Forest plots are clear and helpful. The summary of results can be dense to read due to the multiple scales— low/moderate/high strength of evidence with low/moderate/high risk of bias for short/medium/long-term	Thank you for your suggestions. We have tried to make the tables and forest plots more reader friendly.

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		beneficial effects on pain/function for multiple therapies. A chart that has columns that break down the 3 follow-up periods for each intervention and color-codes the level of evidence could more clearly communicate a summary of the findings.	
Peer Reviewer #1	Results	Page ES-13: With regard to the results on TENS: Knowing the application here is important. Few clinicians expect long-term effects in chronic pain patients with TENS. TENS is thought of something they would continually use in place of stronger pain meds (opioids). When the results speak of long term effects is this with an application of continual application of the TENS over months duration or are we talking about short term application (a few weeks, then measure long term outcomes). I think this needs to be addressed somewhere. If not here, perhaps in the discussion.	We have clarified the lengths of TENS interventions compared with the durations of followup. We also note this issue in the Limitations section.
Peer Reviewer #1	Results	Page ES-13 NMES: NMES is not really used to address pain in knee OA. Most NMES applications are designed to address quadriceps strength with the hope that improvements in quadriceps strength might reduce pain and improve function. Presenting the results on pain and function without knowing that the NMES improved strength or not might be a bit misleading or inappropriate. If no change in pain or function occurs	As improvement in strength was not a prespecified outcome of the review, we did not assess change in strength in relation to changes in pain and function. However, we have re-reviewed these studies and have commented on their assessment of strength in the Discussion.

		because there is no change in quad strength, then it speaks to a dose/application problem with the treatment. If strength improved and still there was no change in pain and function, then perhaps the NMES approach has no value. As presented, the results don't help me with decision-making.	
Peer Reviewer #1	Results	ES-14: What is the difference between a custom knee brace and a custom orthosis? Some use these terms synonymously. This needs to be clarified.	We have revised the wording throughout the report to "Orthoses (knee braces, shoe inserts, and custom shoes)".
Peer Reviewer #2	Results	The amount of data is appropriate. The study characteristics are described adequately. Keep messages are clear Tables are fine	Thank you. No further response needed.
TEP Reviewer #2	Results	I think the report would benefit from a figure that helps the reader see which treatments have no support, minimal, modest and strong support. And whether the treatment effect is minor or more substantial. This info is all available in the tables and texts but a single figure that brings the major messages together would be useful.	We have revised the summary table to improve the clarity of the strength of evidence for each conclusion.
TEP Reviewer #3	Results	Detail presented inadequate. Plots are useful. Readers cannot identify which articles contributed to the specific, detailed findings since citations are not listed. Citations would be helpful within	We realize it would be helpful to provide the citations for each summary point in the Executive Summary but it is quite

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		the findings/results section.	challenging. The citations are provided in the Results section in the main text.
Peer Reviewer #4	Results	The Table following the Executive Summary is helpful, but the text in the Executive Summary and the Results section could add value above and beyond the table by explaining what the particular reasons were for the "insufficient evidence", "low strength of evidence", "moderate strength of evidence" ratings. Right now, if you read the text alone, you are unaware of the less favorable SoE ratings that are included in the table. This led to lots of confusion on my part when I initially read the report.	We have revised the summary table to clarify which outcomes had insufficient evidence to support a conclusion. The Appendix SoE table shows the criteria that went into each SoE decision.
Peer Reviewer #4	Results	There does not appear to be a standard approach to reporting the "Key findings" bullets and sub-bullets. Some primary bullets are useful summaries of the evidence, others report on the evidence which probably should be only reported in the sub-bullets. This inconsistency in how the results are reported makes the executive summary and Results section extremely difficult to read.	We have revised all the Key Points sections to be more uniform in the format and findings they present. We tried various ways to present the information in the clearest ways for each type of intervention and would welcome suggestions on re-organizing it.
Peer Reviewer #4	Results	Another reason for my challenges getting useful information from the executive summary Results section was the inconsistency of the number of "key points" made within each of the therapeutic options.	The number of key points for each intervention definitely depended on the number of outcomes and followup times for which data were available. We have revised

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			the Key Points and Summary table to make them clearer and more uniform.
Peer Reviewer #5	Results	Result section is well organized, making the reading of the result section with such complex stratification easier. Table 2 is helpful, suggest simplification, for practical approach. It is not clear what the investigators have done with studies with high level of risk of bias. did that affect the interpretation of their results.	Risk of bias was considered in assessing the overall strength of evidence of studies for each conclusion, according to the EPC Methods guide, which is based on the GRADE approach: We have made sure that this point is emphasized in the Methods.
TEP Reviewer #4	Results	Page 14 "Description of Included Studies": For the single studies, it might help to provide tables of relevant outcomes including sample sizes. The detail being reported solely in text can make it hard at time to place different results into context. Understanding the difficulties the various scales used, it could help to display effect magnitudes and confidence intervals or p-values (which could all also be expressed as SMDs allowing some comparisons between studies). Generally, except where the text offers interpretations, in my view summary tables would be preferable for reporting quantitative results and provide a map to reader.	We considered including in-text tables that reported study-level details and outcomes for each intervention; however, this information is summarized in the evidence table, and we are striving to keep the report, which is already long, manageable.
TEP Reviewer #4	Results	(Possible correction) Page 15 lines 14-16: The authors might check the confidence interval and lack of a	Thank you. We verified the findings.

		significant difference. I believe the relevant result from the paper is "Los resultados obtenidos al cuarto mes de tratamiento mostraron una diferencia significativa entre ambos grupos; el valor promedio para el grupo 1 fue de 51.2 puntos (± 15.4), y para el grupo 2 de 42.2 puntos (± 14.7) ($p=0.008$)."	
TEP Reviewer #4	Results	(Possible correction) Page 15 lines 54-57: The authors might reconcile the calculated confidence interval (-18.29 to 4.49) with the published p-value--"48.2 puntos (± 15.0) vs 41.3 puntos (± 22.0) ($p= 0.0008$)".	We repeated the calculations of effect sizes and did not find significant differences.
TEP Reviewer #4	Results	Also, if the authors calculated confidence intervals from reported data that might be noted in the methods section (in the unlikely event someone wanted to replicate a result).	We have now noted this in the Methods section.
TEP Reviewer #4	Results	(Possible correction) Page 21 line 45: I believe the effect is a mean difference (not an OR) and there may be an error in the abstracted upper bound of the CI (from the paper 36.64 (95% CI -64.57 to 137.86)).	Yes, that is correct. We have changed OR to MD and rechecked the data on which we based the calculated effect size.
TEP Reviewer #4	Results	Page 24 lines 3-8: First, I assume my brief perusal of the paper is correct. Without noting that at 8 weeks there were 11 participants (after 3 dropouts) in the resistance training arm, and 9 (after 4 dropouts) in the control arm, it is difficult for the reader to understand that "no improvement" is really not	We have now noted in the narrative description of this study that the dropout rate was high and that the baseline values were at least non-significantly different. We have added to the Methods that we assume no

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		informative. In addition, the post-test difference was used to calculate the MD, but the baseline values differed between the 2 arms. I believe the AHRQ "guidance" for continuous outcomes would recommend using the more conservative estimate taking into account baseline difference. Either way, it might be reasonable to state in the methods the approach followed.	significant difference in baseline values. Although we did not exclude the study from the pooled analysis, we did note that it was an outlier and was responsible for the lack of a statistically significant improvement in WOMAC pain and function with strength training.
TEP Reviewer #4	Results	There are some exceedingly small studies in the report (I counted 9 with at least one arm having 10 or fewer participants and many have arms with fewer than 20). This could be made a bit clearer to the reader in the descriptive text and key points. Noting the total sample size is not sufficient.	We reincluded all studies that had been excluded solely for small sample size, with the exception of those that assessed the effects of glucosamine and chondroitin. We have noted this in the Methods section.
TEP Reviewer #4	Results	Similarly, not displaying the number of participants in study arms makes the forest plots difficult to interpret and I would recommend they are added. I also suggest adding tau ² (or better tau) to the forest plots. Although many may focus on I ² values, they can be misleading (e.g., Rucker et al BMC Medical Research Methodology 2008, 8:79).	We have added the numbers of participants as suggested. We simply use the I-squared to be able to compare our findings to those we've obtained in past reports.
TEP Reviewer #4	Results	The methods section (page 50) also states that for strength/resistance training studies with <50 participants were excluded and there appear to be excluded studies listed in Appendix B.	We reincluded all studies that had been excluded solely for small sample size, with the exception of those that assessed the effects of

		Yet 3 of the 5 studies here had fewer than 50 participants.	glucosamine and chondroitin. We have noted this in the Methods section.
TEP Reviewer #4	Results	Page 28 lines 44-49: The results quoted appear to derive from an abstract (reference 49). I believe the study was subsequently published (PMID 24905427) and is listed as an excluded study (Appendix B page 15).	We inadvertently included the abstract in place of the full text article. We have now included the full-text article and reassessed the risk-of-bias.
TEP Reviewer #4	Results	(Possible correction) Page 42 line 55: SMD should be changed to MD (mean difference).	Yes! Thank you! We have changed it.
TEP Reviewer #4	Results	(Possible correction) Page 55 line 31: Is this the Atukorala study or the Makovey study?	They are both the same study. The conference proceeding by Makovey et al., reported the results of the SF-12 noted here. We used the same author name to show it was the same study but have now changed it to the Healthy Weight for Life Study.
TEP Reviewer #4	Results	(Possible correction) References 95 and 110 appear to be duplicates as are 96 and 111.	Reference 95 in the Executive Summary is numbered as 110 in the main text. Likewise, reference 96 in the summary is reference 111 in the main text. We are required to list references separately for the executive summary and main text of the report.
TEP Reviewer	Results	Amount of details varied from treatment	No response needed.

#5		to treatment and could be abbreviated in some cases. However, the figures and tables and appendices are adequate and helpful. No studies were overlooked.	
TEP Reviewer #6	Results	All relevant studies were included. The detail is excellent, but the inconclusiveness of the data will frustrate some (again this isn't a problem unique to this review).	Thank you.
TEP Reviewer #1	Discussion / Conclusion	On page 61, the Discussion refers to a summary of the Results in Table 3. This appears to be Table 2 and if this is not mentioned earlier, it would be useful to do so.	Thank you. We fixed the table numbering.
Peer Reviewer #1	Discussion / Conclusion	ES-19: The point about wide variation in the application of manual therapy is well taken. Most PTs would use a combination of joint mobilization, joint manipulation, and soft tissue mobilization/manipulation as part of a manual therapy treatment. It is probably not realistic to study these in isolation because that is not the way they are used. It might be more useful to study treatment selection approaches.	We have further addressed this point in the descriptions of the interventions and findings as well as in the Discussion.
Peer Reviewer #1	Discussion / Conclusion	ES-21: With regard to multi-component intervention approaches; I tend to disagree with the idea that it is important to study the attributes of single interventions. This, in my opinion, is unrealistic and would result in more studies that have minimal application to real life. Patients with knee OA have	We agree that multicomponent approaches are the approaches used in treating patients in the real world and hope that such interventions, as well as treatment algorithms, can be considered in a future

		multiple problems and thus require multiple interventions during the course of care. In addition, the interactions between interventions are often times not linear so what an intervention may do in isolation may not necessarily predict it's value when applied in conjunction with other treatments. I think it would be more useful to study how and why clinician's select various treatments and which overall approach or approaches may be most effective. Examining isolated treatment effects will likely have limited utility.	review, keeping in mind that studies designed to provide useful results about such interventions are few in number.
Peer Reviewer #1	Discussion /Conclusion	Future Research Recommendations: Consider addressing the point I made above in the General Comments about dosage and application of interventions in future studies.	We have now addressed this point.
Peer Reviewer #2	Discussion /Conclusion	Major findings are stated. Limitations are clear Future research could be better stated. For example, the use of the MRI as an endpoint- could add information on structure and pain correlations.	Although we did not consider imaging or other non-clinical outcomes, we have added a suggestion to the Future Research recommendations regarding use of such methods.
Peer Reviewer #2	Discussion /Conclusion	Also, another outcome measure may be exercise or activity minutes, which can now also be reliably obtained. The lack of this information, might be stated in the discussion as these potential outcome measures will be quite helpful to better assess treatment efficacy	We have added a suggestion to the Future Research section regarding comparatively assessing "dose," which covers this point.

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TEP Reviewer #2	Discussion /Conclusion	The limitations are stated clearly. The conclusion, discussion and future research sections are a bit too detailed. I read them twice carefully and found that they repeated results more than provided points for discussion.	We erred on the side of repeating some information for folks who were likely to read only certain sections.
TEP Reviewer #3	Discussion /Conclusion	yes. I would like to see more discussion in the exercise findings how this systematic review fits with other systematic reviews on these areas.	We tried to discuss how the findings fit with previous findings of the reviews we were updating as well as a small number of recent reviews. We will aim to include a few additional high-quality reviews in the Discussion.
Peer Reviewer #4	Discussion /Conclusion	Generally adequate. Main findings are clearly stated, limitations are well presented. Future research section is clear.	No further response needed.
Peer Reviewer #5	Discussion /Conclusion	The discussion section is a narrative summary of findings of multiple interventions and their strength of evidence. The limitation of the evidence base and limitation of the study quality are described well, Nonetheless, the interpretation of the findings is not well addressed. no argument is made with respect to any intervention. no pooling of results as the results are heterogeneous	We have increased the numbers of outcomes for which we pooled results and show which outcomes are based on pooled results in the summary table, findings, and conclusions sections. We are not sure how to improve the discussion of the findings. We believe the limitations of existing studies prevent further analysis regarding which interventions are better or

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			worse than others.
TEP Reviewer #4	Discussion /Conclusion	Page 65 line 11: I did not see mention of the risk of bias score in the methods and how they should be interpreted. I would argue that risk of bias "scores" (Appendix E) are best avoided as a means to appraise clinical trials (e.g., Cochrane and others). Also, given that the Cochrane ROB tool was used, it could be useful to summarize using the standard Cochrane graphic--according to intervention and possibly overall.	We have augmented our description of the risk-of-bias assessment in the Methods section of the main report to indicate how the individual elements of potential bias were rated and how these elements were used to determine an overall level of risk (as we were asked to do). We did not include the Cochrane graphic because the number of elements and the number of studies made for an unwieldy table.
TEP Reviewer #4	Discussion /Conclusion	Page 67 line 35-27: It appears that trial sample size is a significant issue for many interventions reviewed. Small study effects for pooled effects of OA trials have been emphasized in many publications. While here studies were not often pooled, small study effects on the evidence synthesis are yet a concern and might be given more attention both in the context of study limitations and future research. For example, if my count is correct from 85 non-abstract report studies, some sample size calculation was reported in 38 (55%).	We have now addressed this point.
TEP Reviewer #5	Discussion /Conclusion	There are very limited "major" findings. Limitations and weaknesses are well described in the manuscript. Future	No further response needed.

		research section is clear and relevant to needs for the field.	
TEP Reviewer #6	Discussion /Conclusion	Yes to all questions. The future reserach needs are well-defined, there just isn't enough grant funding to achieve them.	Thank you
TEP Reviewer #1	Clarity and Usability	Overall, this is a useful work that advances understanding.	Thank you. No further response needed.
Peer Reviewer #1	Clarity and Usability	The report is well structured and organized. I don't believe many of the conclusions are relevant to policy or practice decisions for the reasons stated above.	Thank you. No further response needed.
Peer Reviewer #2	Clarity and Usability	The report is well structued and well organized, main points are clearly presented, conclusions are relevant to policy. There is some new information however, not much of it will impact practice for the treatmeant of knee OA very much.	Thank you. No further response needed.
TEP Reviewer #2	Clarity and Usability	My comments about summary tables and / or figures would help usability. The work is clear, rigorous and will be appreciated by investigators, clinicians, others.	We have modified the summary table to improve clarity; we welcome suggestions for additional ways of showing the findings.
TEP Reviewer #3	Clarity and Usability	yes, this was nicely done.	Thank you. No further response needed.
Peer Reviewer #4	Clarity and Usability	Clarity is the major challenge of the report. It's very difficult to read. Not establishing the measurement tools for Risk of Bias and Strength of Evidence for the naive reader is a problem that could be addressed with Tables.	We have further defined the risk of bias measures and have provided the definitions for the SoE categories.

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Peer Reviewer #4	Clarity and Usability	The conclusions/recommendations are relevant to policy and practice decisions and could lead to more impactful research.	No further response needed.
Peer Reviewer #5	Clarity and Usability	The report is organized and well structured, This is an updated version with a narrative summary of reports in the non pharmacological treatment of osteoarthritis of the knee. there is some element of new information updated since 2007. future research directions are limited.	We have added a few further points to the Future research section but otherwise believe we have covered the suggestions for future research to the extent possible.
TEP Reviewer #4	Clarity and Usability	I appreciate the challenges involved for a CER including multiple interventions (often with limited or no evidence) and reporting on multiple scales (often continuous). The authors have done an admirable job. The review is well organized. The writing is factual and clear. Outside a few minor corrections, my comments relate mostly to how and what information is emphasized. My main suggestion in this regard is to consider adding summary tables to the body of report from which a reader can focus on the important results and their context.	We have cleaned up the summary table to make it easier to follow. We have decided not to add additional tables of study level details or findings to the main text to keep the length of the report manageable.
TEP Reviewer #4	Clarity and Usability	I would consider including a table of MCIDs in the main body of the report to which the reader could easily refer. Appendix I includes it, but the table has considerable text making it a little difficult to identify MCID/MCII easily.	Given the limitations of MCIDs, as we discuss, and the small number of interventions and cases for which they have been validated, we would prefer to

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			keep the table in the Appendix.
TEP Reviewer #4	Clarity and Usability	There is use of "moderate strength of evidence" and "moderate level evidence" and "moderate evidence" in the report. I assume all are synonymous, but would suggest consistent usage.	We have replaced "moderate evidence" throughout but have sometimes retained "moderate-level evidence" where it simply sounded better.
TEP Reviewer #5	Clarity and Usability	The organization and structure of this report could be improved. Reviewing this was a bit cumbersome due to poor cues with regard to change of topic or section.	We are somewhat limited by the heading and subheading styles of the template. We have tried to improve readability throughout the results section.
TEP Reviewer #5	Clarity and Usability	The conclusions are not surprising for this disease area. It is difficult to recommend practice or policy changes based on such limited information. The contribution is as an update and is relevant to current understanding of the state of the science	Thank you. No further response needed.
TEP Reviewer #6	Clarity and Usability	The report is well-structured and easy to follow. The organization is standard and appropriate. The main points are clearly identified, and the few topics where there is definitive data can drive clinical practice. I'm not sure there is any new information or greater understanding.	Thank you
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs,	General Comments	Bracing, TENS, and NMES are well known therapies within the knee OA treatment modalities and have been shown to have not only a significant impact on patient satisfaction but also on	Our scope of work limited the outcomes we assessed to pain, function, stiffness, quality of life, and similar clinical outcomes.

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DJO Global		pain and economic burden. These therapies are non-invasive and non-addictive, have been utilized in patients for more than 20 years and have next to no harms associated with the interventions. We would ask the agency to consider further review of some additional outcomes (beyond pain) that we have presented below that demonstrate the effectiveness of these devices as well as their financial benefits to the continuum of care.	
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	Cold Therapy and Ultrasound are also well known therapies within the knee OA treatment modalities in particular in physical therapy and were not explored as a part of this review. These therapies are non-invasive and non-addictive, have been utilized in patients for more than 20 years and have next to no harms associated with the interventions. In addition, DJO has a shoe designed to off-load the medial compartment of the knee by 20% in order to help with both pain and the progression of the OA disease. Please consider the articles listed below that demonstrate the effectiveness of these modalities.	We included interventions that used ultrasound. We agree that cold interventions should be reviewed but were limited in what we could cover.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs,	General Comments	Unloader (Moderate OA) - Brief Summary: Since their introduction in 1989, knee orthoses have become a popular conservative treatment method for patients with unicompartmental knee	We have endeavored to include all studies subsequent to the 2012 AHRQ review that met inclusion criteria. Thus we

DJO Global		<p>osteoarthritis.^{3-5, 7, 8} Designed to help relieve the painful symptoms associated with the disease, the unloader brace applies an external varus or valgus force at the knee in order to relieve the compressive forces on the medial or lateral compartments.^{3, 8} Several studies have demonstrated that these types of braces are effective in reducing pain associated with knee osteoarthritis.^{1-3, 5, 9} Additional research has illustrated the efficacy of unloader braces in redistributing weight-bearing loads.^{1,6,10} Self et al. observed a significant difference in varus moment during stance, and Nadaud et al. demonstrated significant medial condylar separation at heel strike with use of The DonJoy OA adjuster brace.^{6,10} These results suggest that braces specifically designed to unload the diseased compartment of the knee may be an effective, conservative treatment for pain associated with knee malalignment and osteoarthritis.</p>	<p>have considered the studies you cited to determine whether they should be included.</p>
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	<p>Journal Articles: 1. Draganich, Louis, Bruce Reider, Todd Rimington, Gary Piotrowski, Krishna Mallik, and Scott Nasson. "The effectiveness of self-adjustable custom and off-the-shelf bracing in the treatment of varus gonarthrosis." The Journal of Bone & Joint Surgery 88, no. 12 (2006): 2645-2652.</p>	<p>We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.</p>

Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	2. Finger, Simon, and Lonnie E. Paulos. "Clinical and biomechanical evaluation of the unloading brace." The journal of knee surgery 15, no. 3 (2001): 155-8.	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	3. Kirkley, A., S. Webster-Bogaert, R. Litchfield, A. Amendola, S. MacDonald, R. McCalden, and P. Fowler. "The Effect of Bracing on Varus Gonarthrosis*." The Journal of Bone & Joint Surgery 81, no. 4 (1999): 539-48.	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	4. Komistek, Richard D., Douglas A. Dennis, Eric J. Northcut, Adam Wood, Andrew W. Parker, and Steve M. Traina. "An in vivo analysis of the effectiveness of the osteoarthritic knee brace during heel-strike of gait." The Journal of arthroplasty 14, no. 6 (1999): 738-742.	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	5. Lindenfeld, Thomas N., Timothy E. Hewett, and Thomas P. Andriacchi. "Joint loading with valgus bracing in patients with varus gonarthrosis." Clinical orthopaedics and related research 344 (1997): 290-297.	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	6. Nadaud, Matthew C., Richard D. Komistek, Mohamed R. Mahfouz, Douglas A. Dennis, and Matthew R. Anderle. "In vivo three-dimensional determination of the effectiveness of the osteoarthritic knee brace: a multiple brace analysis." The Journal of Bone & Joint Surgery 87, no. suppl_2 (2005):	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.

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		114-119.	
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	7. Pollo, Fabian E. "Bracing and heel wedging for unicompartmental osteoarthritis of the knee." The American journal of knee surgery 11, no. 1 (1997): 47-50.	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	8. Pollo, Fabian E., and Robert W. Jackson. "Knee bracing for unicompartmental osteoarthritis." Journal of the American Academy of Orthopaedic Surgeons 14, no. 1 (2006): 5-11.	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	9. Richards, J. D., J. Sanchez-Ballester, R. K. Jones, N. Darke, and B. N. Livingstone. "A comparison of knee braces during walking for the treatment of osteoarthritis of the medial compartment of the knee." Journal of Bone & Joint Surgery, British Volume 87, no. 7 (2005): 937-939.	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	10. Self, Brian P., Richard M. Greenwald, and Daniel S. Pflaste. "A biomechanical analysis of a medial unloading brace for osteoarthritis in the knee." Arthritis Care & Research 13, no. 4 (2000): 191-197.	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	Guidelines: 1. Hochberg, Marc C., et al. "American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand,	In Appendix G, we provided the recommendations of the ACR and AAOS regarding modalities we included in this review; we have checked them and to the best of our

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		hip, and knee." Arthritis care & research 64.4 (2012): 465-474. *** No recommendations for the use of knee braces in knee osteoarthritis patients	knowledge, they are accurate.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	2. Jevsevar, David S., et al. "The American Academy of Orthopaedic Surgeons Evidence- Based Guideline on Treatment of Osteoarthritis of the Knee." The Journal of Bone & Joint Surgery 95.20 (2013): 1885-1886. *** AAOS Recommendation for the use of a valgus directing force brace (medial compartment unloader) is Inconclusive. Guideline states that there is a lack of "compelling evidence" for their use.	In Appendix G, we provided the recommendations of the ACR and AAOS regarding modalities we included in this review; we have checked them and to the best of our knowledge, they are accurate.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	3. National Institute for Health and Care Excellence. "Osteoarthritis: national clinical guideline for care and management in adults." Royal College of Physicians, 2014. *** Guideline states, "People with osteoarthritis who have biomechanical joint pain or instability should be considered for assessment for bracing/joint supports/insoles as an adjunct to their core treatments."	We included only the US federal guidelines as well as those of our partner organizations
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	TENS - Brief Summary: Transcutaneous electrical nerve stimulation (TENS) offers a noninvasive and non-pharmacological approach to managing acute and chronic arthritic pain. Several studies assessing the	We have reviewed the findings of studies identified in our systematic review of the literature that met our prespecified inclusion criteria.

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		effectiveness of TENS in knee osteoarthritis (OA) have been published. In a review of seven trials utilizing TENS in people with knee OA, Osiri et al. determined that reduction in pain and improvement in knee stiffness from TENS was significantly better than from placebo treatment. ³ Results from two meta-analyses illustrated similar positive treatment effects, highlighting the short-term benefits of this modality for pain relief. ^{1,2}	
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	Journal Articles: 1. Bjordal JM, et al. "Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and musculoskeletal disorders 8.1 (2007): 51.meta-analysis of randomised placebo- controlled trials." BMC	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	2. Brosseau L, et al. "Efficacy of transcutaneous electrical nerve stimulation for osteoarthritis of the lower extremities: a meta-analysis." Physical Therapy Reviews 9.4 (2004): 213-233.	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	3. Osiri, M., et al. "Transcutaneous electrical nerve stimulation for knee osteoarthritis (Review)." (2009).	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public	General	Additional Journal Article	We have considered all

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Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	Comments	1. Vance CGT, et al. "Effects of transcutaneous electrical nerve stimulation on pain, pain sensitivity, and function in people with knee osteoarthritis: a randomized controlled trial." Physical Therapy 92.7 (2012): 898-910.	suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	Notes: • TENS Product Studied: Commercially Available, Maxima (Rehabicare Maxima, DJO Inc) • Double Blind, Randomized Control Trial which demonstrated that TENS is effective for deep pain sensitivity caused by knee OA. Self-reported pain ratings at rest and in motion were similarly reduced by both placebo and active TENS (suggestive of a placebo component to TENS effect).	We have considered all suggested articles to determine whether they meet our prespecified inclusion/exclusion criteria.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	Guidelines: 1. Hochberg, Marc C., et al. "American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee." Arthritis care & research 64.4 (2012): 465- 474. *** Guideline states, "We conditionally recommend that patients with knee OA should: be instructed in the use of transcutaneous electrical stimulation."	In Appendix G, we provided the recommendations of the ACR and AAOS regarding modalities we included in this review; we have checked them and to the best of our knowledge, they are accurate.
Public Reviewer	General Comments	2. Jevsevar, David S., et al. "The American Academy of Orthopaedic	In Appendix G, we provided the recommendations of the

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Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global		Surgeons Evidence- Based Guideline on Treatment of Osteoarthritis of the Knee." The Journal of Bone & Joint Surgery 95.20 (2013): 1885-1886. *** AAOS Recommendation for the use of physical agents (including electrotherapeutic modalities) is Inconclusive. Guideline states that there is a lack of "compelling evidence" for their use.	ACR and AAOS regarding modalities we included in this review; we have checked them and to the best of our knowledge, they are accurate.
Public Reviewer Lisa Holt, Ph.D. VP, Clinical Affairs, DJO Global	General Comments	3. National Institute for Health and Care Excellence. "Osteoarthritis: national clinical guideline for care and management in adults." Royal College of Physicians, 2014. *** Guideline states, "Healthcare professionals should consider the use of transcutaneous electrical nerve stimulation (TENS) as an adjunct to core treatments for pain relief."	In Appendix G, we provided the recommendations of the ACR and AAOS regarding modalities we included in this review; we have checked them and to the best of our knowledge, they are accurate.
Public Reviewer Sandie Preiss VP, Advocacy & Access, Arthritis Foundation	Background and Objectives	We encourage AHRQ to include work presented at the recent Arthritis Foundation – U.S. Food and Drug Administration Accelerating Osteoarthritis (OA) Clinical Trials Workshop in Atlanta, Georgia, USA, held on February 24-25, 2016, where the participants assessed a wide variety of options for demonstrating the efficacy and safety of interventions for OA, with the ultimate goal of lessening the societal and personal impact of this disabling	In Appendix G, we provided the recommendations of the ACR and AAOS regarding modalities we included in this review; we have checked them and to the best of our knowledge, they are accurate.

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		disease". ii Nelson AE, Allen, KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the U.S. Bone and Joint Initiative. <i>Seminars in Arthritis and Rheumatism</i> 43 (2014) 701-712.	
Public Reviewer Sandie Preiss VP, Advocacy & Access, Arthritis Foundation	Limitations	Additional medical research and early aggressive treatment is needed to reduce the incidence of and relieve the disabling symptoms of OA. Unfortunately, there are vast gaps in the literature surrounding OA treatments and clinical trials. We applaud AHRQ for acknowledging the many limitations of the available research being reviewed. However, we seek clarification in the current draft regarding the technical limitation of this review. Further, the current draft may not be clear to patients, clinicians and policy makers that the findings of uncertainty or lack of evidence are due to gaps in the existing literature instead of a lack of overall treatment effectiveness.	We included a description of the limitations of our review. We realize the report may not be as accessible as possible to potential users and will work with AHRQ to create more tailored derivative dissemination products.
Public Reviewer Sandie Preiss VP, Advocacy & Access,	Limitations	In addition, many of the interventions reviewed for effectiveness in improving clinical outcomes in adults with OA of the knee combine a variety of interventions that although	We added a bit of clarification regarding the distinction among types of braces and their lack of comparability but

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Arthritis Foundation		may have surfacelevel similarities, actually rely on unique technologies. As an example, the AHRQ report collectively analyzes ‘braces’ and ‘orthoses’. The report would benefit from clarification of the types of technologies under study in the analyses. In this case, we note that the report blends patellofemoral bracing technologies (eg., Callaghan et al., 2015) with pneumatic unloading (Cherian, et al., 2015) and vargus type braces (Sattari and Ashraf, 2011). Such braces employ different design features, and were studied in a nuanced population limiting the scope of this review.	descriptions of the technical differences go beyond the scope.
Public Reviewer Sandie Preiss VP, Advocacy & Access, Arthritis Foundation	Limitations	The Arthritis Foundation is concerned that any healthcare decision made based on anything less than a comprehensive analysis of OA research and patient plans of care could inadvertently limit access to a full range of treatment options including disease modifying therapeutic treatments, which are critically important for people living with OA.	We agree; however a single review of all treatment modalities is beyond the scope. We hope to review additional treatment modalities in a future report.
Public Reviewer Sandie Preiss VP, Advocacy & Access, Arthritis Foundation	Summary	Reports for public dissemination should be transparent, user-friendly, easily understood by patients and available to all individuals within the health care field. Tools such as this draft report should clearly lay out the background, methods, limitations, summary, and future	Thank you for your comments. We will pass on your comments to AHRQ.

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		research and policy implications. We encourage AHRQ to explore alternative methods for providing the information gained from this report in a format that is easily embraced and understood by an audience of patients not well versed in medical terminology.	
Public Reviewer Sandie Preiss VP, Advocacy & Access, Arthritis Foundation	Summary	The information in this report is intended to help health care decision makers, patients, clinicians, health system leaders and policymakers make well informed decisions to improve the quality of health care services. Therefore, we encourage AHRQ to engage with patients, providers and other stakeholders when drafting research questions and making future research recommendations. We welcome the opportunity to work with AHRQ on this initiative.	Thank you for your comments. We will pass on your comments to AHRQ.