AAOS
American Academy of Orthopaedic Surgeons

Peer Review & Public Comments and AAOS Responses

Evidence-Based Clinical Practice Guideline on the Management of Osteoarthritis of the Knee – 2nd Edition

Treatment of Osteoarthritis of the Knee Evidence-Based Guideline 2nd Edition

The reviews and comments related to this clinical practice guideline are reprinted in this document and posted on the AAOS website. All peer reviewers and public commenters are required to disclose their conflict of interests. Names are removed from the forms of reviewers and commenters who requested that they remain anonymous; however their COI disclosures still accompany their response.

Peer Review

AAOS contacted nineteen organizations with content expertise to review a draft of this clinical practice guideline during the peer review period in November 2012.

- Sixteen individuals from fourteen organizations provided comments on the structured peer review form. One individual asked to be listed as "anonymous."
- The work group considered all comments and made some modifications when they were consistent with the evidence.

Public Comment

The new draft was then circulated for a 30-day Public Comment period ending in March 2013.

- AAOS received forty-two comments including 5 representing specialty societies, 28 from individuals (14 of these requested that they be listed as "anonymous") and 9 from industry (1 is "anonymous").
- If warranted and based on evidence, the guideline draft is modified by the work group members in response to the public comments.

Summary of Changes

Revisions to the drafts are summarized in this report.

General Comment regarding MCII

Several of the peer reviews and public comments referred to the use of Minimum Clinically Important Improvement (MCII) by AAOS. The MCII reflects the smallest clinical change that is important to patients and recognizes that there are some treatment-related statistically significant improvements that are too small to be relevant. Please refer to the Methods section of the guideline for a detailed description.

Whenever the data is available, AAOS identifies MCII treatment effects in addition to statistical significance. In this guideline, recommendations 3a, 6, 8 and 9 include MCII calculations. Following the reviewer comments, AAOS re-calculated the meta-analyses to report in Minimal Important Difference (MID) units. The full guideline now includes both (MCII and MID) presentations of the data.

Treatment of Osteoarthritis of the Knee Evidence-Based Guideline 2nd Edition

Summary of Changes Made Following Peer Review

Line 4 (Summary of Recommendations)
Added, "and includes only alternatives less invasive than knee replacement."

Lines 5-10 (Summary of Recommendations)
Revised to, "Discussion of how and why each recommendation was developed and the evidence report are contained in the full guideline at www.aaos.org. Readers are urged to consult the full guideline for the comprehensive evaluation of the available scientific studies. The recommendations were established using methods of evidence-based medicine that rigorously control for bias, enhance transparency, and promote reproducibility."

Lines 11-14 (Summary of Recommendations)
Revised to, "The summary of recommendations is not intended to stand alone. Medical care should always be based on a physician's expert judgment and the patient's circumstances, preferences and rights. For treatment procedures to provide benefit, mutual collaboration between patient and physician/allied healthcare provider is essential."

Line 262 (Overview)
Added, "nonarthroplasty"

Line 274 (Goals and Rationale)
Added, "evidence-based"

Line 274 (Goals and Rationale)
Revised to, "AAOS staff methodologists assisted the physician/clinician work group in evaluating the existing literature so that they could formulate the following recommendations based on a rigorous systematic process."

Line 284 (Goals and Rationale)
Revised, "in the context of the resources of the treating medical facility" to, "and consideration of locality-specific resources."

Lines 287-288 (Intended Users)
Revised, "orthopaedic surgeons and physicians" to, "orthopaedic surgeons and other healthcare providers."

Lines 287-288 (Intended Users)
Revised, "Thus, the AAOS hopes that this guideline will assist physicians in" to, "The AAOS intends for this guideline to assist treatment providers in."

Line 318 (Intended Users)
Revised, "mutual communication" to, "reciprocal communication."

Lines 395-400 (Differences between the Present and Previous Guidelines)
Revised to, "One change that came about by eliminating systematic reviews was a consensus recommendation became necessary in this update because only one remaining low strength case series met the inclusion criteria for an intervention clinically known to have potentially serious complications and aversive outcomes. Although the direction of the recommendation remained the same, in the former guideline was it possible to assign it a moderate strength of evidence rating."

Line 318 (Intended Users)
Revised, "mutual communication" to, "reciprocal communication."

Line 459 (Preventing Bias in a Clinical Practice Guideline)
Added, "Good interrater reliability is maintained through the involvement of a second reviewer who independently appraises a sampling of 10% of the evidence base."

Line 558 (Selection Criteria)
Added, "of published systematic reviews."

Lines 659-660 (Minimum Clinically Important Improvement)
Revised to, "The MCII reflects the smallest clinical change that is important to patients and recognizes that there are some treatment-related statistically significant improvements that are too small to matter."

Line 775 (Network Meta-Analysis)
Added, "Where all interventions were connected in one network by pairwise relationships, if there was no direct evidence about two analgesics but they were each compared to the same reference treatment then their relative effectiveness was estimated based on their computable effects with the common comparator. Both direct and indirect comparisons contribute to the totality of evidence for selecting the best choices of treatment."

Lines 659-660 (Network Meta-Analysis)
Revised to, "Network meta-analysis assumes that randomization within the individual trials is maintained. Additionally, it is appropriate when interactions and covariates that affect trial AB have similar effects on trial AC, and the same indirect effect BC could be obtained as if it had been evaluated as a true direct effect (i.e. third arm of the RCT). Breaking randomization and permitting effect modifying heterogeneity leads to biased estimates of the indirect comparisons. Consistency, the second important assumption, helps to produce interpretable results along with the first similarity requisite. Similarity is required of the treatment effects among studies; consistency addresses the potential for significant variability between the direct and indirect comparisons.

Network meta-analysis requires statistical consistency between the direct and indirect pairwise effects. We used the "back calculation" method as described by Dias et al.[19] and summarized as

follows. Indirect effect BC was calculated as the difference between direct effects AB and AC and evaluated against the direct effect estimation for BC. The z-statistic for the difference between the direct and indirect effects of BC was compared to a standard normal distribution to test the null hypothesis of consistency. If statistical significance was found, then the model was interpreted as having questionable reliability and would have been excluded from the data analyses. The results of the tests of statistical consistency between the direct and indirect comparisons of the pairs of analgesics examined in this guideline indicated that the consistency assumption was met; the output summary can be found in Appendix XIII.

Network meta-analysis is based on multiple pairwise comparisons across at least three RCTs that connect at least three interventions involving at least one closed loop (i.e. common comparator; direct comparison). It is an extension of traditional meta-analysis that incorporates a process of chance where the outcome of a given comparison can affect the next outcome. It requires the convergence of Markov chains that is based on this type of sampling. A total of k-1 parameters are estimated that allow for multiple pairwise comparisons across a range of k distributions. The results are assessed by examination of the trace plots that graphically display the values that a parameter took during the runtime of the chain."

Lines 855-857 (Peer Review)
Deleted, "and peer reviewers are blinded to the identities of the work group members upon receipt of the guideline materials."

Line 318 (Peer Review)
Revised, "13 content experts were nominated" to, "18 content experts were nominated."

Lines 950-953 (Recommendation 1)
Revised, "We recommend that patients with symptomatic osteoarthritis of the knee (OAK) participate in self-management programs; engage in physical activity consistent with national guidelines; and participate in strengthening, neuromuscular education, and low-impact aerobic exercises," to, "We recommend that patients with symptomatic osteoarthritis of the knee participate in self-management programs, strengthening and low-impact aerobic exercises, and neuromuscular education; and engage in physical activity consistent with national guidelines."

Lines 979-981 (Rationale of Recommendation 1)
Revised, "In addition, 7 of 23 outcomes indicated statistically significant improvements from physical therapy versus control," to, "In addition, 7 of 23 outcomes indicated statistically significant improvements with strengthening exercises, when performed as part of a physical therapy treatment program, versus control."

1019 (Rationale of Recommendation 1)
Added paragraph specifically discussing the 2008 national guidelines on physical activity developed by the U.S. Department of Health and Human Services.

Line 1534 (Recommendation 3A)
Revised, "We recommend not using acupuncture," to "We cannot recommend using acupuncture."

Line 1545 (Recommendation 3B)
Combined physical and electrotheraputic agents into recommendation 3B that was graded Inconclusive.

Line 1557 (Recommendation 3C)
Established a separate recommendation for manual therapy based on one low-strength study on Swedish massage therapy coupled with a lack of evidence on joint mobilization, joint manipulation, chiropractic therapy, patellar mobilization, or myofascial release that was graded Inconclusive.

Lines 1568-1579 (Rationale for Recommendation 3)
Deleted paragraph addressing previous recommendation 3D.

Line 1589 (Rationale for Recommendation 3)
Added, "The strength of this recommendation was based on lack of efficacy, not on potential harm," to discussion on acupuncture findings.

Lines 1591-1596 (Rationale for Recommendation 3)
Deleted the paragraph on spa therapy (i.e. study by Forestier et al.). It was eliminated from the guideline because we did not conduct a systematic search on spa therapy treatments. The study was originally included due to its resemblance to our search term balneotherapy. However, the experimental group could not be accurately described as receiving balneotherapy treatment.

Lines 1598-1618 (Rationale for Recommendation 3)
Combined the information on pulsed electrical stimulation, pulsed electromagnetic stimulation, transcutaneous electrical nerve stimulation, shortwave diathermy, interferential current, and therapeutic application of modulated electromagnetic field therapy into one paragraph.

Lines 1598-1618 (Rationale for Recommendation 3)
Added paragraphs explaining the inconclusive findings for physical and electrotheraputic agents and for manual agents.

Lines 1651-1652 (Rationale for Recommendation 3)
Deleted the paragraph on spa therapy.

Line 1671 (Rationale for Recommendation 3)
Deleted mention of the Forestier et al. study on spa therapy.

Lines 1746-1752 (Evidence Report for Recommendation 3)
Deleted the paragraph discussing results of spa therapy.

Line 1769 (Evidence Report for Recommendation 3)
Deleted outcomes for spa therapy in Figure 18.

Line 1790 (Evidence Report for Recommendation 3)
Deleted quality table on spa therapy.

Line 1808 (Evidence Report for Recommendation 3)
Deleted results table on spa therapy.

Lines 1818-1819 (Recommendation 4)
Added, "(medial compartment unloader)" after "valgus directing force brace."

Line 1846 (Evidence Report for Recommendation 4)
Revised to, "There were two high-[72,73] and one moderate-[74]quality randomized controlled trials that comprised the evidence for this recommendation," to reflect deletion of the high-strength study by Pajareya et al. evaluating a neoprene sleeve rather than a brace.

Line 1852 (Rationale for Recommendation 4)
Revised, "in all four included studies," to, "in all three included studies," to reflect deletion of the high-strength study by Pajareya et al. evaluating a neoprene sleeve rather than a brace.

Line 1862 (Evidence Report for Recommendation 4)
Deleted results of the study by Pajareya et al. in Table 100 to reflect deletion of the high-strength study by Pajareya et al. evaluating a neoprene sleeve rather than a brace.

Lines 1888-1893 (Recommendation 4)
Deleted study by Pajareya et al. evaluating a neoprene sleeve rather than a brace.

Line 1902 (Evidence Report for Recommendation 4)
Deleted results of neoprene sleeve versus usual care in Figure 24.

Line 1908 (Evidence Report for Recommendation 4)
Deleted results evaluating the neoprene sleeve in quality Table 104.

Line 1917 (Evidence Report for Recommendation 4)
Deleted the results table evaluating the neoprene sleeve (Table 104).

Line 1924 (Recommendation 5)
Revised, "we suggest foot orthotics not be used," to, "we do not suggest lateral wedge insoles be used."

Line 1957 (Evidence Report for Recommendation 5)
Deleted paragraph discussing quality of the Masai Barefoot Training Shoe.

Lines 1962, 1966, 1968 (Evidence Report for Recommendation 5)
Deleted discussion of study by Nigg et al. in applicability section.

Line 1977 (Evidence Report for Recommendation 5)
Deleted results of study on Masai Barefoot Training Shoe in quality and applicability Table 112.

Line 1985-1986 (Evidence Report for Recommendation 5)
Deleted sentence on study of Masai Barefoot Training Shoe.

Line 1989 (Evidence Report for Recommendation 5)
Deleted results of study on Masai Barefoot Training Shoe in Figure 25.

Line 1994 (Evidence Report for Recommendation 5)
Deleted findings of the study on Masai Barefoot Training Shoe in quality Table 114.

Line 2000 (Evidence Report for Recommendation 5)
Deleted results on Masai Barefoot Training Shoe in Table 117.

Line 2005 (Evidence Report for Recommendation 5)
Deleted Figure 27 illustrating results for the Masai Barefoot Training Shoe.

Line 2009 (Recommendation 6)
Revised, "We recommend not using glucosamine and chondroitin," to, "We cannot recommend using glucosamine and chondroitin."

Lines 2069 (Rationale for Recommendation 6)
Added, "The strength of this recommendation was based on lack of efficacy, not on potential harm," to discussion on glucosamine and condroitin findings.

Lines 2019-2029 (Recommendation 6)
Deleted recommendation 6B addressing ginger extract, glycosaminoglycan polysulfuric acid, bromelain and gubitong to reflect inappropriate scope.

Lines 2079-2105 (Rationale for Recommendation 6B)
Deleted discussion on ginger extract, glycosaminoglycan polysulfuric acid, bromelain and gubitong to reflect inappropriate scope.

Lines 2109-2116 (Evidence Report for Recommendation 6)
Deleted discussion of ginger extract, glycosaminoglycan polysulfuric acid and gubitong studies.

Lines 2120-2123 (Evidence Report for Recommendation 6)
Deleted discussion of ginger extract, glycosaminoglycan polysulfuric acid and gubitong studies in section on quality.

Line 2128 (Evidence Report for Recommendation 6)
Deleted studies by Altman and Marcussen and Zakeri et al. from quality and applicability summary Table 118.

Line 2142 (Evidence Report for Recommendation 6)
Deleted "gubitong recipe" from the results discussion.

Lines 2177-2179 (Evidence Report for Recommendation 6)
Deleted discussion of results on glycosamionoglycan polysulfuric acid.

Lines 2181-2187 (Evidence Report for Recommendation 6)
Deleted discussion of results on ginger extract.

Line 2208 (Evidence Report for Recommendation 6)
Deleted the results evaluating gubitong (Figure 32).

Lines 2218-2223 (Evidence Report for Recommendation 6)
Deleted quality Tables 121-122.

Lines 2263-2273 (Evidence Report for Recommendation 6)
Deleted results Tables 144-149 of glycosamioglycan polysulfuric acid, ginger extract, and gubitong.

Lines 2316-2317 (Rationale for Recommendation 7)
Added separate paragraphs explaining the recommendation strengths for NSAIDs and tramadol.

Lines 2640-2643 (Rationale of Recommendation 8)
Revised, "Since these two later treatments do not provide enough evidence for a recommendation (they are too few to compute overall effect), the committee interpreted the evidence to be inconclusive as to the benefit of IA corticosteroids," to, "Since the evidence in the guideline did not support the use of hyaluronic acid and tidal irrigation, the work group interpreted the evidence to be inconclusive as to the benefit of IA corticosteroids."

Line 2740 (Recommendation 9)
Revised, "We recommend not using hyaluronic acid," to, "We cannot recommend using hyaluronic acid."

Line 2754 (Rationale of Recommendation 9)
Added explanation for combining hyaluronic acid of varying molecular weights in the meta-analyses.

Line 2754 (Rationale of Recommendation 9)
Added, "The strength of this recommendation was based on lack of efficacy, not on potential harm," at the conclusion of the discussion on hyaluronic acid findings.

Line 2755 (Rationale of Recommendation 9)
Added a paragraph explaining differences between the current and previous guidelines.

Line 2979 (Recommendation 11)
Revised, "We suggest that the practitioner not use needle lavage," to, "we do not suggest that the practitioner use needle lavage."

Line 3063 (Recommendation 12)
Revised, "We recommend not performing arthroscopy with lavage and/or debridement," to, "We cannot recommend performing arthroscopy with lavage and/or debridement."

Lines 3075-3076 (Rationale of Recommendation 12)
Reordered “Kirkley et al., Kalunian et al., and Moseley et al.” to match the ordering of the subsequent paragraphs in lines 3079-3102.

Line 3233 (Recommendation 14)
Revised, “the practitioner might perform valgus producing proximal tibial osteotomies,” to, “The practitioner might perform a valgus producing proximal tibial osteotomy.”

line 3358 (Recommendation 15)
Revised, “free-floating interpositional device,” to, “free-floating (un-fixed) interpositional device.”

Treatment of Osteoarthritis of the Knee Evidence-Based Guideline 2nd Edition

Summary of Changes Made Following Public Comments

Lines 5, 13, 14
Word changes -less invasive, values, with shared decision-making.

Line 380
Added "to patients".

Lines 463-953
Revised "page 7" to "page 13" indicating where selection criteria are listed.

Lines 541-542
Modified verbs to present tense for consistency.

Line 631-633
Added, "Low strength studies influence recommendation grades if they constitute the best available evidence."

Lines 636-639
Revised to, "Without consideration of clinical significance to patients, analysis of statistical significance is limited. The latter provides information about sample size and does not quantify the size of the effect that differentiates the treatment groups" (to better explain emphasis on MCII in this guideline).

Line 641 (Table 4)
Revised to, "and recognizes that there are some treatment-related statistically significant improvements that are too small to be relevant." See Appendix XIV for a visual presentation of the descriptive terms," (to adjust for the first modification above).

Line 644
Revised "important" to "significant" to clarify proper use of term.

Lines 648-651
Revised MCII "values" to "thresholds."

Lines 653-656
Revised to, "We used the effect sizes reported by Angst et al. to compute the MCII of pain (0.39) and function (0.37) for the WOMAC instrument[14] and calculated effect sizes reported in their data to compute the MCIIs of stiffness (0.39) and total score (0.40)" to eliminate redundant use of *for the WOMAC instrument.*

Lines 678-679
Corrected to "and role physical (0.26) composite scores" and "and global assessment (1.0) subscale scores."

Lines 685-686
Revised to, “overall strength is also based on clinical appropriateness, volume of the evidence” to eliminate possible confusion around use of “quality” since it is a grading domain in APPRAISE, and to be more specific in lieu of stating “quantity”.

Lines 696-697
Revised “Recommendations based on RCTs are assigned a stronger strength rating and recommendations based on studies with less control of measurement error are given weaker grades,” to “Since RCTs tend to have higher scientific merit, they are usually associated with higher evidence strengths than case series studies.”
Line 725
Revised “final grade of each recommendation” to “the evidence strengths” (for conciseness).

Line 726
Revised “difference” to “discrepancy.”

Line 742
Revised “When it is not possible to issue a recommendation” to “When a recommendation is equivocal” (for accuracy).

Line 747
Revised “methodologists” to “staff” (for clarification).

Line 750
Revised “In the systematic review” to “During evidence appraisal” (for accuracy).

Line 781
Added “explained below” and revised “Where there were” to “For all.”

Line 783
Revised “involving” to “where there is.”

Lines 820-822
Deleted “of chance.”

Lines 825-827
Revised to “The only data available examined the treatment efficacy of osteotomy using the VAS; so only placebo controlled trials that measured change in VAS pain following osteotomy were incorporated.”

Lines 908-909
Revised to “Data from 48 articles were extracted to predict differences between baseline and treatment scores in the experimental and placebo groups of two case series designed studies.”

Lines 915-917

Revised “on how it could be accessed” to “instructing them on access.”

Line 971
Revised to “During the public comment period, 42 stakeholders returned the structured review form commenting on the clinical practice guideline (see Appendix X).

Lines 974-975
Revised, “Final approval of guidelines is approved by” to, “The work group submits the final guideline for approval by.”

Lines 1010-1013
Inserted citation.

Lines 1104-1106
Revised, “All eight outcomes were statistically significant favoring the combined treatment group with clinically important treatment effects for WOMAC Function, SF-36 Physical Function, and SF-36 Pain,” to “All eight outcomes were statistically and clinically significant favoring the combined treatment group measured by WOMAC Function and the SF-36 Physical Function and Bodily Pain subscales.”

Lines 1106-1107
Revised, “The outcomes that were compared to the attention control had uncertain group comparability at baseline as well as flaws in the group assignment domain (due to lack of allocation concealment),” to “In the comparison to attention control, there was uncertain group comparability at baseline and lack of allocation concealment.”

Line 1132
Lines 1219-1220
Revised, “The outcomes that were compared to usual care by Allen et al. were flawed not only in these domains but also in blinding,” to “In the comparison to usual care, the same limitations occurred and the blinding domain was also flawed.”

Line 2691
Removed extra section break.

Line 2850
Corrected “statistically insignificant” to “not statistically significant.”

Line 3032
Corrected significance column to “Needle Lavage” and revised “Tidal Irrigation” to “Needle Lavage” in Table 174.

Line 3034
Revised Figure 78 Results Summary to differentiate the molecular weights of the paired comparisons of hyaluronic acid evaluated in the literature for consistency with the quality section of the recommendation

Line 3038
Changed column title to “Needle Lavage” and revised “Tidal Irrigation” to “Needle Lavage” in Table 199, and corrected standard mean differences to authors’ reported values adjusting for baseline group differences.

Line 3040
Corrected column title to “Needle Lavage” and revised “Tidal Irrigation” to “Needle Lavage” in Table 200, and corrected standard mean differences to authors’ reported values adjusting for baseline group differences.

Line 3041
Corrected column title to “Needle Lavage” and revised “Tidal Irrigation” to “Needle Lavage” in Table 201, and corrected standard mean differences to authors’ reported values adjusting for baseline group differences.

Line 3133
Corrected column title to “Needle Lavage” and revised “Tidal Irrigation” to “Needle Lavage” in Table 202, and corrected standard mean differences to authors’ reported values adjusting for baseline group differences.

Line 3135
Corrected column title to “Needle Lavage” and revised “Tidal Irrigation” to “Needle Lavage” in Table 203.

Entire draft
Corrected “et al” to “et al.”

Entire draft
Reformatted page numbers to be consecutive.

Lines 864-917
Inserted section titled, “New to Meta-Analysis in this Guideline” Minimal Important Difference (MID) Units.”

Lines 1894-1896
Added Figures 22 and 23 to Results Summary of Recommendation 3a (forest plots in MID units).

Lines 1894, lines 2285-2295
Added Figures 34-37 to Results Summary of Recommendation 6 (forest plots in MID units).

Lines 2786-2825
Inserted revisions to Rationale of Recommendation 9 discussing meta-analysis in MID units.

Lines 2973-2980
Added Figures 85-87 to Results Summary of Recommendation 9 (forest plots in MID units).

Line 2700
Revised “Tidal Irrigation” to “Needle Lavage” in Table 168.

Line 2750
Revised “Tidal Irrigation” to “Needle Lavage” in Table 171.

Line 3097
Revised “Tidal Irrigation” to “Needle Lavage” in Table 195.

Line 94
Line 2012
Revised “do not” to “cannot” in Recommendation 5 of the Summary of Recommendations and full guideline.

Lines 201-202
Lines 3253-3255
Lines 3265-3267
Deleted inclusion of “loose body” and “mechanical symptoms” in Recommendation 13 of the Executive Summary and in complete guideline and deleted inclusion of “loose body” in Rationale of Recommendation 13 to be consistent with the evidence.

Appendix XIV
Replaced MCII chart to one used in previous AAOS guideline meetings and deleted “a”-“e” notation corresponding to previous diagram.

Description of Strong Rating
Changed description for clarity:
A **Strong** (positive) recommendation means that the benefits of the recommended approach clearly exceed the potential harm, and that the strength of the supporting evidence is high.
A **Strong** (negative) recommendation means that the quality of the supporting evidence is high.
A harms analysis on this recommendation was not performed.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Structured Peer Review Form

ALL REVIEW COMMENTS, RESPONSES AND REVIEWER CONFLICTS OF INTEREST DISCLSOURE WILL BE AVAILABLE ON OUR WEBSITE FOLLOWING APPROVAL OF THIS DOCUMENT.

Review of any AAOS confidential draft allows us to improve the overall guideline but does not imply endorsement by any given individual or any specialty society who participates in our review processes. The AAOS review process may result in changes to the documents; therefore, endorsement cannot occur until the AAOS Board of Directors officially approves the final guideline.

Please note that if you return a review:

- **Your review comments will be published on the AAOS website with our explanation of why we did or did not change the draft document in response to your comments.**
- **Your conflicts of interest disclosures will be published on the AAOS website with your review comments.**

Reviewer Information:

Name of Reviewer: Steven W. Strode

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Specialty Area/Discipline: family medicine

Work setting: group, government Credentials: MD, MEd, MPD

May we list you as a Peer Reviewer in the final Guidelines? X☐ Yes ☐ No

PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your review comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? **X**☐ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? X☐ Yes ☐ No

Society Name: American Academy of Family Physicians

(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

If the boxes below are not checked and/or the reviewer does not attach his/her conflicts of interest, the reviewer's comments will not be addressed by the AAOS nor will the reviewer's name or society be listed as a reviewer of this GL. If a committee reviews the guideline, only the chairperson or lead of the review must declare their relevant COI.

X☐ **I have declared my conflicts of interest on page 2 of this form.**

☐ **I have declared my conflicts of interest in the AAOS database; my customer # is _____**

☐ **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.**

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Structured Peer Review Form

REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

Each item below requires an answer. Please report information for the last 12-months.

Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes X☐ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company:	☐ Yes X☐ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes X☐ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify:	☐ Yes X☐ No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify: Council of the Southern Medical Association, House of Delegates of the AR Med Society	X☐ Yes ☐ No

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Structured Peer Review Form

Structured Peer Review Form Instructions

Please read and review this Draft Clinical Practice Guideline with particular focus on your area of expertise. Your responses will be used to assess the validity, clarity and accuracy of the interpretation of the evidence. If applicable, **please specify the draft page and line numbers in your comments**. Please feel free to also comment on the overall structure and content of the document. If you need more space than is provided, please attach additional pages.

Please complete and return this form electronically in **WORD format** to song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **November 2, 2012**.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	X☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	X☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	X ☐
4. The guideline's target audience is clearly described	☐	☐	☐	X☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	X☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	X☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	X☐
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	X☐
9. The validity of the studies is appropriately appraised	☐	☐	☐	X☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	X☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	X☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	X☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☐	X☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	X☐
15. The grades assigned to each recommendation are appropriate	☐	☐	☐	X☐

COMMENTS

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P 1-6, lines 14-257	**The replication of the explanation of the strength of the recommendation with each recommendation really helps clarity, as does the consistent use of verbs with each level of strength.**
P 6, line 446	**Although it appears that the superscript numbers for footnotes at the bottom of pages are in bold font, even stronger differentiation from "regular footnotes" might be considered for more clarity.**
P 11, lines 659-660	**The sentence included in these two lines is confusing.**
P 10, line 1126, table 9	**Should the duration units be listed as weeks?**
P 16, line 1141, table 15	**Should the duration units be listed as weeks?**
P 129	**Is a summary similar to Figure 12 on page 108 possible for Recommendation 2?**
P 198, line 1815, figure 22	**Under Study, do 4 to 5, 6 to 8, and 12 to 14 refer to weeks?**
P 938, line 3306	**Is there a period missing after "material" or is there more of the sentence that is missing?**

Congratulations on the methodology, format of this paper, clear wording, and rigor of the studies necessary in this guideline's preparation.

Dear Dr. Strode.
Thank you for your expert review of this clinical practice guideline and for your attention to detail. We will address your suggested edits in the order you listed them.

- We formatted the foot notes on page 6 to bold font.
- The sentence in lines 659-660 that you found confusing was revised to, "The MCII reflects the smallest clinical change that is important to patients and recognizes that there are some treatment-related statistically significant improvements that are too small to matter."
- We inserted "weeks" as the measurement unit in Tables 9 and 15.
- Unfortunately, it is not possible to generate a forest plot for recommendation 2. Ten homogeneous studies are the optimal number for accurate results in meta-analysis and four is considered the minimum. There were too few studies evaluating weight loss to compare overall effect size to statistical and clinical significance.
- We indicated "weeks" as the measurement unit in Figure 22.
- We added a period at the end of line 3306.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

☒ Strongly recommend

☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
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Please note that if you return a review:

- **Your review comments will be published on the AAOS website with our explanation of why we did or did not change the draft document in response to your comments.**
- **Your conflicts of interest disclosures will be published on the AAOS website with your review comments.**

Reviewer Information:

Name of Reviewer: Brian J. McGrory, M.D.

Address: 5 Bucknam Road, Suite 1D

City: Falmouth State: Maine Zip Code: 04105

Phone: 207-781-1551 Fax: 207-781-1552 E-mail: mcgrob1@mmc.org

Specialty Area/Discipline: Total Joint Replacement

Work setting: _____ Credentials: _____

May we list you as a Peer Reviewer in the final Guidelines? x☐ Yes ☐ No

PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your review comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? **x**☐ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? x☐ Yes ☐ No

Society Name: AAHKS

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Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company:	☐ Yes ☐ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes ☐ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify:	☐ Yes ☐ No
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Please complete and return this form electronically in **WORD format** to song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **November 2, 2012**.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	x☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	x☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	x☐
4. The guideline's target audience is clearly described	☐	☐	☐	x☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	x☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	x☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	x☐
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	x☐
9. The validity of the studies is appropriately appraised	☐	☐	☐	x☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	x ☐
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14. The writing style is appropriate for health care professionals.	☐	☐	☐	x☐
15. The grades assigned to each recommendation are appropriate	☐	☐	x☐	☐

COMMENTS

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Of the outlined recommendations, RECOMMENDATION 9 (We recommend not using hyaluronic acid for patients with symptomatic osteoarthritis of the knee) needs further clarification for a "Strong" strength of recommendation. If the definition of a strong recommendation means that that the potential harm clearly exceeds the benefits, and that the quality of the supporting evidence is high, the manuscript does not outline the "harm." If this is financial "harm," meaning that the cost is too high for a clinically irrelevant benefit, then that should then be explained clearly. This is an important distinction if clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

Dear Dr. McGrory.
Thank you for your expert review of this clinical practice guideline. The grade *Strong* is assigned to recommendations with empirical evidence comprised of at least two high-strength studies with consistent findings. For Recommendation 9, there were three high- and 11 moderate- strength studies that did not show minimum clinically important improvements to patients treated with viscosupplementation; therefore, the evidence grade was *Strong.* For clarity, we amended the wording of this recommendation to read, "We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee." The designation of *Strong* was based on the quality and applicability of the evidence and not on financial costs. We hope we have provided adequate clarification.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

☐ Strongly recommend

x☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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Reviewer Information:

Name of Reviewer: **ANONYMOUS – Name and identifying information withheld upon request**
Address:
City: State: Zip Code:
Phone: Fax: E-mail:
Specialty Area/Discipline:
Work setting: Credentials:

May we list you as a Peer Reviewer in the final Guidelines? ☐ Yes **X No**

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Are you reviewing this guideline as a representative of a professional society? **X Yes** ☐ No

If yes, may we list your society as a reviewer of this guideline? **X Yes** ☐ No

Society Name: _____

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Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes **X** No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company: Sanofi, Smith & Nephew, LINK	**X** Yes ☐ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes **X** No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Sanofi, Smith & Nephew, LINK	**X** Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Tornier, Wright Medical Technology, Exactech	**X** Yes ☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes **X** No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes **X** No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes **X** No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes **X** No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify: Arthroscopy Journal	**X** Yes ☐ No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify: AANA Education Foundation Secretary	**X** Yes ☐ No

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
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Please complete and return this form electronically in **WORD format** to song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **November 2, 2012**.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	X	☐	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	X	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	X	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	X	☐
5. The patients to whom this guideline is meant to apply are specifically described	X	☐	☐	☐
6. The criteria used to select articles for inclusion are appropriate	X	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	X	☐	☐	☐
8. All important studies that met the article inclusion criteria are included	X	☐	☐	☐
9. The validity of the studies is appropriately appraised	X	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	X	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	X	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	X	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	X	☐	☐
14. The writing style is appropriate for health care professionals.	X	☐	☐	☐
15. The grades assigned to each recommendation are appropriate	X	☐	☐	☐

COMMENTS

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Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline

Thank you for the offering us opportunity to review the current version of the AAOS OA Knee CPGs. We congratulate the authors on their efforts to assemble, interpret, and analyze the literature to produce useful guidelines for practitioners managing osteoarthritis. If the goal of the CPG is to educate the practicing physician on the limitations of the existing evidence-based literature, then this CPG has succeeded. The goal of the CPG should be, however, to assist the practitioner in making evidence-based decisions in the management of an individual patient. Unfortunately, we believe the guidelines have failed in that regard.

As written, if clinicians follow only the strong or moderate recommendations as written, we can encourage appropriate physical activity, weight loss, spa therapy or ultrasound and prescribe NSAID's or Tramadol. However, based upon the CPGs, there are specific treatments which we would be deterred from recommending prior to total joint arthroplasty. We offer the comments below in an effort to remain constructive, yet critical about the conclusions within the CPG noting that these observations are by no means inclusive of all our concerns. Some of the most obvious deficiencies are related below.

COMMENTS ON SPECIFIC RECOMMENDATIONS

RECOMMENDATION 3B: We suggest the use of spa therapy (massage, showers, mud and pool sessions) and ultrasound therapy for functional improvement in patients with symptomatic osteoarthritis of the knee.

STRENGTH OF RECOMMENDATION: Moderate.

To include a moderate recommendation for spa therapy based on just one randomized control trial is biased based upon the inadequacies of the control arm of that specific study. Over a three-week period, the treatment arm received more than 18 one-hour spa treatments, while the control arm was instructed to do their own exercises. The treatment effect garnered from the therapeutic bond between the patient and the therapist is potentially significant. This is likely to introduce a significant placebo effect not present within the control group being handed an exercise sheet and being told to do the exercises at home. Careful reading of this paper would suggest that the quality of the study should be downgraded and the Strength of Recommendation should be lowered or eliminated entirely. We remain concerned that the AAOS CPG Committee would make a **moderate** recommendation based solely upon literature of this quality.

RECOMMENDATION 7A: We recommended NSAID's (oral or topical) or Tramadol for patients with symptomatic osteoarthritis of the knee.

STRENGTH OF RECOMMENDATION: Strong.

We believe including Tramadol with the non-steroidal anti-inflammatory drugs is a major flaw of this recommendation. Tramadol has been associated with physical dependence and a withdrawal syndrome. Although not classified as a narcotic by the FDA, multiple publications have noted the withdrawal phenomenon lumping it with non-NSAID's in a CPG may lead have serious medical implications. In addition, combining NSAID's and Tramadol is reported to be contra-indicated by some practitioners. Finally, a Cochrane review showed only small benefits for Tramadol in the treatment of osteoarthritis and that the risks outweigh the benefits for some patients.

Complicating the issue is that a significant percentage of patients with osteoarthritis are over the age of 65 and there is a noted increase in complications with the use of NSAIDs (risk of adverse event is 2.4 times greater in patients over age 65 versus younger patients). In addition, many patients over 50 are on blood pressure medications, and non-steroidals have a significant adverse effect on blood pressure control. Given the nuances associated with these medications and the potential for serious medical complications, we remain challenged to understand why the AAOS would engage in a CPG that has **strong** recommendations in this regard.

RECOMMENDATION 9: We recommend not using Hyaluronic acid for patients with symptomatic osteoarthritis of the knee.

STRENGTH OF RECOMMENDATION: Strong.

We believe that this CPG has overlooked a large body of literature on the use of viscosupplementation for the treatment of osteoarthritis of the knee. The Cochrane Review of Viscosupplementation for the Treatment of Osteoarthritis of the Knee, which was published in 2009 included studies conducted through 2005 and identified 40 trials that included comparisons of Hyaluronic acid with a placebo (either saline or arthrocentesis). The revised AAOS guideline identified only 14 studies, and yet included papers through 2011. The conclusions of that Cochrane Collaboration Review of Viscosupplementation are diametrically opposed to your current recommendation. The committee has ignored numerous meta-analyses which confirm subjective improvement of symptoms in patients

when cross-linked HA preparations are utilized. Effect Size (ES) greater than .20 has been confirmed by the FDA in cross-linked HA compounds. In addition, failure to use the studies that compare intra-articular viscosupplementation to non-steroidal anti-inflammatory drugs (all of which seem to identify equal efficacy, with potential improved safety with HA injections) has resulted in a strong recommendation for oral non-steroidals, at the same time a strong recommendation against viscosupplementation, while in head-to-head comparison the two are equal with improved safety with the viscosupplementation. Once again, we remain concerned that the CPG is flawed relative to these recommendations.

Recommendation 13: We are unable to recommend for or against arthroscopic partial menisectomy or loose body removal in patients with osteoarthritis of the knee and mechanical symptoms consistent with torn meniscus and/or loose body.

Strength of Recommendation: Inconclusive

This is clearly an area where AANA cannot support the current recommended revision of the AAOS guidelines on osteoarthritis of the knee. Patients with mechanical symptoms from loose bodies and meniscal tears with concomitant osteoarthritis are appropriately treated with arthroscopy consistent with the AAOS Knee OA Guideline of 2008. To our knowledge, there has been no additional evidence since that time which would change this recommendation. Limiting patient access to arthroscopy in this scenario may hasten the need for more costly total joint surgery and potentially prevent them from achieving symptom relief and functional return following a minimally invasive alternative.

In conclusion, AANA contends that the AAOS is doing a tremendous disservice to the practicing orthopedic surgeon by publishing confusing recommendations regarding conservative and surgical care. Furthermore, to publish recommendations, which will clearly be misinterpreted by the media and insurers and potentially result in limiting access to care, is harmful to our patients.
In addition, the potential legal ramifications of this revised CPG are significant and unacceptable. For example, if a patient develops a severe adverse event (SAE) consisting of arthralgia or significant synovitis which results in some type of post-injecton arthropathy, the effect of the AAOS recommendation that VS should not be utilized for OA could become a devastating legal liability. This document, Revision of the AAOS OA Knee Guidelines of the Knee, has created inconsistencies and conflicts between the CPG and the standard of care as well as make recommendations that are confusing and misleading to practitioners and the public.
While the AAOS Clinical Practice Guidelines initiative is a laudable objective, activities in this area and past experience with previous CPG's continue to stress our excellent relationship and unity. Our organizations have had, and hopefully will continue to have, incredible synergy and mutual respect. AANA however cannot be associated with this CPG.

We therefore, respectfully request that the AAOS:

1. Carefully consider this position statement and these suggested revisions.
2. Withhold any further action on these guidelines until further discussion with appropriate collaborative subspecialty societies.
3. Do not release CPG's until the supporting appropriate use criteria have been created and completed.

Board of Directors,
Arthroscopy Association of North America

Dear Anonymous Reviewer from AANA,
Thank you for your expert review of this clinical practice guideline. We will address your comments in the order you presented them.

Recommendation 3 was revised to address physical agents in 3b and manual agents in 3c to make it consistent with our original intent. "Spa therapy" was not one of our search terms; and consequently, this treatment lacked a full systematic review. The Forestier et al. study initially appeared in our literature search because spa therapy resembled a term that we did include (balneotherapy; see Appendix V). However, a careful re-reading of the article found that the experimental group could not be accurately described as receiving balneotherapy so the study was excluded (please read the rationale section in the full guideline). Both revised recommendations 3b and 3c were graded as Inconclusive, which resolves your concern about recommendation strength.

Regarding Recommendation 7, we agree with your concern about the risks to patients who use opiate pain medications to treat a chronic condition. Tramadol is a centrally-acting analgesic. In our systematic review, five studies evaluated tramadol either alone or as an adjunctive therapy. It has been used to treat moderate to severe pain and in patients who have an adverse drug reaction, contraindication, or no response to selective and nonselective NSAIDs and acetaminophen. Although it has opiate-like properties, it is not in the same FDA drug classification. For clarity, we have revised the rationale to summarize the evidence related to NSAIDs (19 studies) and tramadol (5 studies) separately. We have the same motivation as you to prevent harm to patients but our assessment of risks was broader and relative to all the available treatments collectively.

In developing Recommendation 9, we were aware of the Cochrane Review published in 2009 on *Viscosupplementation for the Treatment of Osteoarthritis of the Knee*. Generally speaking, the studies differed from the evidence in our data base because selection criteria were not the same. Those authors (Campbell et al.) listed a total of five parameters for article inclusion beginning on their page 4. Our selection criteria are listed beginning on page 8. The primary difference was that clinical efficacy greater than four weeks was required for studies to be included as evidence in this AAOS guideline. Other differences involved their inclusion of, as one example, a study by Kirchner and Marshall published in 2006. Our research analyst reviewed it closely and had determined that effectiveness of cross linked Hylan G-F 20 was not demonstrated. Rather, it was shown that low molecular weight hyaluronic acid was not inferior to Hylan G-F 20 and that both groups reported post-treatment improvements. A case series interpretation constitutes lesser strength evidence than the randomized clinical trials on which the grade of our recommendation was based.

The 2008 edition of this guideline that found benefits of viscosupplementation to be inconclusive rather than non-affirming used a systematic review from AHRQ incorporating meta-analysis of Hylan G-F 20 compared to placebo. Although there was a statistically significant treatment effect, different pain measurement outcomes (WOMAC and VAS pain) were combined. Clinical significance could not be determined. Also, the authors found evidence of publication bias (publicizing of primarily favorable studies). We excluded the AHRQ review because the selection criteria did not match ours and because we also required original research. The current guideline has meta-analyses that combine the same measurement instruments, making it possible to determine that the overall effect does not meet the minimum clinically important improvement (MCII) threshold. Knowing the relationship of the overall effect to the MCII mitigates concern about potential publication bias (that skews the effect in a favorable direction); the result remained clinically insignificant.

At the same time, when we differentiated high- versus low- molecular weight viscosupplementation, our analyses did show that most of the statistically significant outcomes were associated with high-molecular cross linked hyaluronic acid. However, when it was compared to mid-range molecular weights, statistical significance was not maintained. Treatment comparisons between any weights greater than 750 kDa were not significantly different.

For Recommendation 13 there were no included studies in the 2008 edition of the guideline evaluating arthroscopic partial menisectomy or loose body removal in patients with knee osteoarthritis and mechanical symptoms consistent with torn meniscus and/or loose body. Therefore, the previous work group established a consensus recommendation. This updated guideline included one moderate-strength study (Herrlin et al.) that was downgraded from low to inconclusive because 40% of patients declined participation and the arthroscopic group performed poorer on their ADLs and in sports and recreation at baseline than the comparison group to the point of not being comparable. Heterogeneity between treatment groups was one of our exclusion criteria since significance testing is likely to be skewed. Additionally, there were no significant treatment benefits of meniscectomy using any of the outcomes at eight weeks and six months.

In evidence-based medicine, it is essential for developers to be transparent, provide unbiased analysis and reporting, and follow the standards established by the Institute of Medicine. This guideline represents total adherence to those principles. Our goal is to develop tools that make it possible for patients to receive optimal care based on the best available evidence. When high strength studies are lacking, recommendations are graded Inconclusive and the need for further research is identified. We added an explanatory statement explicitly stating that practitioners should “exercise clinical judgment, be alert for emerging evidence, and take patient preference into account” (see Clinical Implications in Table 6). The way to raise a recommendation grade from “Inconclusive” to “Strong” or “Moderate” is to encourage and support additional research of high strength.

We have carefully considered your comments and suggested revisions.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

X Would not recommend AT THIS TIME

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

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Reviewer Information:

Name of Reviewer: David J. Kennedy, M.D.

Address: 450 Broadway St MC 6342

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Phone: 650-721-7800 Fax: 650-721-3470 E-mail: djkenned@stanford.edu

Specialty Area/Discipline: Physical Medicine and Rehabilitation

Work setting: Academic MSK practice Credentials: M.D.

May we list you as a Peer Reviewer in the final Guidelines? ☒ Yes ☐ No

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Are you reviewing this guideline as a representative of a professional society? ☒ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? ☒ Yes ☐ No

Society Name: American Academy of Physical Medicine and Rehabilitation

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Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes ☒ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company: Kimberly-Clark - Radiofrequency - cited	☒ Yes ☐ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: RS Medical	☒ Yes ☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes ☒ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify: (AAP) Association of Academic Physiatry – Board of Governors	☒ Yes ☐ No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify: International Spine Intervention Society – Research Committee and Annual Program planning committee; (AAPM&R) American Academy of Physical Medicine and Rehabilitation – Medical Education Committee	☒ Yes ☐ No

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Please complete and return this form electronically in **WORD format** to song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **November 2, 2012**.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	☒
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☒	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☒	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☒	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☒	☐	☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☒	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	☒
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	☒
9. The validity of the studies is appropriately appraised	☐	☐	☒	☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☒	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☒	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☒	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☒	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☒	☐
15. The grades assigned to each recommendation are appropriate	☒	☐	☐	☐

COMMENTS

PLEASE RETURN ALL COMMENTS IN WORD FORMAT

Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline

This review had several positive aspects. The literature review was exceptional and comprehensive. To date this is the most comprehensive review and recommendations on knee osteoarthritis. Overall the recommendations are clear and match the literature. There are however several areas that must be addressed prior to this document being relevant and recommendable for clinical practice.

All the recommendations regarding injection therapy (corticosteroids, hyaluronic acid, etc) fail to address a systemic problem with the literature. It has been repeatedly documented that anatomic landmark (aka "blind") injection into the knee has a miss rate among experienced orthopedic surgeons of 20-30%. This is a MAJOR confounding variable that must be considered when presenting evidence that did not use image guidance for appropriate placement. Without accurate evidence the ability to give a "Strong" recommendation must be questioned. There could be strong evidence for not giving (or giving) a treatment without image guidance, but inconclusive data remains regarding accurate injection therapy.

When appropriate the recommendations should clearly state for how long the treatments are considered effective (i.e. short, intermediate, or long term use). Spa therapy falls into this category as the outcome effects were strong via a high quality study, but the duration of effect needs to be more clearly spelled out. This also applies to NSAIDs. The literature on this section was ideal, and did discuss complication rates. However, NSAID complications may be dependent upon duration of treatment, with the true complications rates not accurately reported in a clinical study (even with 12-24 month follow-up). Given OA is a chronic disease, clear definitions of expected duration of effects needs to be clarified. Should patients be on NSAIDs and daily spa treatments for life?

In the bracing section (both knee braces and lateral wedge insoles) firm conclusions are difficult to ascertain based on the published data. When looking at knee OA in isolation these recommendation levels are correct. However, it is not clear it there are subsets of patients that may or may not respond to these treatments. For instance do patients with pes planus feet do better or work with insoles for knee OA? This is clearly not been elucidated in the literature to date, and thus any generic recommendations for knee OA, must be tempered with inconclusive data on these specific patient subgroups.

Dear Dr. Kennedy.
Thank you for your expert review of this clinical practice guideline. We will respond to your comments in the order you presented them.

After reexamining all the included studies in recommendations 8-11 on injection therapies, we confirmed that patients in the treatment groups did undergo imaging prior to receiving intra-articular corticosteroids, viscosupplementation, growth factor and platelet rich plasma injections, and needle lavage. Additionally, the researchers consistently evaluated Kellgren-Lawrence criteria prior to administering the treatments. This guideline on knee osteoarthritis addressed non-arthroplasty alternatives to relieving pain and increasing function typically for early to moderate disease progression. The clinical practice guideline on surgical management expected to be released in 2014 will focus on arthroplasty for the end-stages. Once the series is completed, the collection of the two guidelines will reflect the broad spectrum of severities.

Our selection criteria for all included studies in the full guideline required a treatment follow up period of at least four weeks. Although this duration period was stated as part of the inclusion criteria in the methods section, we reworded several of the rationales to reference the follow up period so that the time requirement is clearer. Additionally, recommendation 3 was revised to address physical agents in 3b and manual agents in 3c to make it consistent with our original intent. "Spa therapy" was not one of our search terms; and consequently, the treatment lacked a full systematic review. The Forestier et al. study initially appeared in our literature search because spa therapy resembled a term that we did include (balneotherapy; see Appendix V). However, a careful re-reading of the article found that the experimental group could not be accurately described as receiving balneotherapy so the study was excluded (please read the rationale section in the full guideline).

The treatment follow up periods in the studies evaluating the efficacy of NSAIDs ranged from six weeks to two years. We realize the potentially serious side effect profile associated with analgesics and consider their proper use to be as needed for managing pain flare ups and with adjunctive nonpharmacologic interventions. The appropriate use criteria that will be

developed in conjunction with this guideline can better identify precise indications likely to incorporate expected duration and effects.

All included studies on lateral wedge insoles excluded patients who could not tolerate them or had causes of symptomatic deformity unrelated to osteoarthritis of the knee. While flat feet were not specifically mentioned, the condition was presumably considered exclusionary. The studies on the valgus producing brace did not note any concerns about foot deformities. Again, the appropriate use criteria currently under development are where patient subgroups most likely to benefit can be appropriately specified.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

- ☐ Strongly recommend
- ☒ Recommend (with provisions or alterations) — Depending on provisions
- ☐ Would not recommend
- ☐ Unsure

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Reviewer Information:

Name of Reviewer: John Hatzenbuehler, MD

Address: 272 Congress ST.

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Specialty Area/Discipline: Primary Care Sports Medicine

Work setting: Maine Medical Center Credentials: MD, FACSM

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Society Name: ACSM – American College of Sports Medicine

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Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes X☐ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify:	☐ Yes X☐ No
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Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	X☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	X☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	X☐	☐
4. The guideline's target audience is clearly described	☐	☐	☐	X ☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	X☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	X☐	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	X☐	☐
8. All important studies that met the article inclusion criteria are included	☐	X☐	☐	☐
9. The validity of the studies is appropriately appraised	☐	X ☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☐	X☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	X☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	X☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	X☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	X☐	☐
15. The grades assigned to each recommendation are appropriate	X☐	☐	☐	☐

COMMENTS

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General Comments:
Introducing the term NOT in the recommendations of 6A, 3A, 3C, 6B, and 9 complicates the results of the reference studies. This term using the recommendation definitions implies that each study referenced actually studied the question that the method suggestion is NOT beneficial and/or is harmful to the patient. The problem is that in each case, the authors use as references studies that assessed the efficacy of the treatment and decided there was no supportive evidence to conclude it was beneficial. They did NOT provide evidence regarding the potential complications or risk to patients that would create a risk/benefit assessment for use on patients. Since they did not perform such a risk/benefit analysis they should NOT be allowed to conclude the negative. That is to say they should NOT be allowed to conclude that their recommendation is that these alternatives NOT be used. Rather it should be stated there is no evidence to support their use, if indeed the evidence fails to show positive efficacy in a majority of the studies evaluated.

Based on this, I strongly recommend that in each case that the authors not use the term NOT in their conclusions and where they "recommend it NOT be used" that each is revised to a positive recommendation avoiding the confusing negative recommendation.

Specific Recommendation Comments:

Recommendation #3A – regarding the use of acupuncture: A strong negative recommendation indicates that the authors of the guidelines believe that the potential harm of the treatment clearly exceeds the benefits. This assertion relies on a significant potential for harm by acupuncture.

Regarding the documented benefits of acupuncture in osteoarthritis, Vickers et al[1] demonstrated that acupuncture was superior to both controls and sham acupuncture for OA in 29 studies, representing almost 18,000 patients. The data continued to show a significant benefit for acupuncture, even after exclusion of a set of studies that more robustly supported acupuncture, than did the other studies considered. Not all studies are supportive of acupuncture in OA. A Greek study[2] examined the addition of acupuncture to a pharmacologic (COX-2 inhibitor) regimen and compared it to the COX-2 plus sham acupuncture and to a COX-2 inhibitor alone. The addition of real acupuncture did provide statistically significant improvements, compared to the other two treatment arms. On the other hand, a study comparing real and sham acupuncture[3] showed no benefit for real acupuncture, compared to sham. This study included 221 knee OA patients awaiting arthroplasty. Another of its findings was that patient expectations or beliefs regarding their treatment regimen affected their pain outcome, a result also obtained in a study by Grotle.[4]

Undoubtedly, the literature on the use of acupuncture in knee OA is varied, and it may be true that patients' belief systems about their treatment exerts a strong influence. Nonetheless, the AAOS document asserts that the risks of acupuncture significantly exceed its benefit. A search[5] of the National Patient Safety Agency database for a 3-year period beginning in 2009 showed 468 total reports of patient injury, 325 of which were analyzed. A total of 95% of these were considered as causing little to no harm, although 31% of the incidents involved retained needles and 19% loss of consciousness or unresponsiveness, although the latter could easily be attributed to other medical conditions, rather than a complication of acupuncture per se.

Thus, it would seem that a strong recommendation against the use of acupuncture in OA is unwarranted. The risks are minimal, and while the literature is varied in showing its benefits, it cannot be true that its risks clearly outweigh its benefits.

Recommendation #6A - regarding the use of glucosamine: The references cited for support of the recommendation show no difference compared to placebo for very specific measures (WOMAC), but don't include other outcome measures that put glucosamine in a more favorable position.

A Cochrane review from 2009 cites RCT's that favored glucosamine with 22% improvement from baseline pain and 11% improvement in function over placebo. Though these results may not be statistically significant, they are clinically relevant in dealing with

osteoarthritis safely. Particular preparations of glucosamine showed consistently better results favoring the use of glucosamine for both pain relief and improved function; findings clinically significant for the osteoarthritic.

McAlindon's AJSM article demonstrates no difference from placebo, but over one-half of the subjects evaluated used glucosamine for only six weeks. Clearly, based on other studies of glucosamine, this time frame may have been too brief to draw clinically appropriate conclusions.

On a more subjective note, patients with osteoarthritis need all the non-operative weapons available to combat the symptoms of their joint disease. Glucosamine, though not overwhelmingly successful, has been effective for many people. Compared to other pharmaceuticals, glucosamine is inexpensive and safe. Given that profile, glucosamine should still be considered for early treatment of osteoarthritis and a trial offered to people with osteoarthritis.

Recommendation #9 - regarding the use of hyaluronic acid (HA): Fourteen studies were included in this review, of which three were considered high quality as they were randomized controlled trials. There was a STRONG recommendation AGAINST the use of hyaluronic acid, which implies there were two or more "high strength" studies with consistent findings in support against the intervention. I do not find this conclusion to be correct.

The three studies referenced as high quality were Lundsgaard et al 2008; Huang et al 2011 and Puhl et al 1993. Lundsgaard et al found no significant difference between 4 HA injections and placebo using pain as the main outcome. The patient population was > 60 years of age and predominantly female and had severe osteoarthritis (Kellgren–Lawrence grade 3 or 4).

Huang et al concluded that five weekly HA injections could improve pain and function in a Taiwanese population when Western Ontario and McMaster Universities (WOMAC) scores were compared with placebo at baseline and 25 weeks.

Puhl et al found the Lequesne Index criterion showed a significant superiority of HA injection patients after the third injection up to the final follow-up examination nine weeks after the last injection. This RCT was performed in Germany in the early 1990s.

Two out of the three of the "high quality" studies hence are in support of the use of HA injections. The Guideline's strong recommendation against the use of HA was given because of not meeting the Minimum Clinically Important Improvement (MCII) threshold. I do not feel is the correct interpretation of the scientific literature. Certainly discretion is advisable in selection of patients likely to benefit from HA injection, as greater age, lower baseline activity level and higher severity of knee OA are likely to diminish the therapeutic benefit of HA injections.

I do not feel it is appropriate to strongly recommend against HA injections because the MCII was within the confidence limit. The strength of the recommendation should be altered to reflect that it is inconclusive.

Recommendation #10 - regarding the issue of PRP. In this case, the conclusion should be inconclusive since the lack of data one way or the other does not overwhelmingly support its use. In addition, the authors should avoid making "standard of care" recommendations on things that are as of yet unproven. It should be left in the realm of inconclusive with not evidence based overwhelming conclusions available at this time

Recommendation #11 – regarding needle lavage. This conclusion is flawed because it was based on two studies alone and predominantly only on one (admittedly high quality study). I completely agree that there is NO evidence to support the routine use of this modality at this time; however based on their criteria, I am not sure if it is fair to conclude an overwhelming recommendation not to use it based on a single study that even within their discussion they offer some potential critiques and weaknesses. Once again, the conclusion should be inconclusive, not enough data available to definitively conclude one way or the other. Data is clearly not overwhelming to recommend routine use in all cases.

Recommendation #13 – regarding arthroscopy. This piece blends with both 11 and 13 and truly targets the issue of whether it is OK to do knee arthroscopy on patients with arthritis. Ultimately, the conclusion of 13 is fair as it does not prevent surgeons from taking care of mechanical pathology which clearly has been shown to be helpful to some patients. The use of the term inconclusive here is appropriate since the data does not clearly and overwhelming show that it SHOULD be done on all patients but rather that it could be done.

References

1. Vickers AJ, Cronin AM, Maschino AC, Lewith G, Macpherson H, Foster NE, Sherman KJ, Witt CM, Linde K. Acupuncture for Chronic Pain: Individual Patient Data Meta-analysis. Arch Intern Med 2012, Sep 10; 1-10.
2. Mavrommatis CI, Argyra E, Vadalouka A, Vasilakos DG. Acupuncture as an adjunctive therapy to pharmacological treatment in patients with chronic pain due to osteoarthritis of the knee: a 3-armed, randomized, placebo-controlled trial. Pain. 2012 Aug;153(8):1720-6.

3. White P, Bishop FL, Prescott P, Scott C, Little P, Lewith G. Practice, practitioner, or placebo? A multifactorial, mixed-methods randomized controlled trial of acupuncture. Pain. 2012 Feb;153(2):455-62.
4. Grotle, M. Traditional Chinese acupuncture was not superior to sham acupuncture for knee osteoarthritis but delivering treatment with high expectations of improvement was superior to delivering treatment with neutral expectations. J Physiother 2011; 57(1): 56.
5. Wheway J, Agbabiaka TB, Ernst E. Patient safety incidents from acupuncture treatments: a review of reports to the National Patient Safety Agency. Int J Risk Saf Med 2012; 24(3): 163-9.

Dear Dr. Hatzenbuehler.
Thank you for your expert review of this clinical practice guideline. Your general comments are consistent with statistical (i.e. Bayesian) principles. We agree that when a treatment does not show significant benefit the researcher has failed to prove its superiority, rather than show harmful outcomes per se. At the same time, the language stems *we recommend*, *we suggest*, and *the practitioner might* require comparable counter statements to reflect the full range of evidence rating possibilities. After considering your input, the work group decided to modify the phrase "we recommend not using" to "we cannot recommend using." We appreciate your input, and hope that these minor revisions to the language of the recommendations will enhance the accuracy of their interpretation. The new wording is:

Recommendation 3a:	We cannot recommend using acupuncture in patients with symptomatic osteoarthritis of the knee.
Recommendation 6:	We cannot recommend using glucosamine and chondroitin for patients with symptomatic osteoarthritis of the knee.
Recommendation 9:	We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee.

We will respond to your remaining recommendation-specific comments in the order you presented them.

We reexamined Figures 81 through 84 to respond to your comments about recommendation 9. The confidence interval exceeding the minimum clinically important improvement threshold for WOMAC pain is associated with the effect found by Huang et al. (Figure 81). The confidence interval that showed MCII to patients for WOMAC stiffness is Patrella et al. (Figure 84). Heybelli et al., Altman et al., and Patrella et al. each individually showed effects that were possibly clinically important to patients (Figure 83). Clinical importance was not or possibly not achieved in any of the analyzed studies examining VAS weight bearing pain (Figure 82). While we appreciate your detailed orientation, interpretation of a single data point in meta-analysis is not appropriate. We formulated our conclusions by determining that the overall effects of the outcomes (symbolized by the diamonds) did not meet the MCII thresholds. The confidence intervals of the overall effects are reflected in their widths with the lower confidence limits on the left and higher limits on the right. Demonstrating statistical and clinical significance to patients treated with hyaluronic acid will require improved evidence quality and applicability in the totality of existing studies; merely increasing the volume of research does not improve meta-analytic findings.

As you highlighted, your view on the efficacy of platelet rich plasma is consistent with our evidence-based finding in recommendation 10.

Recommendation 11 was based on two studies: one high-strength study by Bradley et al. and one moderate-strength study by Vad et al. The evidence showed little or no benefit from needle lavage for osteoarthritis of the knee. Most all outcomes were not statistically significant, including three critical pain and three critical functional outcomes. The benefit to patients from needle lavage was not measurable. A recommendation based on strong- and moderate- strength evidence cannot be graded inconclusive, which is defined as comprising a single low-strength study or conflicting evidence that prevents direction of endorsement (see Table 6).

We appreciated the consistency of your view with recommendation 13.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Structured Peer Review Form

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- **Your conflicts of interest disclosures will be published on the AAOS website with your review comments.**

Reviewer Information:

Name of Reviewer: Andreas H. Gomoll

Address: Brigham and Women's Hospital, 850 Boylston Street

City: Chestnut Hill State: MA Zip Code: 02467

Phone: 617-732-9812 Fax: 617-732-9730 E-mail: agomoll@partners.org

Specialty Area/Discipline: Sports Medicine

Work setting: Academic Credentials: MD, Orthopaedic Surgeon

May we list you as a Peer Reviewer in the final Guidelines? ☒ Yes ☐ No

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Are you reviewing this guideline as a representative of a professional society? ☒ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? ☒ Yes ☐ No

Society Name: AOSSM

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Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes ☐ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company:	☐ Yes ☐ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
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Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify:	☐ Yes ☐ No

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Please complete and return this form electronically in **WORD format** to song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **November 2, 2012**.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☒	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	☒
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☒	☐
4. The guideline's target audience is clearly described	☐	☐	☐	☒
5. The patients to whom this guideline is meant to apply are specifically described	☐	☒	☐	☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	☒
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	☒
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	☒
9. The validity of the studies is appropriately appraised	☐	☐	☐	☒
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	☒
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	☒
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	☒
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☐	☒
14. The writing style is appropriate for health care professionals.	☐	☐	☐	☒
15. The grades assigned to each recommendation are appropriate	☐	☐	☐	☒

COMMENTS

PLEASE RETURN ALL COMMENTS IN WORD FORMAT

Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline

I applaud the committee for a monumental task well done. The methodology is sound and the literature review extremely thorough. Limitations of studies are clearly pointed out and the recommendations follow the presented evidence.

My two comments below:

- **Many studies distinguish between early (Kellgren-Lawrence 1-3) and end-stage OA (K-L 4), frequently excluding the latter. The guidelines would be strengthened if that distinction were pointed out more clearly, since the efficacy of certain interventions might differ between these groups.**
- **The guidelines are missing recommendations on formal, supervised physical therapy, as well as on total and partial knee replacement surgery. Both are very common interventions for the treatment of OA, and their omission critically weakens the guidelines.**

Dear Dr. Gomoll.
Thank you for your expert review of this clinical practice guideline. We reexamined the included studies of the conservative treatments evaluated as part of recommendation 1 and have clarified in the rationale section that the exercise interventions were predominantly conducted under supervision, most often by a physical therapist. We understand the importance of distinguishing between early and severe stages of knee osteoarthritis for identifying appropriate treatments. Most of the included studies did evaluate Kellgren-Lawrence criteria. However, differences between K-L 1-3 and K-L 4 patient groups were generally not controlled for so we were not able to specify disease progression as part of the final recommendations. Additionally, while this clinical practice guideline addressed non-arthroplasty alternatives for early to moderate degrees of affliction, the guideline on surgical management of osteoarthritis of the knee expected to be released in 2014 will focus on arthroplasty used for the end-stages. Once the series is completed, the collection of the two guidelines will reflect the broad spectrum of severities.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

☐ Strongly recommend

☒ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

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Reviewer Information:

Name of Reviewer: Bryan Heiderscheit

Address: University of Wisconsin,1300 University Ave

City: Madison State: WI Zip Code: 53706-1532

Phone: 608-263-5428 Fax: 608-262-7809 E-mail: heiderscheit@ortho.wisc.edu

Specialty Area/Discipline: Physical Therapy

Work setting: research/clinical Credentials: PT, PhD

May we list you as a Peer Reviewer in the final Guidelines? ☒ Yes ☐ No

PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your review comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? ☒ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? ☒ Yes ☐ No

Society Name: American Physical Therapy Association

(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

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Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes ☒ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company: North American Seminars	☒ Yes ☐ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Össur, Inc; Visual Health Information, Inc	☒ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Vibetech, Inc	☒ Yes ☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes ☒ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify: J Orthop Sports Phys Ther	☒ Yes ☐ No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify:	☐ Yes ☒ No

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	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	☒
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☒	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	☒
4. The guideline's target audience is clearly described	☐	☐	☐	☒
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	☒
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	☒
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	☒
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	☒
9. The validity of the studies is appropriately appraised	☐	☐	☐	☒
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	☒
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	☒
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	☒
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☐	☒
14. The writing style is appropriate for health care professionals.	☐	☐	☐	☒
15. The grades assigned to each recommendation are appropriate	☐	☐	☒	☐

COMMENTS

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Overall, the updated AAOS guidelines nicely reflect the contemporary state of the science regarding clinical management of knee OA. Compared to the 2008 guidelines, the specific recommendations made in the current version provide a greater degree of detail with a more transparent grading system. The use of original research only is also seen as a positive step to avoid potential bias from secondary analyses.

One general comment. It would seem that some of the Recommendations would partially depend on the anatomical location of knee OA (medial compartment, lateral compartment, patellofemoral). For example, a valgus directed knee brace would likely not be used for those with lateral uni-compartmental OA. The 2008 guidelines included this differentiation in some instances. Why was this removed from the current version?

Ln 286 – please comment on limiting the scope of the guideline for use by orthopaedic surgeons and physicians. Consider expanding it to include all health care practitioners involved in the clinical management and care of patients with knee OA.

Regarding Recommendation 1 (ln 949), it is not clear from the combination of included studies whether supervision of the exercise program is necessary to achieve the positive clinical outcomes. Some studies involved home exercise programs, whereas many others are described as "physical therapy," which can mean any number of interventions and is performed under the supervision of a physical therapist. If supervision plays a key role in improving outcomes, then it should be considered as an additional differentiator. Because the initial phrase of the Recommendation specifies "self-management programs," the concern is this self-management idea may be interpreted to equally apply to the other phrases of the Recommendation. It is also important to delineate what specific interventions were included in physical therapy: I believe this encompassed more than just strengthening, neuromuscular education and low-impact aerobics for some of the included studies.

ln 1833 – it is unclear why reference #76 (Pajareya et al) was included in determining Recommendation 4. It appears this study used only an elastic sleeve and not a valgus directed brace.

Ln 2823, 2824 – several cited Figure numbers are incorrect

Ln 2908 – it is unclear why growth factor injections and platelet rich plasma (PRP) injections were combined into one recommendation. Was this based on potential biological mechanism? Considering the only PRP injection study included was of moderate quality with possible clinical importance, this would seem to qualify for the strength of recommendation score of Limited rather than Inconclusive. In prior recommendations (e.g., 3B), separating the interventions led to a Moderate strength of recommendation based on a single study. By combining PRP injection and growth factor injections into a single Recommendation, the potential benefit of one may be overshadowed by the other.

Dear Dr. Heiderscheit.
Thank you for your expert review of this clinical practice guideline. We will respond to your comments in the order you presented them.

After reexamining the included studies, we inserted anatomical location into the wording of the recommendations consistent with our evidence database. Specifically, we added "medial compartment" to recommendation 5, valgus producing proximal tibial osteotomy to recommendation 14, free-floating interpositional device to recommendation 15, and inserted "medial compartment unloader" in recommendation 4 on the valgus producing knee brace. Thank you for this suggestion that has improved and clarified these modified recommendations.

We also broadened the intended use in the introduction to include other healthcare providers.

We reexamined the included studies of the conservative treatments evaluated as part of recommendation 1 and have clarified in the rationale section that exercise interventions were predominantly conducted under supervision, most often by a physical therapist.

Since the elastic sleeve potentially improves sense of proprioception and does not provide mechanical support to manage varus deformity, we have excluded the Pajareya et al. study from the evidence in recommendation 4. The original guidance was to address bracing but the recommendation was subsequently revised to focus on medial compartment disease based on the available evidence.

We corrected the numbering of the figures and modified their hyperlinks to reflect the current version of the text. Thank you for pointing out this detail.

Our thinking behind combining growth factor and platelet rich plasma injections into one recommendation was based on the fact that they are both biological treatments.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

☒ Strongly recommend

☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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Reviewer Information:

Name of Reviewer: Santiago M. de Solo MD

Address: 7190 SW 87 Avenue, Suite 304

City: Miami State: FL Zip Code: 33173

Phone: 305-661-4644 Fax: 305-661-0851 E-mail: drsdesolo@gmail.com

Specialty Area/Discipline: Rheumatology

Work setting: Private Practice Credentials: MD

May we list you as a Peer Reviewer in the final Guidelines? ☒ Yes ☐ No

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Are you reviewing this guideline as a representative of a professional society? ☒ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? ☒ Yes ☐ No

Society Name: Arthritis Foundation

(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

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Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes X☐ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify:	☐ Yes X☐ No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify: Arthritis Foundation	X☐ Yes ☐ No

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	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	X☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	X☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	X☐
4. The guideline's target audience is clearly described	☐	☐	☐	X ☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	X☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	X ☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	X☐
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	X ☐
9. The validity of the studies is appropriately appraised	☐	☐	☐	X☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	X ☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	X ☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	X☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☐	X ☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	X ☐
15. The grades assigned to each recommendation are appropriate	☐	☐	☐	X ☐

COMMENTS

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The only suggestion on to the AAOS Recommendations for OAK is in regards to Recommendation #1 (line950-953). The 2012 ACR (American College of Rheumatology) guidelines for OAK specify Tai chi exercise as a conditional recommendation. This recommendation does not specifically exist for the hip, hand, or other joint. On page 469 of the reference stated below, second column, second paragraph, the recommendation reads as follows:

Arthritis Care & Research
Vol. 64, No. 4, April 2012, pp 465–474
DOI 10.1002/acr.21596

"The TEP (Technical Expert Panel) conditionally recommends that patients with knee OA should 1) participate in self management programs that may include psychosocial interventions, 2) use thermal agents and manual therapy in combination with exercise supervised by a physical therapist, 3) use medially directed patellar taping, 4) participate in tai chi programs, and 5) use walking aids, if necessary."

Thank you for allowing me this opportunity. Your panel has obviously been busy preparing this detailed manuscript and the recommendations are sound, detailed, and very well referenced. I can be reached at drsdesolo@gmail.com or 305-661-4644 EST.
Jim de Solo

Dear Dr. de Solo.
Thank you for your expert review of this clinical practice guideline and for pointing out the American College of Rheumatology's guideline recommendation regarding the potential benefit of tai chi for symptomatic osteoarthritis of the knee. We did use tai chi as one of the search terms (see Appendix V) but there were no empirical studies that met our inclusion criteria.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

☒ Strongly recommend

☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Structured Peer Review Form

ALL REVIEW COMMENTS, RESPONSES AND REVIEWER CONFLICTS OF INTEREST DISCLSOURE WILL BE AVAILABLE ON OUR WEBSITE FOLLOWING APPROVAL OF THIS DOCUMENT.

Review of any AAOS confidential draft allows us to improve the overall guideline but does not imply endorsement by any given individual or any specialty society who participates in our review processes. The AAOS review process may result in changes to the documents; therefore, endorsement cannot occur until the AAOS Board of Directors officially approves the final guideline.

Please note that if you return a review:

- **Your review comments will be published on the AAOS website with our explanation of why we did or did not change the draft document in response to your comments.**
- **Your conflicts of interest disclosures will be published on the AAOS website with your review comments.**

Reviewer Information:

Name of Reviewer: John C. Richmond, MD

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Specialty Area/Discipline: Orthopaedic Sports Medicine

Work setting: Private practice, Orthopaedic Specialty Hospital Credentials: MD, FAAOS

May we list you as a Peer Reviewer in the final Guidelines? X Yes ☐ No

PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your review comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? X Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? X Yes ☐ No

Society Name: Eastern Orthopaedic Association

(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

If the boxes below are not checked and/or the reviewer does not attach his/her conflicts of interest, the reviewer's comments will not be addressed by the AAOS nor will the reviewer's name or society be listed as a reviewer of this GL. If a committee reviews the guideline, only the chairperson or lead of the review must declare their relevant COI.

☐ **I have declared my conflicts of interest on page 2 of this form.**

X **I have declared my conflicts of interest in the AAOS database; my customer # is** 20201

X **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.**

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REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

Each item below requires an answer. Please report information for the last 12-months.

Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes ☐ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company:	☐ Yes ☐ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes ☐ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify:	☐ Yes ☐ No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify:	☐ Yes ☐ No

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Please read and review this Draft Clinical Practice Guideline with particular focus on your area of expertise. Your responses will be used to assess the validity, clarity and accuracy of the interpretation of the evidence. If applicable, **please specify the draft page and line numbers in your comments**. Please feel free to also comment on the overall structure and content of the document. If you need more space than is provided, please attach additional pages.

Please complete and return this form electronically in **WORD format** to song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **November 2, 2012**.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	X
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	X
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	X	☐
4. The guideline's target audience is clearly described	☐	☐	☐	X
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	X	☐
6. The criteria used to select articles for inclusion are appropriate	X	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	X	☐
8. All important studies that met the article inclusion criteria are included	X	☐	☐	☐
9. The validity of the studies is appropriately appraised	☐	X	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☐	X	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	X	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	X	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	X	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	X	☐
15. The grades assigned to each recommendation are appropriate	X	☐	☐	☐

COMMENTS

PLEASE RETURN ALL COMMENTS IN WORD FORMAT

Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline

As an overall comment on the Guideline, I congratulate the authors on their tireless efforts to put together this vast analysis of the literature. Unfortunately, I question the applicability of this Guideline for practitioners managing the epidemic of osteoarthritis of the knee. If we follow only the strong and moderate recommendations of the Guideline as written, we can encourage appropriate physical activity and weight loss, use of spa therapy or ultrasound, and prescribe NSAID's or tramadol. There are many things we should not do based on this Guideline. We have few, if any, options in the over-65 patient with medical co-morbidities or taking anti-hypertensives. If the goal of the Guideline is to educate the practicing physician on the inadequacy of our evidence-based literature, then this Guideline has succeeded. If the goal of the Guideline is to assist the practitioner in making evidence-based decisions in the management of an individual patient with osteoarthritis of the knee then, unfortunately, the process of the AAOS has failed.

COMMENTS ON SPECIFIC RECOMMENDATIONS

RECOMMENDATION 3B: We suggest the use of spa therapy (massage, showers, mud and pool sessions) and ultrasound therapy for functional improvement in patients with symptomatic osteoarthritis of the knee.

STRENGTH OF RECOMMENDATION: Moderate.

To include a recommendation for spa therapy and not downgrade it to inconclusive based on just one randomized control trial, which has the huge potential for bias, seems inappropriate. That bias potential is based on the control arm of that study. The treatment arm received, over a three week period, 18 spa treatments, each lasting more than one hour, while the control arm was just told to do their own exercises. Clearly, there is going to be a therapeutic bond between the spa therapy treatment arm and their massage therapist, et al. This is likely to carry a significant placebo effect compared to the control group, being handed an exercise sheet and being told to do the exercises at home. Careful reading of this paper would suggest that the quality of the study should be downgraded and the Strength of Recommendation should be lowered. I would also question its inclusion in this recommendation by the American Academy of Orthopedic Surgeons for physicians practicing in the United States, since a three week visit to a spa in France is likely not covered by any insurance plan available here in the United States.

RECOMMENDATION 7A: We recommended NSAID's (oral or topical) or tramadol for patients with symptomatic osteoarthritis of the knee.

STRENGTH OF RECOMMENDATION: Strong.

I believe including tramadol with the non-steroidal anti-inflammatory drugs is a major flaw of this recommendation. Tramadol has been associated with physical dependence and a withdrawal syndrome. Although not classified as a narcotic by the FDA, multiple publications have noted the withdrawal phenomenon and to lump it with non-steroidals in this Guideline, I believe is inappropriate.

Additionally, with a significant percentage of the patients with osteoarthritis over the age of 65, and the noted increase in complications with the use of non-steroidal anti-inflammatory drugs (risk of adverse event is 2.4 times greater in patients over age 65 versus younger patients). These two recommendations taken together really do a disservice to the physician treating osteoarthritis in the elderly. In addition, many patients over 50 are on blood pressure medications, and non-steroidals have a significant adverse effect on blood pressure control.

RECOMMENDATION 9: We recommend not using hyaluronic acid for patients with symptomatic osteoarthritis of the knee.

STRENGTH OF RECOMMENDATION: Strong.

I am concerned that this recommendation has overlooked a large body of literature on the use of viscosupplementation for the treatment of osteoarthritis of the knee. The Cochrane Review of Viscosupplementation for the Treatment of Osteoarthritis of the Knee, which was published in 2009 based on the literature up through 2005, identified 40 trials that included comparisons of hyaluronic acid with a placebo (either saline or arthrocentesis). This guideline only identified 14 studies, and yet included studies up through 2011. The conclusions of that Cochrane Collaboration Review of Viscosupplementation are diametrically opposed to your current recommendation. In addition, failure to use the studies that compare intra-articular viscosupplementation to non-steroidal anti-inflammatory drugs (all of which seem to identify equal efficacy, with potential improved safety with the intra-articular injections versus oral non-steroidals) has resulted in a strong recommendation for oral non-steroidals, at the same time a strong recommendation against viscosupplementation, while in head-to-head comparison the two are equal with improved safety with the viscosupplementation.

RECOMMENDATION 10: We are unable to recommend for or against arthroscopic partial meniscectomy or loose body removal in patients with osteoarthritis of the knee and mechanical symptoms consistent with a torn meniscus and/or loose body.

SRENGTH OF RECOMMENDATION: Inconclusive

I am concerned that the only cited study (Herrlin et al) specifically patients with loose bodies, and only included patients without any traumatic event and pain, likely in actuality excluding any patient with mechanical symptoms from their meniscal tear. There is a large body of Level II literature that demonstrates the efficacy of arthroscopic treatment of mechanically significant meniscal tears and loose bodies in patients with mild to moderate osteoarthritis that were exclude from your analysis, and the cited paper essentially excluded the group to whom you decided to apply it.

Dear Dr. Richmond.
Thank you for your expert review of this clinical practice guideline. We will respond to your comments in the order that they are written.

Recommendation 3 was revised to address physical agents in 3b and manual agents in 3c to make it consistent with our original intent. “Spa therapy” was not one of our search terms; and consequently, the treatment lacked a full systematic review. The Forestier et al. study initially appeared in our literature search because spa therapy resembled a term that we did include (balneotherapy; see Appendix V). However, a careful re-reading of the article found that the experimental group could not be accurately described as receiving balneotherapy so the study was excluded (please read the rationale section in the full guideline).

We agree with your concern about the risks to patients who use opiate pain medication to treat a chronic condition. In our systematic review, five studies (two high-strength and three moderate-strength) evaluated tramadol either alone or as an adjunctive therapy. It has been used to treat moderate to severe pain and in patients who have an adverse drug reaction, contraindication, or no response to selective and nonselective NSAIDs and acetaminophen. Risk factors point to the importance of using tramadol appropriately. The appropriate use criteria that will be developed in conjunction with this guideline will identify precise indications, likely including the ones you emphasized.

We reexamined the Cochrane Review published in 2009 on *Viscosupplementation for the Treatment of Osteoarthritis of the Knee*. Generally speaking, the studies reviewed differed from the evidence in our data base because selection criteria were not the same. Those authors (Campbell et al.) list a total of five parameters that begin on page 4 of their systematic review. Our selection criteria are listed beginning on page 7. The primary difference is that clinical efficacy greater than four weeks was required for the AAOS analyses.

Other differences involved their inclusion of low-strength studies. As one example, a study by Kirchner and Marshall published in 2006 was included in the Cochrane and other systematic reviews but did not influence the evidence grade in this guideline. We determined that effectiveness of cross linked Hylan G-F 20 was not demonstrated. Rather, it was shown

that low molecular weight hyaluronic acid was not inferior to Hylan G-F 20 and that both groups reported improvements from baseline. A case series interpretation constitutes lesser strength evidence than the randomized clinical trials on which the grade of our recommendation was based. Additionally, when we differentiated high- versus low- molecular weight, our analyses did show that most of the statistically significant outcomes were associated with high-molecular cross linked hyaluronic acid but that when compared to mid-range molecular weight, statistical significance was not maintained. Treatment comparisons between any weights higher than 750 kDa were not significantly different.

The 2008 edition of this guideline that found benefits of viscosupplementation to be inconclusive rather than non-affirming used a systematic review from AHRQ incorporating meta-analysis of Hylan G-F 20 compared to placebo. Although there was a statistically significant treatment effect, different pain measurement outcomes (WOMAC and VAS pain) were combined. Clinical significance could not be determined. Also, the authors found evidence of publication bias (publicizing of primarily favorable studies). We excluded the AHRQ review because the selection criteria did not match ours and secondary data were excluded in favor of primary research studies. The current guideline has meta-analyses that combine the same measurement instruments, which made it possible to determine that the overall effect was not clinically significant. Knowing the relationship of the overall effect to the MCII mitigates concern about potential publication bias (that skews the effect in a favorable direction); the result remained clinically insignificant.

We evaluated all possible studies that were generated by the search terms listed in Appendix V. You will see that we included “Anti-inflammatory agents, Non-steroidal” and attempted to access every research study on hyaluronic acid and viscosupplementation. Non-inclusion occurs when either none matched the selection criteria or they were of very low research design strength and could not be used to influence the recommendation grade.

Level II evidence typically suggests relatively good adherence to principles of research construction. In our search terms we placed asterisks after meniscectomy and osteotomy (and included the term *loose bodies*) so that all related studies of all evidence strengths would be extracted. We also manually searched existing systematic reviews for possibly pertinent studies that might have been missed. You have suggested that a large body of literature has been overlooked in this guideline that demonstrates the efficacy of arthroscopic treatment of mechanically significant meniscal tears and loose bodies in patients with mild to moderate osteoarthritis. The AAOS guideline development process entails an exhaustive systematic review of the literature and exclusion of studies that do not meet the selection criteria. The one that has repeatedly led to differences between our systematic review and that of others is the required treatment follow up period of four weeks. If you provide additional citations, we can confirm that the specific articles were considered and will indicate detailed reasons for exclusions.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

X Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

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- **Your conflicts of interest disclosures will be published on the AAOS website with your review comments.**

Reviewer Information:

Name of Reviewer: Stephen J. Incavo, MD

Address: 6550 Fannin, Suite 2600
City: Houston State: Texas Zip Code: 77030

Phone: 713-441-3569 Fax: 713-790-6614 E-mail: sjincavo@tmhs.org

Specialty Area/Discipline: Orthopaedic surgery - adult reconstruction

Work setting: The Methodist Hospital Credentials: The Knee Society, the Hip Society, Professor of Clinical Orthopaedic Surgery - Weill Cornell Medical College, Attending Surgeon - The Methodist Hospital, Houston.

May we list you as a Peer Reviewer in the final Guidelines? **X** Yes No

PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your review comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? **X** Yes No

If yes, may we list your society as a reviewer of this guideline? **X** Yes No

Society Name: Knee Society

(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

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X I have declared my conflicts of interest on page 2 of this form.

X I have declared my conflicts of interest in the AAOS database; my customer # is 19372

X I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.

REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

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Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device: Innomed Surgical Instruments, Nimbic Systems - cement spacer molds	**X** Yes No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company:	Yes **X** No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	Yes **X** No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	Yes **X** No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	Yes **X** No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier: *MAKO Surgical Corp.*	**X** Yes No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	Yes **X** No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	Yes **X** No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	Yes **X** No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify: *Journal of Arthroplasty*	**X** Yes No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify:	Yes **X** No

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Please complete and return this form electronically in **WORD format** to song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **November 2, 2012**.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated			X	
2. There is an explicit link between the recommendations and the supporting evidence			X	
3. Given the nature of the topic and the data, all clinically important outcomes are considered		X		
4. The guideline's target audience is clearly described				X
5. The patients to whom this guideline is meant to apply are specifically described			X	
6. The criteria used to select articles for inclusion are appropriate			X	
7. The reasons why some studies were excluded are clearly described			X	
8. All important studies that met the article inclusion criteria are included			X	
9. The validity of the studies is appropriately appraised			X	
10. The methods are described in such a way as to be reproducible.				X
11. The statistical methods are appropriate to the material and the objectives of this guideline			X	
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed		X		
13. Health benefits, side effects, and risks are adequately addressed			X	
14. The writing style is appropriate for health care professionals.			X	
15. The grades assigned to each recommendation are appropriate		X		

COMMENTS

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Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline

The authors and work group of this extensive work should be commended on their efforts toward rational recommendations concerning the treatment of osteoarthritis of the knee. Unfortunately, this reviewer has several very serious concerns about the recommendations.

1.) Table 6 (Line 726, Page 14) - Recommendations Strengths, Definitions, and Clinical Implications - would be better if there was another column stating what is in the text. For example, under evidence rating strong, the appropriate column should read, "We recommend..." Under Moderate, "We suggest..." Under limited, "the practitioner might consider..." Under inconclusive, "We were unable to recommend..." Under consensus, "The opinion of the work group is..."

2.) Recommendation 3B (Line 1544, Page 130) and 3D (Line 1568, Page 130) are problematic. In recommendation 3B, the guidelines "suggest the use of spa therapy, massage, showers, and mud and pool sessions..." Recommendation 3D reads, "We are unable to recommend for or against...Swedish massage therapy.." Based on this, the recommendations suggest massage at one point and are unable to recommend Swedish massage in another point. This is confusing and strains credulity. Does the committee really wish to recommend massage, showers, and mud and pool sessions but have no recommendation on Swedish massage? This is an untenable position to take.

In spite of the committee's statement that our practice guidelines are not to be used by payers, etc., this will unleash a decade of massage and mud and pool sessions.

3.) The committee should be commended on Recommendation 6A (Line 2008, Page 236), not using glucosamine and chondroitin. In the last decade, there has been an explosion of these drugs with no demonstrable evidence and, finally, this will be put to rest. This leads, however, to a major problem in Recommendation 6B (Line 2019, Page 236).

4.) Recommendation 6B (Line 2019, Pages 236-237), "Might advise use of giner extract." This statement is based on essentially two studies. The panel itself states in the text that these two studies are both flawed for not using comparable groups and because of possible investigative bias. In contrast, the recommendations on NSAIDs utilized 52 studies. It is hard to believe that the committee could use two flawed studies to recommend an anecdotal substance for the important issue of knee osteoarthritis. This is how the glucosamine/chondroitin medication boom began - with **no benefit to patients and great cost to individuals and society. I recommend this either be changed or removed entirely.**

5.) For Recommendation 8 (Line 2623, Page 746), the committee was "unable to recommend for or against the use of intra-articular corticosteroids." This recommendation flies in the face of an extensive history and clinical judgement. While most orthopaedic surgeons do not use corticosteroids indiscriminately, they are unquestionably of substantial benefit as a temporizing measure in patients with knee osteoarthritis, especially early (grade 1,2,3 but not grade 4) osteoarthritis. Perhaps part of this dilemma is that corticosteroids have been used in patients with end-stage arthritis, for which no longterm benefit is possible. Nonetheless, this defies common sense.

6.) For Recommendation 9 (Line 2739, Page 769), the committee recommends not using hyaluronic acid for patients with symptomatic osteoarthritis of the knee. I have similar comments as with Recommendation 8. Many orthopaedic surgeons find these medications extremely helpful for patients with early osteoarthritis of the knee. It is difficult for me to believe that potential harm from these injections strongly outweighs the benefits in delaying the use of joint replacement, especially in young or middle-aged patients. They are especially useful in early osteoarthritis.

7.) Recommendation 10 (Line 2907, Page 847) is quite surprising to me. While the committee recommends against corticosteroids and intra-articular hyaluronic acid injections (both of which nearly all orthpaedic surgeons utilize), they are unable to recommend for or against a hypothetical, unproven, and extremely expensive procedure such as growth-factor injections and/or platelet-rich plasma. This, again, does not make sense viewed from a "big picture."

8.) Recommendation 14 (Line 3232, Page 932) shows a limited recommendation for valgus-producing proximal tibial osteotomies. This brings up the question of varus-producing distal femoral osteotomies. The clinical literature on femoral osteotomies is quite good, and if the committee does not wish to take up this question it would be important to say that they will not comment on that based on lack of appropriate studies.

9.) For Recommendation 15 (Line 3356, Page 962), I believe the concensus recommendation is entirely correct, even in the absence of reliable evidence.

Dear Dr. Incavo.
Thank you for your expert review of this clinical practice guideline. We will respond to your comments in the order you presented them.

The language stems you have requested to be added in Table 6 are provided immediately above it (see Table 5).

Recommendation 3 was revised to address physical agents in 3b and manual agents in 3c to make it consistent with our original intent. “Spa therapy” was not one of our search terms; and consequently, this treatment lacked a full systematic review. The Forestier et al. study initially appeared in our literature search because spa therapy resembled a term that we did include (balneotherapy; see Appendix V). However, a careful re-reading of the article found that the experimental group could not be accurately described as receiving balneotherapy so the study was excluded (please read the rationale section in the full guideline).

Recommendation 6 was modified to address only glucosamine and chondroitin and no longer includes ginger extract. One of our search terms was neutraceuticals and we initially maintained a broad focus. However, the original guidance was to evaluate methylsulfonylmethane, omega-3, gelatin, vitamin D, dimethylsulfoxide, antioxidants, and coenzyme Q10. The general term was intended to guide the search of the specific terms. Additionally, the evidence for neutraceuticals was variable and could not be easily summarized. Two moderate-strength studies comparing ginger extract to placebo arose in the included evidence. The only improvement in pain associated with both statistical and clinical significance was measured using WOMAC stiffness. Clinical significance could not be determined for four other pain measures, or they did not meet the minimum clinically important improvement threshold. The findings on outcomes of function were contradictory and low in count, which rendered them inconclusive. Glycosaminoglycan polysulfuric acid (GAGPS) produced a true negative finding statistically and clinically, and gubitong was associated with higher WOMAC total scores than glucosamine in a non-control matched study where clinical significance was not determined.

Regarding your concern about Recommendation 8 on intra-articular corticosteroids, in our systematic review only four placebo comparison studies met selection criteria that evaluated pain relief for a minimum treatment period of 4 weeks. One study found IA corticosteroids to be superior to placebo in WOMAC total scores at four weeks. Another study found IA corticosteroid injections inferior to hyaluronic acid injections and a third study found IA corticosteroids inferior to tidal irrigation. Since the evidence in the guideline did not support recommendations for the use of hyaluronic acid and tidal irrigation, the work group concluded that the evidence for the benefit of IA corticosteroids was inconclusive.

Regarding your concern about Recommendation 9 on viscosupplementation, besides not meeting the minimum clinically important improvement threshold, the studies included in this guideline were required to show favorable outcomes of duration longer than four weeks. We found that although the overall effect of the included studies was statistically significant, it did not meet or exceed the minimum clinically important improvement (MCII) threshold.

We heard your concern for perceived lack of clinical utility in recommendations 8-10 taken together. Direction of endorsement refers only to the results reported by the researching authors. Inconclusive recommendation grades do not indicate potential endorsement or affirmation of a treatment. They are defined as consisting of only one low-strength study or of contradictory evidence that renders assigning a definitive grade unachievable (see Table 6). There was a paucity of articles on the use of platelet concentrates in the treatment of osteoarthritis. In two studies, activated platelet aggregates in a fibrin matrix were used; a platelet concentrate was used in a third study. None of the researchers controlled for platelet volume. They all used hyaluronic acid with the control group. The studies showed decreased levels of pain in the post injection period but they lacked homogeneity for a comparative analysis of clinical effectiveness. The lack of placebo-controlled prospective and blinded randomized clinical trials prevented us from making any recommendation on the use of platelets or platelet derived growth factor concentrates for treating osteoarthritis of the knee. The recommendation grade is not meant to establish a view of clinical efficacy.

We inserted the addendum that you suggested to the rationale section of recommendation 14. Thank you for your comments regarding recommendation 15.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

Strongly recommend

Recommend (with provisions or alterations)

X Would not recommend

Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Structured Peer Review Form

ALL REVIEW COMMENTS, RESPONSES AND REVIEWER CONFLICTS OF INTEREST DISCLSOURE WILL BE AVAILABLE ON OUR WEBSITE FOLLOWING APPROVAL OF THIS DOCUMENT.

Review of any AAOS confidential draft allows us to improve the overall guideline but does not imply endorsement by any given individual or any specialty society who participates in our review processes. The AAOS review process may result in changes to the documents; therefore, endorsement cannot occur until the AAOS Board of Directors officially approves the final guideline.

Please note that if you return a review:

- **Your review comments will be published on the AAOS website with our explanation of why we did or did not change the draft document in response to your comments.**
- **Your conflicts of interest disclosures will be published on the AAOS website with your review comments.**

Reviewer Information:

Name of Reviewer: Victoria Anne Brander MD

Address: 680 North Lake Shore Drive, Suite 924

City: Chicago State: IL Zip Code: 60611

Phone: 312-475-5566 Fax: ____ E-mail: vabrander@gmail.com

Specialty Area/Discipline: Physical Medicine and Rehabilitation

Work setting: clinical/academic Credentials: Associate Professor, PM & R Northwestern University Feinberg School of Medicine

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May we list you as a Peer Reviewer in the final Guidelines? X☐ Yes ☐ No

PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your review comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? **X**☐ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? X☐ Yes ☐ No

Society Name: Mid-America Orthopedic Association

(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

If the boxes below are not checked and/or the reviewer does not attach his/her conflicts of interest, the reviewer's comments will not be addressed by the AAOS nor will the reviewer's name or society be listed as a reviewer of this GL. If a committee reviews the guideline, only the chairperson or lead of the review must declare their relevant COI.

X☐ **I have declared my conflicts of interest on page 2 of this form.**

X☐ **I have declared my conflicts of interest in the AAOS database; my customer # is ____**

X☐ **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.**

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REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

Each item below requires an answer. Please report information for the last 12-months.

Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes X☐ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company: I serve on the Speakers Bureau of Sanofi	X☐ Yes ☐ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Speakers Bureau and consultant Sanofi Pharmaceuticals Consultant, Neurotech company	X☐ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Principal Investigator of a national, prospective randomized double blinded clinical trial of verapamil (Cal-20) in osteoarthritis of the knee. Company is Calosyn	X☐ Yes ☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes X☐ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication?	☐ Yes X☐ No

If YES, please identify:	
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify:	☐ Yes X☐ No

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Please complete and return this form electronically in **WORD format** to song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **November 2, 2012**.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	X☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	X☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	X☐
4. The guideline's target audience is clearly described	☐	☐	☐	X☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	X ☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	X ☐	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	X ☐	☐
8. All important studies that met the article inclusion criteria are included	☐	☐	X☐	☐
9. The validity of the studies is appropriately appraised	☐	X☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☐	X☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	X ☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	X ☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☐	X ☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	X ☐
15. The grades assigned to each recommendation are appropriate	☐	X☐	☐	☐

COMMENTS

PLEASE RETURN ALL COMMENTS IN WORD FORMAT

Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline

Recommendation 1:
" We recommend that patients with symptomatic osteoarthritis of the knee participate in self-management programs; engage in physical activity consistent with national guidelines; and participate in strengthening, neuromuscular education, and low-impact aerobic exercises."

Since specific physical interventions, like high resistance strength training, neuromuscular education, proprioceptive training, etc are strongly recommended, I would encourage this guideline to specifically recommend physical therapy as a way to develop the customized exercise programs described. Patients, particularly the elderly (many of whom also have significant comorbid disabling conditions), are often not able to independently develop their own exercise programs. These patients need the guidance of a physical therapist to establish a safe and effective program, and to teach them how to perform the exercises accurately and safely. Many older patients with arthritis will not exercise – they are "kinesthesiophobic" - afraid that they will hurt themselves or not convinced that they will feel better with exercise. The structured, individualized encouragement and guidance from a physical therapist is an important way to help patients achieve self-efficacy, move past their fears, and dedicated to exercise.

I strongly encourage the guideline to be modified to include a specific reference to physical therapy as an appropriate and encouraged method to achieve the outcome of exercise. Otherwise, health insurance providers will likely interpret this guideline as encouraging self-directed exercise only, and continue or accelerate restricting access to physical therapy. The unfortunate but real fact about self-directed exercise is that it fails because of poor patient compliance, often a consequence of fear, ignorance and lack of patient experience with exercise. Physical therapy enforces exercise compliance and enhances self-efficacy.

Recommendation 3B
"We suggest the use of Spa therapy (mud and pool sessions, showers, massage) and ultrasound therapy for functional improvement in patients with symptomatic osteoarthritis of the knee:"

My concern with this recommendation is that it is made on the basis of one study that exhibits numerous flaws. Secondly, from a practical, clinical perspective, the intervention of 18 days of passive therapies seems very unlikely to affect function 6 months later. When such a suspicious conclusion is reached, reviewers need to look at other trials confirming or repudiating the findings before offering such a strong recommendation. This recommendation might undermine the credibility of the entire guideline process. The spa therapy study looked at 18 days of spa treatments (mud baths etc) and then assessed outcome at 6 month followup. Spa treatments were done at multiple centers. There was no rigorous control of "usual care" treatments, no standardization of subjects for disease severity or other comorbidities, no standardization of the type, frequency or duration of treatment or of the frequency or intensity of home exercise. A higher standard was used, it would appear, when evaluating more widely recognized treatments, such as hyaluronic acid (HA). In a methodologically similar study, (Renauld), which is reviewed and reported in the guidelines, looked at the addition of hylan GF-20 injections to usual care programs following ACR guidelines in knee OA. This was also a multicenter study that looked at various pain and functional outcome scores. This study also documented clinical improvement in the group receiving treatment. Unlike spa therapy, high molecular weight HA injections have been the subject of

numerous clinical trials, mostly positive, and yet are not recommended by the guidelines. Is this inconsistency because different reviewers were responsible for different parts of the guidelines?

Therefore, because of the presence of data from only one study, and the numerous patient specific and uncontrolled variables which might influence the conclusions of this study, I suggest the recommendation should be neutral – cannot recommend for or against without further studies.

Recommendation 5
"We suggest foot orthotics not be used for patients with symptomatic osteoarthritis of the knee"

All of the studies described looked at lateral wedge insoles and compared them to neutral insoles. Lateral wedge insoles are primarily used for medial compartment knee osteoarthritis with varus malalignment. Many clinicians (including myself) do not prescribe lateral insoles for varus knees as these often encourage foot pronation and resultant pain, gait disturbances, hip problems etc. Therefore I think this recommendation is valid. However, what appears to be clinically much more effective and more relevant are MEDIAL wedges to reduce foot pronation in patients with the combination of VALGUS knees and pronated or flat feet. This was not addressed in the articles you reviewed. This is an important and clinically relevant distinction.

Therefore, I strongly encourage the recommendation to specify that there is a neutral (neither for nor against) recommendation regarding MEDIAL wedge insoles/orthotics in the case of valgus knees with foot pronation.

Recommendation 9.
"We recommend not using HA for patients with symptomatic OA knee"

I agree that the evidence presented does not support the use of lower molecular weight hyaluronic acid products for knee osteoarthritis, as there is limited data on clinically relevant improvement. However, studies consistently suggest significant, clinically relevant differences between high and low molecular weight hyaluronic acid drugs. The physiological effects of high molecular weight appear to make a difference in efficacy. Several investigators (Wang /Cochrane 2009, Reichenbach, Bannuru, and Rutkes) report that higher molecular weight cross linked single injection products carry higher effect sizes as opposed to non cross linked products.

The Draft Guidelines appear to agree with this concept (lines 2843-2860) "There was evidence to suggest that high molecular weight HAs were more effective than those with lower molecular weights. 8 or 12 pain outcomes significantly favored Hylan GH 20 (6 mi Da) over placebo. 9 of 12 statistically significant pain outcomes were of HAs of at least 2.4 mi Daltons. 5 of 6 placebo compared functional outcomes that compared HA of at least 2.4 mi Daltons to placebo were statistically significant in favor of treatment group. Also high MW HA accounted for the five of seven significant pain outcomes. One out of 8 stiffness outcomes, the only one that was statistically significant compared to placebo was for hylan G-F 20. Six of seven pain outcomes were statistically significant in favor of hylan GF 20 over HAs with molecular weight of .5-.75 Daltons. These treatments represented the highest and lowest HAs and the results suggest statistically and possibly clinically important differences in favor of Hylan GF20..."

Therefore, since evidence suggests that high MW HA (hylan GF20) offers more statistically significant and clinically relevant pain relief and function improvement, that there is a physiological and scientific rationale for differentiating high from low molecular weight agents, and that there is a large body of evidence suggesting that all of the HA products (low and high MW) offer some statistically significant (albeit not all clinically relevant)

improvement with very few adverse effects, it appears that recommending against the use, specifically, of high MW HA (hylan G-F20) is not justified. Instead, I strongly support maintaining the recommendation against the use of low molecular weight HA products for lack of clinical effectiveness, but adding a limited or inconclusive recommendation with respect to high molecular weight HA (hylan GF20).

Dear Dr. Brander.
Thank you for your expert review of this clinical practice guideline. We will respond to your comments in the order you presented them.

We reexamined the included studies of the conservative treatments evaluated as part of recommendation 1 and have clarified in the rationale section that the exercise interventions were predominantly conducted under supervision, most often by a physical therapist.

Recommendation 3 was revised to address physical agents in 3b and manual agents in 3c to make it consistent with our original intent. “Spa therapy” was not one of our search terms; and consequently, this treatment lacked a full systematic review. The Forestier et al. study initially appeared in our literature search because spa therapy resembled a term that we did include (balneotherapy; see Appendix V). However, a careful re-reading of the article found that the experimental group could not be accurately described as receiving balneotherapy so the study was excluded (please read the rationale section in the full guideline). Both revised recommendations 3b and 3c were graded as Inconclusive, which is consistent with your comments.

AAOS follows the standards of the Institute of Medicine for developing evidence-based clinical practice guidelines. The evaluation methods are described in the methods section of this guideline beginning on page 7 and in Appendix 6. The evidence evaluation process minimizes inconsistencies due to between-member variability.

Thank you for your suggestion to enhance recommendation 5. We appreciate your expert opinion; however it is not possible to add additional recommendations at this point in the guideline development process. After reviewing our evidence database, we added language to the existing recommendation that specifies *lateral* wedge insoles and *medial compartment* to distinguish anatomical location of knee osteoarthritis.

When we differentiated high- versus low- molecular weight viscosupplementation, our analyses did show that most of the statistically significant outcomes were associated with high-molecular cross linked hyaluronic acid but when compared to mid-range molecular weight, statistical significance was not maintained. Treatment comparisons between any weights greater than 750 kDa were not significantly different.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

☐ Strongly recommend

☒ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

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Reviewer Information:

Name of Reviewer: Andrew H. Schmidt, M.D.

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Specialty Area/Discipline: Orthopaedic trauma, Adult reconstruction

Work setting: Academic, teaching hospital Credentials: President elect, OTA; Professor, Univ. of Minnesota

---

May we list you as a Peer Reviewer in the final Guidelines? ☒ Yes ☐ No

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Are you reviewing this guideline as a representative of a professional society? ☒ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? ☒ Yes ☐ No

Society Name: Orthopaedic Trauma Association

(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

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Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Medtronic Inc, AGA	☒ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Conventus Orthopaedics, Anthem Orthopaedics VAN, Twin Star ECS.	☒ Yes ☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier: Conventus Orthopaedics, Anthem Orthopaedics VAN, Twin Star Medical, Twin Star ECS, Exos	☒ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher: Thieme, Inc.	☒ Yes ☐ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify: Journal of Orthopaedic Trauma, Journal of Knee Surgery	☒ Yes ☐ No

Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify: Orthopedic Trauma Association	☒ Yes ☐ No

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Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☒	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	☒
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	☒
4. The guideline's target audience is clearly described	☐	☐	☐	☒
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☒	☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	☒
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	☒
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	☒
9. The validity of the studies is appropriately appraised	☐	☐	☐	☒
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	☒
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	☒
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	☒
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☐	☒
14. The writing style is appropriate for health care professionals.	☐	☐	☒	☐
15. The grades assigned to each recommendation are appropriate	☐	☐	☒	☐

COMMENTS

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Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline

This is an unbelievably thorough and detailed guideline. The amount of work completed and summarized is almost beyond belief. The staff who prepared all of this data are to be congratulated, as is the Committee who sifted through a huge amount of information in order to produce this 1200 page document. I have some comments below that mostly get at the way that the information is conveyed. I have no reservations at all about the methodology used to produce this report, which seems to define the standard for how such work should be done.

1) Recommendation #1: What are the “national guidelines” that are referred to? This seems vague and undermines what is stated to be a “strong” recommendation.
2) Recommendation #3C: The phrase “practitioner might not use” seems awkward. There was Moderate quality evidence that these modalities did not provide any symptomatic relief. Why not just say that instead of the awkward phrase provided, which doesn’t convey any information? It seems the wording could be much more clear.
3) Recommendation 4: The phrase “valgus direction force brace” is also awkward and not how “unloader” braces are usually described. They are usually described as “valgus-producing” braces or an “unloader” brace. Please note that a valgus-producing brace would be specific to osteoarthritis of the knee with varus deformity. It would not apply to osteoarthritic knees with valgus deformity or neutral alignment. This recommendation needs to be clarified with respect to what type of osteoarthritic knee is being considered (all, those with varus deformity only, those with valgus deformity (in which a valgus-producing brace makes no sense at all).
4) Recommendation 5: Does the term “foot orthotics” refer to lateral heel wedges too? This is a fairly generic term. Specifically, lateral (or medial) heel wedges have been used for OA of the knee with varus (or valgus) malalignment. Cushioned inserts, arch supports, etc would also fall into this category. It would seem that the guidelines should be more specific about the type of orthotic.
5) Recommendation 6B: See item 2). Again, the use of “might” and “might not”, here in the same recommendation, seems odd.
6) Recommendation 9: A strong recommendation is given for not using viscosupplementation. The definition of strong when applied to a negative recommendation are that the “potential harm clearly exceeds the benefits”. That seems incorrect for something with essentially no risk (except that it might not work or work for very long), which had 14 studies that all showed statistically significant (although clinically minor) improvement. How could something that is extremely low risk and provides some small benefit be given a Strong recommendation not to use, especially when it is often the last alternative for patients aside from surgery, which has a much greater risk profile? This does not seem right. A strong recommendation not to use something should (as the definition states have a strongly negative profile (harmful, risky); this is minimal benefit, no risk, which does not meet the definition provided.
7) Recommendation 9 and 10: Taken together, these seem backwards. A strong recommendation is given against a commonly used and basically harmless modality (viscosupplementation), while an inconclusive, neutral recommendation is given for growth factors and PRP. These are much more expensive, potentially harmful, and unproven therapies. It seems they should have the negative recommendation (pending publication of evidence), while viscosupplementation should have the inconclusive or more neutral recommendation.
8) Recommendation 15: is “free-floating” and appropriate description. They are “un-fixed”, but not moving around freely. Why not just “un-fixed interpositional device”?

Dear Dr. Schmidt.
Thank you for your expert review of this clinical practice guideline. We will respond to your comments in the order you presented them.

A number of fitness-related organizations have disseminated guidelines for physical activity. They generally emphasize the importance of aerobic conditioning and muscle- and bone- strengthening, regular activity, and balance exercises for older adults. In 2008, the federal government for the first time published national guidelines. Here is the link to the U.S. Department of Health and Human Service's physical activity guidelines: DHHS guidelines 2008.

At the inception of the AAOS guideline development process, predetermined language stems were established so that all *limited* recommendations (formerly called "*weak*") begin with the phrase, "the practitioner might" (or "might not"). Recommendation 3 has been modified to address physical agents in 3b and manual agents in 3c. Because the strengths of the evidence had to be re-categorized as "Inconclusive" to reflect the resulting high degree of variability (please read the rationale section in the full guideline), your concern for this particular recommendation has been resolved.

After reexamining the included studies we inserted "medial compartment unloader" in recommendation 4 to specify anatomical location. We also revised recommendation 5 to specify "lateral wedge insoles" and inserted *medial compartment*. The clarifications were consistent with our evidence database.

Recommendation 6 was revised so that instead of saying "we recommend not using" it now reads "we cannot recommend using." We hope this amending will be less awkward and better understood.

The recommendation grade *Strong* corresponds to empirical evidence comprised of at least two high-strength studies (see Table 6), and is not related to safety risk. For recommendation 9, there were three high- and 11 moderate- strength studies that did not show minimum clinically important improvements to patients treated with viscosupplementation. We hope you have found our clarification sufficient.

The 14 studies failing to endorse hyaluronic acid (recommendation 9) adhered to principles of research design, and the three addressing growth factor and platelet rich injections (recommendation 10) did not control for platelet volume nor did they represent the knee osteoarthritis patient population appropriately due to their design flaws. The strong versus inconclusive evidence strengths of the recommendations referred to methodology not to clinical efficacy of the treatments.

We added "unfixed" in parentheses before "interpositional device" in recommendation 15 as you suggested.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

☐ Strongly recommend

☒ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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Reviewer Information:

Name of Reviewer: Paul Jude Duwelius, MD

Address: 16925 Scott Court

City: Lake Oswego State: Or Zip Code: 97034

Phone: 503-730-8080 Fax: _____ E-mail: paul.duwelius@ofc-oregon.com

Specialty Area/Discipline: Adult Reconstruction/Trauma

Work setting: Private Practice Credentials: MD

May we list you as a Peer Reviewer in the final Guidelines? x☐ Yes ☐ No

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Are you reviewing this guideline as a representative of a professional society? **x**☐ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? y☐ Yes ☐ No

Society Name: OTA

(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

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y☐ **I have declared my conflicts of interest in the AAOS database; my customer # is** AAOS:16686

y☐ **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.**

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Structured Peer Review Form

REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

Each item below requires an answer. Please report information for the last 12-months.

Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes ☐ No
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Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes ☐ No
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Please complete and return this form electronically in **WORD format** to song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **November 2, 2012**.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	x☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	x☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	x ☐
4. The guideline's target audience is clearly described	☐	☐	☐	x☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	x ☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	x☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	x☐
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	x☐
9. The validity of the studies is appropriately appraised	☐	☐	☐	x☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	x☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	x ☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	x☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	x☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	x ☐
15. The grades assigned to each recommendation are appropriate	☐	☐	☐	x ☐

COMMENTS

PLEASE RETURN ALL COMMENTS IN WORD FORMAT

Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline

This was an extensive review on the treatment of knee arthritis. I congratulate this committee. I have no negative comments. The literature review and peer review process was extensive. The extent that bias was eliminated was impressive. This is an outstanding contribution from the AAOS to help the practitioner and patients sort through what is relevant in the treatment of osteoarthritis of the knee. I would definitely have a shortened version as this is somewhat onerous to review in present fashion.

Dear Dr. Duwelius.
Thank you for your expert review of this clinical practice guideline. There is a separate executive summary of only the recommendations that will accompany the full document. An editorial and appropriate use criteria will also be developed following the approval and publication of the full guideline.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

☒ Strongly recommend

☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
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ALL REVIEW COMMENTS, RESPONSES AND REVIEWER CONFLICTS OF INTEREST DISCLSOURE WILL BE AVAILABLE ON OUR WEBSITE FOLLOWING APPROVAL OF THIS DOCUMENT.

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Reviewer Information:

Name of Reviewer: Matthew Matava, M.D.

Address: 14532 S. Outer Forty Dr.

City: Chesterfield State: MO Zip Code: 63017

Phone: 314-514-3569 Fax: 314-514-3689 E-mail: matavam@wudosis.wustl.edu

Specialty Area/Discipline: Sports Medicine

Work setting: Full-time Academic Credentials: M.D.

May we list you as a Peer Reviewer in the final Guidelines? X☐ Yes ☐ No

PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your review comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? X☐ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? X☐ Yes ☐ No

Society Name: Southern Orthopedic Association

(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

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REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

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Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: ISTO Technologies; Schwartz Biomedical	**X**☐ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes **X**☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes **X**☐ No
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Please complete and return this form electronically in **WORD format** to song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **November 2, 2012**.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	X☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	X☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	X ☐
4. The guideline's target audience is clearly described	☐	☐	☐	X☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	X☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	X☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	X☐
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	X☐
9. The validity of the studies is appropriately appraised	☐	☐	☐	X ☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	X ☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	X☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	X☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	X☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	X☐
15. The grades assigned to each recommendation are appropriate	☐	☐	☐	X☐

COMMENTS

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Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline

This is an extremely thorough review of the non-arthroplasty treatment options commonly utilized for osteoarthritis of the knee. I was often unclear as to the rationale for the allocation of a grade to a specific recommendation. However, in reviewing the statistical methods used to develop a specific grade, I can now say that each grade appears appropriate given the often limited data dealing with a specific treatment intervention. I think that orthopedists who read these AAOS-sponsored guidelines frequently do not agree with a specific grade based on their clinical experience. Perhaps further explanation of the rationale for each grade would be helpful in explaining the apparent conflict between the surgeons' clinical experience and the AAOS' recommendations.

Dear Dr. Matava,
Thank you for your expert review of this clinical practice guideline. We are pleased that our evidence grading system is clear. Your comments underscore the need for the AAOS to provide additional education on the evidence-based medicine guideline development process and appropriate interpretation of the levels of evidence. Summary statements describing implications for clinical practice following each of the recommendation strengths were recently added (see Table 6). We hope they provide further explanation of the standards that guide the determination of each grade.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

X☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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Reviewer Information:

Name of Reviewer: Jeffrey M. Nakano

Address: 627 251/2 Road

City: Grand Junction, CO State:Colorado Zip Code: 81505

Phone: 970-242-3535 Fax: 970-255-6670 E-mail: jnakano@rmodocs.com

Specialty Area/Discipline: Trauma and Total Joint Arthroplasty

Work setting: Private Single Specialty Credentials: MD

May we list you as a Peer Reviewer in the final Guidelines? + Yes ☐ No

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Are you reviewing this guideline as a representative of a professional society? + Yes No

If yes, may we list your society as a reviewer of this guideline? + Yes ☐ No

Society Name: Western Orthopaedic Association

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	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	X	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	X	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	X	☐
4. The guideline's target audience is clearly described	☐	☐	☐	X
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	X
6. The criteria used to select articles for inclusion are appropriate	☐	☐	X	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	X
8. All important studies that met the article inclusion criteria are included	☐	☐	X	☐
9. The validity of the studies is appropriately appraised	☐	☐	☐	X
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	X
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	X
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	X	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	X	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	X
15. The grades assigned to each recommendation are appropriate	☐	☐	X	☐

COMMENTS

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Paul Collins, MD and Jeffrey M. Nakano, MD reviewed the CPG: "Treatment of Osteoarthritis of the Knee" as representatives of the Western Orthopaedic Association. We consider ourselves to be general orthopedic surgeons and feel that we are representative of the large majority of orthopaedic surgeons who will be utilizing these guidelines. Dr. Nakano is a member of the AAHKS.
Overall we feel this review and commentary program is excellent. Here are our comments on each topic.

1. **Recommendation 1**
   We agree with this recommendation about osteoarthritis of the knee and the recommendations. The clinical assistance will be excellent.

   I (Nakano) am not sure if the omission of the term physical therapy from the recommendation was intentional or not. Several of the articles seemed to involve physical therapy (physiotherapy, center based physical therapy - these terms are all used and are confusing, there is an implication that they mean different things.). With the recent MAC audits, preoperative physical therapy is one of the criterion used to determine whether a patient is a surgical candidate. It would be helpful to have the specific term" physical therapy" in the recommendation, either "for" or "against."

2. **Recommendation 2**
   We agree with this recommendation.

   I (Collins) must say I would make this recommendation strong. I understand how the limited investigational results may make this recommendation moderate, however, I am disappointed that even this upgrade was difficult. It certainly suggests more studies of high quality.

3. **Recommendation 3A**
   We agree that the recommendation against the use of acupuncture is strong, however, clinically this is a difficult issue. The risk of infection from an injection (it after all is an injection!) should be emphasized. That said, in our experience the public use/acceptance of this procedure suggests that while the lack of there being clinical evidence for use, the psychological issue associated with the procedure should be further investigated. Perhaps with this strong recommendation against this procedure, further studies should be suggested.

4. **Recommendation 3B**
   We agree with this recommendation for a moderate level.

5. **Recommendation 3C**
   We agree with this recommendation as limited, however, we are surprised that there is any support.

6. **Recommendation 3D**
   We agree with this recommendation as inconclusive.

7. **Recommendation 4**
   We agree with this recommendation as inconclusive.

8. **Recommendation 5**
   We agree with this recommendation as moderate against orthotics for symptomatic OA of the knee.

9. **Recommendation 6**
   I (Collins) am surprised at the opinion about this recommendation, and would feel that at best it would be inconclusive.

   (Nakano)Why is there no mention of MSM? This is more common in the lay population as a treatment for DJD than ginger.

10. **Recommendation 6B**
    Given the recommendation 6, this is also surprising. I (Collins) would at best feel this is inconclusive.

11. **Recommendation 7A**
    We agree with this recommendation.

12. **Recommendation 7B**
    Overall we agree with this recommendation.

13. **Recommendation 8**
    We agree with this overall recommendation.

14. **Recommendation 9**
    We agree with this overall recommendation.

    I (Nakano) should preface the following discussion with the statement that I agree with the strong recommendation for not using hyaluronic acid

    However, this would seem to fly in the face of 1. common clinical practice, 2. the approval of this category of drugs by the FDA, and 3. advertisements in JBJS. While the MAC audits may not specifically mention viscosupplementation, they do use the lack of previous cortisone shots as a possible cause for denial of payments. In addition, patients often ask about this modality ("doctor, what about the chicken comb injection").

    The main basis for the recommendation against using hyaluronic acid seems to be the inability to meet the MCII thresholds. As a general orthopedic surgeon, the concept of MCII is understandable, but the technical explanation offered in the guidelines is difficult to follow. Other general orthopedic surgeons may have this same problem and as a result, question the recommendation of the CPG. Perhaps the methodology to determine MCII could be clearer.

15. **Recommendation 10**
    We agree with this overall recommendation.

16. **Recommendation 11**
    We agree with this recommendation, but would change this to “recommend”, not “suggest”.

17. **Recommendation 12**
    We agree with this recommendation.

18. **Recommendation 13**
    Overall we agree with this inconclusive recommendation.

19. **Recommendation 14**
    We agree with this recommendation.

20. **Recommendation 15**
    We agree with this recommendation.

(Nakano) Why were articles prior to 1966 excluded? The answer is probably obvious, but does not appear to be stated.

(Nakano) Line #545: "excluded" should be bolded?

Dear Drs. Nakano and Collins.
Thank you for your expert review of this clinical practice guideline. We will respond to your comments in the order you presented them.

We reexamined the included studies of the conservative treatments evaluated as part of recommendation 1 and have clarified in the rationale section that exercise interventions were predominantly conducted under supervision, most often by a physical therapist.

While your suggestion to recommend further study into the high volume use of acupuncture is well received, we are no longer at the phase in the guideline development process where new recommendations are considered. The section on directions for future research is where gaps in the literature identified by our systematic review are typically discussed. Additionally, the original guidance was to evaluate the evidence of treatment options for osteoarthritis of the knee, which is why risk of infection and psychological benefits of using acupuncture were not addressed.

Recommendation 3 has been modified to address physical agents in 3b and manual agents in 3c. Because the strengths of the evidence had to be re-categorized to reflect the high degree of variability in the regrouped treatment modalities (please read the rationale section in the full guideline), your concern about recommendation strength has been resolved.

Recommendation 6 has been modified to address only glucosamine and chondroitin. The recommendation grade *Strong* corresponds to empirical evidence that is comprised of at least two high-strength studies. Twenty-one studies were included as evidence for this recommendation; all were prospective. A grade of *Strong* referred to degree of adherence to proper methodology, and not clinical efficacy of treatment.

The original guidance was to evaluate methylsulfonylmethane (MSM), omega-3, gelatin, vitamin D, dimethylsulfoxide, antioxidants, and coenzyme Q10. We were unable to recommend for or against MSM due to the lack of studies examining it. Similarly, no studies evaluating omega-3, gelatin, vitamin D, dimethylsulfoxide, antioxidants, and coenzyme Q10 were found that met our inclusion criteria.

We added a table and text addressing the MCII that helps to explain its application in the AAOS guideline development process. The preponderance of the evidence for recommendation 9, three high- and 11 moderate- strength studies, did not meet the minimum clinically important improvement (MCII) threshold in patients treated with viscosupplementation.

The language stem *we suggest* is required for recommendations that have a moderate grade of evidence strength. Use of *we recommend* is only appropriate when the strength of the evidence is strong (i.e. high quality and no lower than moderate applicability). At the inception of the AAOS guideline development process, predetermined language stems were established independent of the content of recommendations to minimize potential bias of individual opinion and of views that might exert influence on the final recommendations after the evidence analysis is reviewed.

The selection criteria to include articles published after 1966 has existed in all the AAOS evidence-based clinical practice guidelines. The Library of Congress first began numerically tracking written materials after 1965 using the ISBN system. Many scientific journals cannot provide access to archived issues that were published prior to 1966.

Finally we changed “excluded” in line 545 to bold face.

Respectfully,
2012 OA of the Knee Work Group

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (Check one)

X Strongly recommend

☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Structured Peer Review Form

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Reviewer Information:

Name of Reviewer: Paul Collins MD

Address: 613 West Sandstone Court

City: Boise State:Idaho Zip Code: 83702

Phone: 208-861-8257 Fax: _____ E-mail: collins04@cableone.net

Specialty Area/Discipline: General Orthopaedics

Work setting: Office Credentials: MD

May we list you as a Peer Reviewer in the final Guidelines? + Yes ☐ No

PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your review comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? + Yes No

If yes, may we list your society as a reviewer of this guideline? + Yes ☐ No

Society Name: Western Orthopaedic Association

(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

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+**I have declared my conflicts of interest in the AAOS database; my customer # is** 020529

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REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

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Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes + No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes + No
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Please complete and return this form electronically in **WORD format** to song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **November 2, 2012**.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

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10. The methods are described in such a way as to be reproducible.	☐	☐	☐	X
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	X
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14. The writing style is appropriate for health care professionals.	☐	☐	☐	X
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Phone: 208-861-8257 Fax: _____ E-mail: collins04@cableone.net

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Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes + No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes + No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes + No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes + No
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6. The criteria used to select articles for inclusion are appropriate	☐	☐	X	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	X
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9. The validity of the studies is appropriately appraised	☐	☐	☐	X
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	X
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	X
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	X	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	X	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	X
15. The grades assigned to each recommendation are appropriate	☐	☐	X	☐

COMMENTS

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2012 OA of the Knee Work Group

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American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Public Comment Review Form

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Reviewer Information:

Name of Reviewer – William Beach, MD

Address – PO Box 71690

City- Henrico State - VA Zip Code - 23255

Phone - 804-285-2300 Fax _____E-mail - beach@orv.com
Specialty Area/Discipline: sports medicine/arthroscopy

Work setting: private practice Credentials: 2nd VP AANA, member of the AAOS CCR Committee

---

May we list you as a Peer Reviewer in the final Guidelines (GL)? X☐ Yes ☐ No
PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your public comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? **X**☐ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? X☐ Yes ☐ No

Society Name: Arthroscopy Association of North America
(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

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X☐ **I have declared my conflicts of interest in the AAOS database; my customer # is 0027975**

☐ **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.**

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Please complete and return this form electronically in **WORD format** to Song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **March 8, 2013.**

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	X☐	☐	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	X☐	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	X ☐	☐
4. The guideline's target audience is clearly described	☐	☐	X ☐	☐
5. The patients to whom this guideline is meant to apply are specifically described	X☐	☐	☐	☐
6. The criteria used to select articles for inclusion are appropriate	X☐	☐	☐	☐
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8. All important studies that met the article inclusion criteria are included	☐	X ☐	☐	☐
9. The validity of the studies is appropriately appraised	X☐	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	X☐	☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	X☐	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	X☐	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	X☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	X☐
15. The grades assigned to each recommendation are appropriate	X☐	☐	☐	☐

COMMENTS

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This Draft Clinical Practice Guideline has already completed peer review and has been reviewed by content experts. The feedback provided during this process is attached in the PDF. If you have any other brief additional comments, please feel free to provide them here. If applicable, please specify the draft page and line numbers in your comments.

American Academy of Orthopaedic Surgeons (AAOS)

The Arthroscopy Association of North America (AANA) and its 3651 members appreciate the opportunity to comment on the newest AAOS guideline on "***Treatment of Osteoarthritis of the Knee (Non-arthroplasty).***"

We would like to initiate discussion regarding our concerns over the AAOS CPG philosophy and process and specifically Recommendations 9 and Recommendation 13.

Philosophically, AANA has concerns regarding the AAOS commitment to CPG creation. The AAOS CPG "program" has created a very limited number/percentage of the recommendations that have a conclusion, " the evidence analysis accompanying each CPG has uncovered the paucity of high quality evidence supporting orthopedic practice; only 46% of all guideline recommendations have a strong, moderate or weak strength." "Future Directions in Evidence-Based Guideline Development" by Michael J. Goldberg, MD at the Spring 2012 Orthopaedic Quality Institute. The paucity of high-level data is illustrated by each of the CPG's the AAOS has released. The "OPTIMIZING THE MANAGEMENT OF ROTATOR CUFF PROBLEMS" and "TREATMENT OF OSTEOARTHRITIS OF THE KNEE (NON-ARTHROPLASTY)" have highlighted AANA's experience with the CPG process. Each of these CPG's have created significant "fall-out" for our association and our membership. The paucity of definitive recommendations jeopardizes the goals/missions of the CPG process: the improvement and standardization of patient care. Unfortunately, the AAOS CPG's have not improved patient care but have introduced significant risks. These risk include but are not limited to coverage and reimbursement, access to care and disparity of standards of care with the newly created CPG's. With these concerns, AANA proposes that the AAOS Board of Directors require the simultaneous release of Appropriate Use Criterion with the release of all new CPG's.

AANA is concerned that the CPG process as currently defined is inherently biased against surgical procedures. This is evidenced by the relative wealth of high-level evidence concerning non-operative modalities in the CPG and the paucity of similar level evidence for non-arthroplasty surgical procedures. For example, the one high level study cited regarding arthroscopy, Herrlin et al., contains a serious selection bias forcing a downgrading of the level of evidence. The recruitment, cost and ethical problems of level one studies in surgical patients are well documented and illustrated by this study. The relative ease of recruiting and

maintaining a level 1 study for non-operative treatments compared to surgical ones presents a significant bias. Since bias is a paramount concern in the CPG process, we believe that the AAOS needs to take this into consideration when formulating CPG' both now and in the future.

Specific to the Proposed 2013 CPG, "TREATMENT OF OSTEOARTHRITIS OF THE KNEE (NON-ARTHROPLASTY)" AANA has concerns with Recommendations 9 and 13.

RECOMMENDATION 9

We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee.
Strength of Recommendation: Strong

Description: A **Strong** recommendation means that the benefits of the recommended approach clearly exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a strong negative recommendation), and/or that the quality of the supporting evidence is high.
Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

- **Study Selection:**
  - The selection process failed to account for product differences – dosing schedule, dose size, formulation, concentration, source material, etc. The studies utilized several different HA products yet were treated as if they were all the same.
  - Two studies included were on products that are not approved for use in the US.

- **Study Results:**
  - Only two studies, Huang and Maheu (1,2), have been published since the last review. Both concluded that HA improved function and relieved pain. This begs the question, what new evidence is there to change the 2009 recommendation?
  - The AAOS analysis concluded *"...WOMAC pain, function and stiffness subscales scores all found statistically significant treatment effects..."* Based on this outcome overall, there does not seem to be justification to change a neutral recommendation to a negative. At worst, this conclusion should lead to the same neutral recommendation that was reached in 2009.

- **Control:**
  - Saline is not a placebo but rather an active control due to the lavage/dilution effect - however HA was still statistically significantly superior in every one of the four analyses AAOS reviewed. WOMAC pain, VAS weight bearing pain, function, WOMAC stiffness.
  - In the real world, patients feel the difference from baseline, not from active control.

- **Patient Inclusion:**

- Kellgren-Lawrence grade I-IV patients were included in the studies reviewed as part of the meta-analysis. That is not a homogeneous patient population.
- It is widely recognized that some patients are responders and others are not. These are difficult to pre-identify. Inclusion of both in clinical trials can result in a small mean change although many individual patients are helped significantly.

- **MCII Effectiveness Measure**
  - The MCII may help standardize the review process however there is no apparent correlation to the treatment of real world patients in a clinical setting. The MCII lens therefore may not be the best tool for developing clinical practice guidelines
  - We believe that MCII was not applied correctly. The measurement of MCII should be from baseline, not from the active, saline control. (Please see attached explanation of this argument)

- Please note some unique facts regarding HA treatment vs. other treatments/technologies reviewed:

- HA products are approved by FDA as class III medical devices. This requires proof of efficacy and safety demonstrated in randomized controlled trials.
  - Many other therapies reviewed have not successfully gone through this rigorous process
- HA products are indicated for the treatment of pain
  - They are not indicated for functional improvement or stiffness yet they were superior to saline in these two categories as well.

- HA products have a stellar safety record
  - Adverse events are mild and transitory

Recommended Treatment Alternatives

AAOS reviewed 15 treatments for OA. Only 4 of these were recommended. They were exercise, weight loss, proximal tibial osteotomy and NSAIDS.

- **Exercise:** Although exercise has many benefits, the challenge for the treating physician is in getting patient compliance. The pain of OA makes it that much more difficult for patients to engage in exercise.

- **Weight Loss:** Weight loss usually requires life style changes that many patients have difficulty achieving. OA pain experienced during and post activity make weight loss and exercise very challenging.

- **Proximal Tibial Osteotomy**: This may benefit only a subset of patients. Also, this requires patients to be good candidates for surgery, which is not always the case,

and the treatment carries all the inherent risks of anesthesia and a surgical procedure.

- **NSAIDs:** The safety risks of NSAIDs are well documented. Quote from New England Journal of Medicine (1999): *"It has been estimated conservatively that 16,500 NSAID-related deaths occur among patients with rheumatoid arthritis or osteoarthritis every year in the United States. This figure is similar to the number of deaths from the acquired immunodeficiency syndrome and considerably greater than the number of deaths from multiple myeloma, asthma, cervical cancer, or Hodgkin's disease. If deaths from gastrointestinal toxic effects from NSAIDs were tabulated separately in the National Vital Statistics reports, these effects would constitute the 15th most common cause of death in the United States. Yet these toxic effects remain mainly a "silent epidemic," with many physicians and most patients unaware of the magnitude of the problem. Furthermore the mortality statistics do not include deaths ascribed to the use of over-the-counter NSAIDS."*

MCII Effectiveness Measure Application

The AAOS has chosen to apply minimum clinically important improvement (MCII) criteria to their measurement of the treatment effects of hyaluronic acid. In their draft guideline document they state, *"Analysis of statistical significance is limited without consideration of clinical importance to patients. Whenever the data was available, we identified minimum clinically important improvement (MCII) treatment effects in addition to statistical significance.* ***The MCII reflects the smallest clinical change that is important to patients*** *and recognizes that there are some treatment-related statistically significant improvements that are too small to matter."*

Angst et. al. developed an algorithm for measuring the minimum clinically important difference of conservative OA treatments against baseline and provided standards for measurement that AAOS has utilized in their analysis of HA therapy. However, in our opinion AAOS applied the standard incorrectly. Here is why:

AAOS used the standards to measure the treatment effect delta between patients who received saline and patients who received HA treatment. We believe that the standard was developed for, and should have been applied, to the baseline (pre-treatment) vs. the patients who received HA treatment. This would have produced a much different result.

Our argument is based on the treatment effect of saline, which we contend is an active treatment, not a "placebo" or "sham" as it is often referred to. Our understanding is that AAOS believed it was adjusting for "placebo effect" when they chose to measure MCII as they did, however we contend that there is a true therapeutic benefit to saline that is not recognized when it is used as a control in clinical trials.

Because AAOS intended to measure the smallest clinical improvement that is important to patients, we contend that AAOS should repeat their analysis-measuring baseline to HA treatment.

1. Huang TL, Chang CC, Lee CH, Chen SC, Lai CH, Tsai CL. Intra-articular injections of sodium hyaluronate (Hyalgan(R)) in osteoarthritis of the knee. a randomized, controlled, double blind, multicenter trial in the asian population. BMC Musculoskelet Disord 2011;12):221.
2. Maheu E, Zaim M, Appelboom T et al. Comparative efficacy and safety of two different molecular weight (MW) hyaluronans F60027 and Hylan G-F20 in symptomatic osteoarthritis of the knee (KOA). Results of a non inferiority, prospective, randomized, controlled trial. Clin Exp Rheumatol 2011;29(3):527-535

RECOMMENDATION 13 (2013)
We are unable to recommend for or against arthroscopic partial meniscectomy or loose body removal in patients with osteoarthritis of the knee and mechanical symptoms consistent with a torn meniscus and/or a loose body.
Strength of Recommendation: Inconclusive
Description: An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.
Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

First and most importantly, AANA recognizes that the entirety of this recommendation is based on one peer reviewed, randomized clinical trial, Herrlin et. al. Yet, the "BEST EVIDENCE SYNTHESIS" of the "TREATMENT OF OSTEOARTHRITIS OF THE KNEE (NON-ARTHROPLASTY)"states, "We included only the best available evidence for each outcome in every recommendation. We first examined the highest quality evidence that was available. If there were not two or more findings at the highest rating, we considered outcomes of the next highest strength until at least two or more consistent findings were produced. For example, if there were two "moderate" strength studies evaluating a recommendation then we did not incorporate "low" graded findings."

The use of Herrlin et. al. alone violates the evidence rules for this CPG. AANA, in the strongest language available, suggests the following options for Recommendation 13 of the 2013 OA CPG:

1. Recommendation 13 reverts to recommendation 19 of the 2008 OA CPG.
2. Recommendation 13 is deleted from the 2013 OA CPG.
3. Recommendation 13 is returned to the 2013 OA CPG work group for further refinement and modification.

In the remote possibility that the AAOS could suggest any other approach, AANA has prepared

a review of the Herrlin et al. article.

We have additional concerns regarding the wording of recommendation 13 in light of the fact that the Herrlin article is cited as the justification for the change in recommendation 19 in the 2008 guidelines. The Herrlin article excludes patients with a history of trauma and those with loose bodies. How then is recommendation 13 worded as to be all inclusive of patients with osteoarthritis? Why is loose body included when Herrlin specifically excludes patients with loose bodies? AANA contends that the inclusion of an article that excludes patients with the condition (loose bodies) and then draws conclusions regarding the excluded patients (recommendation 13) is well below the standard of evidence the AAOS has set for itself in the creation of CPG's and any AAOS scientific work. AANA is frankly disappointed in the inclusion of Herrlin et al., for this recommendation.

We believe including the Herrlin article violates the selection criteria for the inclusion of level 1 studies. The guidelines state, "To be included an article had to meet the following selection criteria: 1) Study was of osteoarthritis of the knee 2) Study reported on 80% of the patient population of interest". The population of interest this in this study included 180 patients with osteoarthritis. Only 99 of patients agreed to be randomized and included in the study (55%). The study should be eliminated based on the selection criteria.

Herrlin et al, states "preoperatively all the KOOS scores of the AE-group were numerically lower than the E-group. The differences were 11 and 10 points for ADL and Sport/Recreation, respectively. Despite this fact no statistical differences between the groups at the start in KOOS regarding ADL and Sport/Recreation were found." What is the statistical chance that 47 patients in the arthroscopy group will have a KOOS score lower than the 43 patients in the exercise group?! This is almost impossible from a statistical standpoint. The chances that could occur as a random event is 47 factorial ? (258623241511168180642964355153611979969197632389120000000000). Not very likely! SELECTION BIAS?

Herrlin, et al. was published in January of 2007. This is well before the first guidelines were published in 2008. The 2008 CPG "APPENDIX IV LITERATURE SEARCHES FOR SYSTEMATIC REVIEWS" states: "search for eligible literature began with a search for applicable systematic reviews. The search for systematic reviews was performed using the following databases. The full search strategies are displayed below:

PubMed (from 1966 through February 22, 2008)

The Cochrane Database of Systematic Reviews (through February 22, 2008)

All literature searches were supplemented with manual screening of bibliographies in publications accepted for inclusion into the evidence base. In addition, the bibliographies of recent review articles were searched for potentially relevant citations.

The search for systematic reviews using PubMed included the follow search strategy, with limits of publication dates 1966 to present, English language and humans:

("knee"[MeSH Terms] OR knee[Text Word]) AND ("osteoarthritis"[MeSH Terms] OR osteoarthritis[Text Word]) AND "humans"[MeSH Terms] AND English[lang] AND systematic[sb]

Our search for systematic reviews using the Cochrane Database of Systematic Reviews in Cochrane Reviews included the following search strategy:

knee osteoarthritis AND (knee AND osteoarthritis)

Our initial search of PubMed and the Cochrane Database yielded 278 systematic reviews, of which 48 were retrieved and evaluated. Seven systematic reviews met all inclusion criteria."

AANA would like to inquire why this study was not included in the first CPG on knee osteoarthritis. Was it not identified in 2008? Was it identified and dismissed because of the obvious study flaws? Or was it dismissed because the patients addressed in this study are fundamentally different than the patients referred to in recommendation 19 (2008) ? AANA strongly agrees with your contention of 2008, "No studies investigating the use of arthroscopic partial meniscectomy and/or loose body removal in patients with a primary diagnosis of a torn meniscus and/or intra-articular loose body and secondary OA of the knee were identified by our systematic literature searches." Herrlin et al., did not and does not apply to this group of patients.

Ambiguously or improperly worded recommendations will be used by third party payers to limit access to care; this concern is not theoretical. Even guidelines that appear to be fairly clear are at risk for misinterpretation. In 2012 the New York State Medicaid Redesign taskforce used the 2008 knee arthritis CPG as justification for not covering knee arthroscopy in patients with a diagnosis of osteoarthritis. Specifically the NY MRT stated, "Many patients with joint space narrowing are older with multiple medical comorbidities. Such patients are more prone to complications and, *consistent with the recommendations of the AAOS, there is no proven clinical benefit to arthroscopy of the knee for osteoarthritis (in the absence of mechanical destruction of the knee joint).*(Italics added) The AAOS quickly and correctly replied to this mischaracterization of the guidelines with a letter from John Tongue MD, president of the AAOS, with input from AANA members. He stated: "We recommend the Redesign Team immediately revise recommendation C-2 of the Basic Benefit Review Workgroup to exactly mirror the AAOS Guideline and only apply arthroscopic debridement and lavage of the knee when the primary diagnosis is symptomatic OA of the knee. We strongly encourage the Redesign Team to allow coverage of other arthroscopic treatments of OA of the knee including partial meniscectomy or loose body removal when there are signs or symptoms of a torn meniscus or loose body." The NYS MRT overturned their non-coverage decision that would have limited access to important healthcare services to a vulnerable population based on this letter.

AANA's concern is that New York State will; 1) reinstate its previous non-coverage

decision because the AAOS has changed its recommendation from "is an option" to "unable to recommend for or against" and 2) New York State has spent hundreds of thousands of dollars since the reversal of the non-coverage decision based on information that was available to the AAOS prior to the 2008 CPG. The NY MRT would have to wonder why there has been a change in the AAOS's recommendation based on a single article that was available in 2007, prior to the 2008 CPG. Will our next effort to defend the ability of symptomatic arthritic New York Medicaid patients to have access to arthroscopic services be as effective with the currently worded guideline number 13?

Besides the selection bias and inclusion criteria issues with Herrlin, we call to attention the additional potential power problem. Also, 9 (almost 10%) out of the 99 patients recruited into the study dropped out; 3 because they wanted an arthroscopy and 6 because they felt improved and did not want to continue in the study. We assume the 3 who wanted surgery were in the exercise arm of the study but no mention is made of which group any of these patients came from. This also clouds the result and strength of the paper.

In conclusion, AANA would like the AAOS to reconsider the wording and strength of recommendation 13 based upon our concerns noted above. We believe that using one article to change a guideline violates the CPG process rules and that the article employed is sufficiently flawed to prohibit a change in the recommendation. AANA requests that recommendation 9 be returned to the OA CPG work group for reconsideration based on concerns of methodology and the strength of the recommendation. On a larger scale, the AAOS must be sensitive to the needs of its members. CPG's must have an AUC released contemporaneously otherwise we will continue to waste valuable time and effort, risking losing our cohesion in a time when external pressures require absolute solidarity.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
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ALL REVIEW COMMENTS, OUR RESPONSES AND REVIEWER COI WILL BE AVAILABLE FOR REVIEW ON OUR WEBSITE FOLLOWING BOD APPROVAL OF THIS DOCUMENT.

Review of any AAOS confidential draft allows us to improve the overall guideline but does not imply endorsement by any given individual or any specialty society who participates in our review processes. The AAOS review process may result in changes to the documents; therefore, endorsement cannot occur until the AAOS Board of Directors officially approves the final guideline.

Please note that if you return a review:

- **Your comments will be published on the AAOS website with our explanation of why we did nor did not change the draft document in response to your comments.**
- **Your conflicts of interest will be published on the AAOS website with your review.**

Reviewer Information:

Name of Reviewer___Thomas Trojian, MD_____

Address_99 Woodland Street_____

City__Hartford_____ State___CT_____ Zip Code____06105_____

Phone _860-714-4577_____Fax __860-714-8080_____E-mail____ttrojian@uchc.edu_____

Specialty Area/Discipline: __Sports Medicine_____

Work setting: Orthopaedic/Team Physician Credentials: _CAQ SM, Osteoarthritis Action Alliance, Arthritis Health Disparity Committee_

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☒ Yes ☐ No
PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your public comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? ☒ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? ☒ Yes ☐ No

Society Name: _American Medical Society for Sports Medicine_____
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Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

If the boxes below are not checked and/or the reviewer does not attach his/her conflicts of interest, the reviewer's comments will not be addressed by the AAOS nor will the reviewer's name or society be listed as a reviewer of this GL. If a committee reviews the guideline, only the chairperson/or lead of the review must declare their relevant COI.

☒ **I have declared my conflicts of interest on page 2 of this form.**

☐ **I have declared my conflicts of interest in the AAOS database; my customer # is** _____

☒ **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.**

REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

Each item below requires an answer. Please report information for the last 12-months as required by the Accreditation Council for Continuing Medical Education (ACCME) guidelines.

Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes ☒ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company:	☐ Yes ☒ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes ☒ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify: Section Editor of Current Sports Medicine Reports and Associate Editor for CJSM	☒ Yes ☐ No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify: AMSSM	☒ Yes ☐ No

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Reviewer Instructions
Please read and review this Draft Clinical Practice Guideline and its associated Technical Report with particular focus on your area of expertise. Your responses are confidential and will be used only to assess the validity, clarity and accuracy of the interpretation of the evidence. If applicable, **please specify the draft page and line numbers in your comments**. Please feel free to also comment on the overall structure and content of the guideline and Technical Report.

Please complete and return this form electronically in **WORD format** to Song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **March 8, 2013.**

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☒	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☒	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☒	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☒	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☒	☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☒	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	☒
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	☒
9. The validity of the studies is appropriately appraised	☐	☐	☐	☒
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	☒
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	☒
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	☒
13. Health benefits, side effects, and risks are adequately addressed	☐	☒	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☒	☐
15. The grades assigned to each recommendation are appropriate	☐	☐	☒	☐

COMMENTS

PLEASE RETURN ALL COMMENTS IN WORD FORMAT

This Draft Clinical Practice Guideline has already completed peer review and has been reviewed by content experts. The feedback provided during this process is attached in the PDF. If you have any other brief additional comments, please feel free to provide them here. If applicable, please specify the draft page and line numbers in your comments.

Thank you for offering us the opportunity to review the current version of the AAOS OA knee clinical practice guidelines. We congratulate the authors on their efforts to assemble, interpret, and analyze the literature to produce a comprehensive guideline for practitioners managing osteoarthritis. We applaud your work in identifying non-operative modalities that provide a clinical benefit and not just a statistically significant benefit. There are aspects of the CPG that we believe need further clarification and/or revision. We have included these comments below for your consideration.

Comments on Specific Recommendations:

RECOMMENDATION 9:
"We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee"
Strength of recommendation: Strong

We believe that this recommendation is not consistent with the studies you have included in your review.
The group identifies that there is a difference between molecular weight products greater than 750 kDa and those below 750 kDa (Line 2712-2717). This is a significant finding that needs to be addressed. If there is a difference between products, then they should not be grouped together in the analysis. However, the CPG does group them together. Therefore, we believe that the recommendation should be "We cannot recommend using low-molecular weight hyaluronic acid for patients with symptomatic osteoarthritis of the knee" Strength of recommendation: Strong

We find that Strand 2012 (line 9555) is included in the references but not in the studies used in the analysis. It is a double blind placebo controlled study of a HMW hyaluronic acid product compared to placebo for 13 weeks and showed a statistical difference between groups favoring HMW product for OMERACT-OARSI Responders. As you are aware there is a highly significant association between achieving an OMERACT-OARSI Response and having an MCII for each of the 3 domains, especially pain and function. As well, you include Navarro-Sarabia (2011) (line 2852 Table 177) in the evidence table but I did not see it in the analysis. This study was a double-blinded placebo controlled study using a hyaluronic acid of >750 KDa that showed a significant difference in the OMERACT-OARSI Responders at multiple stages of the study. MCII is an important clinical feature for recommendation of a product not just statistical significance to determine effectiveness of the product. OMERACT-OARSI response should be considered as a MCII equivalent. Again two studies with MW > 750 KDa show effectiveness.

Moderate and high molecular weight products would need to be looked at separately. Our interpretation of the data would indicate that a MCII would be "We suggest the use of moderate or high molecular weight hyaluronic acid for patients with symptomatic osteoarthritis of the knee" Strength of Recommendation: Moderate (less than 2 high quality).

Furthermore, we believe that the CPG should not have grouped those studies with Kellgren-Lawrence <3 and >=3. We believe that these groups are not the same. Hyaluronic acid injections have been beneficial in patients with lower KL scores allowing them to participate in other recommended modalities (like RECOMMENDATION 1). In your analysis, you also state "In all but two studies, there was uncertainty about whether the patients were representative of the typical patient population" (line 2762-2764) who are meant to receive these guidelines. We understand that your criteria require studies to meet MCII not just statistical significance but if the studies do not represent normal clinical practice and the patient population that would receive the medication then the conclusions should not apply and perhaps your recommendations should remain inconclusive.

RECOMMENDATION 8:
"We are unable to recommend for or against the use of intraarticular (IA) corticosteroids for patients with symptomatic osteoarthritis of the knee."
Strength of Recommendation: Inconclusive

Of the four studies that met the criteria of 4 weeks MCII, IA were found to be beneficial in one study. One was inferior to a high MW hyaluronic acid injection, and in one IA corticosteroid inferior to needle lavage (tidal irrigation).
The following needs clarification: Line 2691 Table 174 has multiple measures that favor IA over Tidal irrigation with possible clinical significance , yet line 2667 Figure 75 indicates possible clinical significance in favor of tidal irrigation and line 2597-2598 states IA inferior to tidal irrigation.

We believe that the conclusion the AAOS group has come to concerning the use of IA corticosteroids is incorrect from the studies you have included in the review.

We find the inclusion of Arden (2008) is not a fair comparison between treatments. Subjects were given anesthesia and then knee joint was entered with a large bore needle. The sham treatment for this modality has a positive effect. Bradley (2002) showed no difference between tidal irrigation and sham but both groups improved. The IA group was injected by the medial joint line approach which studies have identified enter the joint 75% of the time. Therefore, IA group is compared against a treatment that has effect as a sham and the treatment was done in a manner that is less efficacious in guaranteeing intra-articular delivery of the medication. As well, Arden states that they used a larger bore needle, which may have provided better results compared to the Bradley study. Therefore, we believe that comparison to tidal irrigation is not appropriate for evaluating clinical usefulness.

In addition from our previous discussion of RECOMMENDATION 9, we would point to the IA corticosteroid inferior to high MW hyaluronic acid injections not as a determent for corticosteroids but as a re-enforcement of our findings that medium and high MW hyaluronic acids are beneficial. The group's findings on hyaluronic acids (RECOMMENDATION 9) needs adjustment since they have combined those products above and below 750 kDa despite these products having different effects. It is inconsistent to strongly recommend against hyaluronic acid injections but be inconclusive for or against corticosteroid injections when data suggests that HA injections provide more benefit than corticosteroids.

From our evaluation of the studies, we would recommend that the strength of the recommendation is still inconclusive, but "The practitioner might use intraarticular (IA) corticosteroids for patients with symptomatic osteoarthritis of the knee." We are uncertain if you would include for the short-term relief of symptoms, since the clinically significant changes are not found beyond 4 weeks.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☒ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

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- **Your conflicts of interest will be published on the AAOS website with your review.**

Reviewer Information:

Name of Reviewer: **ANONYMOUS – Name and identifying information withheld upon request**
Address:
City: State: Zip Code:
Phone: Fax: E-mail:
Specialty Area/Discipline:
Work setting: Credentials:

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☐ Yes ☒ No
PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your public comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? ☒ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? ☒ Yes ☐ No

Society Name: AOSSM
(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

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☐ **I have declared my conflicts of interest on page 2 of this form.**

☒ **I have declared my conflicts of interest in the AAOS database; my customer # is** 17368

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REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

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Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes ☐ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company:	☐ Yes ☐ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes ☐ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify:	☐ Yes ☐ No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify:	☐ Yes ☐ No

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Reviewer Instructions

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Please complete and return this form electronically in **WORD format** to Song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **March 8, 2013.**

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	☒
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☒	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	☒
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10. The methods are described in such a way as to be reproducible.	☐	☒	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☒	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☒	☐	☐
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14. The writing style is appropriate for health care professionals.	☐	☐	☒	☐
15. The grades assigned to each recommendation are appropriate	☐	☒	☐	☐

COMMENTS

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Recommendation #1, Line 963: The term "self management" is confusing and needs to be better defined.

Recommendation #2: No comment.

Recommendation #3: Is there really enough scientific literature to support this? Are these examples of treatments that don't have very good science so they are listed as inconclusive? This is the same comment I could have used for PRP and stem cell treatment. There are very few articles, so was the term *inconclusive* used because there was lack of evidence against? In the case of #9, HA, there are many clinical and basic science articles written and, after putting all of the most recent ones together, the Committee elected to classify it as strong for not using HA. This seems very inconsistent to me. I am sure we can find more than 5 articles of good science showing that HA does have significant benefits. But there are also 5 articles that will say that it doesn't.

Recommendation #4: No comment.

Recommendation #5: No comment

Recommendation #6: No comment

Recommendation #7: No comment

Recommendation #8: No comment

Recommendation #9: The basis for the HA analysis to determine the efficacy of HA is comparing the outcomes to a published minimally clinically important difference (MCID) as the reference point or benchmark. While the concept may be valid, I am not sure using the MCID which was taken from the publication by Angst et al. is valid. Angst, et al, reported the MCID as a difference between pre- and post-therapy scores in a group of hip and knee OA patients, not the difference between a therapy group and a control group. Common outcomes methodology requires that you use an outcomes tool that was developed for the population in which it is being used. Obviously this was for hip and knee OA patients, whose outcomes of treatment may be influenced by well known differences of symptomatic and functional limitations these different joint maladies. I understand that the MCID is not an outcomes tool, but I am not sure using this number from this study is valid.
Using this MCID to compare treatment outcomes between a group being treated and a control group, when the MCID number was determined for pre and post therapy is likely invalid. The MCID is a numerical concept taken from an outcomes tool for a specific use – to determine the effects of therapy on the same patient. That is not how it is being used by the OAK group. They are using it to compare 2 groups of patients undergoing 2 types of treatments to determine if the treatment is efficacious. Again, this is likely not scientifically valid. It would be like using the IKDC (a knee ligament score) to compare the outcomes of 2 different knee prostheses or to study 2 cartilage treatments. There are different factors that are likely important in patient outcomes when treating different things and in different age groups. The IKDC is a validated score for the knee - but for ligaments. The stability of the knee for cartilage or OA is not the main issue. The groups are different, the goals are different, and the complaints of the patients may be different. Further, the score is likely to not really show what is going on. Another similar misconception, very much along the same lines, is taking questions from a validated questionnaire like the WOMAC, and some from other validated questionnaires, such as the International Knee Society (IKS) score, KOOS, Oxford and the HSS scores, then saying your new questionnaire is validated, because it uses questions from other validated questionnaires. It is not.
Additionally, there are many variables in treating a patient with OA – such as severity of arthritis, compartment(s) involved, alignment, age, body weight, activity level, medical co-morbidities, etc, which are not addressed in this CPG, particularly as they relate to particular treatments studied. Certainly the CPG makes a detailed attempt at trying to find science to support or refute what we are doing, but the studies are just lacking. They lack the current scientific rigor and they lack the detail necessary to treat specific patients with certain constellation of above modifying factors. But what the CPG should be is a call to arms that we need to do better research to answer the specific questions. The blanket statements about the given treatments for OA do not apply to the patient sitting in front of you. How I approach a patient with good alignment, medial joint space narrowing, who is young and athletic, normal BMI and has pain is different from how I treat the 60 year old overweight sedentary smoker with mal-alignment and severe bone on bone tricompartmental arthritis. The CPGs cannot provide the same guidelines to the 2 groups. Unfortunately, there is very little literature, and obviously no good literature, that guides us here...I understand that is the purpose of the AUC, but the CPGs will be looked at by the insurance companies and/or other payors, as a reason to not pay. I hate to admit it, but our science is just lacking and cannot support the great goal of the AAOS to support making the CPGs.

Another comment is about the HA - most data would suggest the higher molecular weight HA is efficacious, especially compared to the low molecular weight group. And the OAK group showed that. However, when they added in the middle weight group to the high molecular weight group, the statistical significance was lost.

Recommendation #10: No comment

Recommendation #11: Why is the term "suggest" used and why is it italicized?

Recommendation #12: This recommendation is concerning because it is based solely on 3 studies, Moseley (strong) , Kirkley(moderate strength study) and Kalunian (moderate) . Based on the CPG development and recommendation guidelines, 2 or more "high" strength studies are required to make a strong recommendation, only one was presented here.
In addition, there were weaknesses in all three of these studies. In particular, the Kirkley study excluded patients with large meniscal tears, and therefore patients with possibly mechanical symptoms from large meniscal tears in the face of OA were not studied. This is exactly the population that may benefit from arthroscopy in the face of OA. The Kalunian study compared 2 groups undergoing arthroscopic lavage but no control group that did not undergo arthroscopic lavage. Both groups benefitted from the arthroscopic lavage, and the therefore a statement about the lack of benefit of arthroscopy cannot be made because there was no comparison non arthroscopy control group. It seems that making a strong recommendation in the face of weak evidence is contradictory to the purpose of the OA Work Group.

Recommendation #13: There needs to be a clearer distinction made between #12 and #13. Many knees that we perform arthroscopy and meniscal surgery on have a certain degree of arthritis (especially the ones over age 50). I am concerned that some of these patients will be considered and grouped in with patients who fall under Recommendation #12.

Recommendation #14: I am pleased that the work group included a recommendation for valgus producing proximal tibial osteotomies. I am concerned with the recommendation of limited. Limited means that the supporting evidence is unconvincing or that well conducted studies show little clear advantage to one approach over another. I doubt that there will ever be a Level 1 study or what the group would consider strong quality research in this area because it is a procedure that is not frequently done.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☒ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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Reviewer Information:

Name of Reviewer___Paul F Lachiewicz MD_____

Address_____101 Conner Drive , Suite 200_____

City__Chapel Hill_____ State____NC_____ Zip Code__27514_____

Phone _____Fax _____E-mail__paul.lachiewicz@gmail.com_____

Specialty Area/Discipline: Adult Reconstructive surgery_____

Work setting: Private practice and part-time VA_____Credentials: _____

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Are you reviewing this guideline as a representative of a professional society? **X**☐ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? X☐ Yes ☐ No

Society Name: __Knee Society_____
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Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
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Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	X☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	X☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	X☐
4. The guideline's target audience is clearly described	☐	☐	☐	X☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	X☐
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12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	X☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	X☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	X☐
15. The grades assigned to each recommendation are appropriate	☐	☐	☐	X☐

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These guidelines appear to be an improvement compared to the previous ones, with more rigorous evaluation of published studies. No major objections.

In recommendation 1, suggest the words "professionally supervised" or something like this, be added before "self-management programs, as the papers did discuss under the supervision of a rheumatologist, therapist, etc.
Although the definition of "national guidelines" was given in the text, do not believe most health care providers will know what this means.

The recommendation regarding intra-articular corticosteroid injections will certainly be met with dis-belief and scorn by the vast community of health care providers, who regularly use this treatment. Personally, I only use these injections when the patient has an effusion, and supposedly "synovitis', rather than as a routine treatment.

The recommendation against viscosupplementation will also be extremely poorly received for a variety of reasons. However, this recommendation is in line with a recent meta-analysis published in the Annals of Internal medicine, which concluded that "viscosupplementation is associated with a small and clinically irrelevant benefit and an increased risk for serious side effects" Rutjes, Anne WS et al

Finally, there is obvious concern about the recommendation for the use of tramadol, but the discussion did state that it was beyond the scope of the document to discuss adverse reactions to medications.

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☐ Strongly recommend

☐ Recommend (with provisions or alterations)

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Reviewer Information:

Name of Reviewer____Laura M Bruse Gehrig MD_____

Address_____2349 Fresno drive_____

City_____Bismarck_____ State_____ND_____ Zip Code___58504_____

Phone _____701-595-2878_____Fax _____E-mail_____laura.gehrig@gmail.com_____

Specialty Area/Discipline: ____Foot and Ankle, General Orthopaedics_____

Work setting: _____Hospital_____Credentials: _____ABOS (recertified 2011)_____

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x☐ Recommend (with provisions or alterations) as indicated as each reviewer sent in their critique

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☐ Unsure

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Alterations as indicated by all those responding as listed as reviewers.

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Reviewer Information:

Name of Reviewer_____Thomas Best _____

Address_____2050 Kenny Rd_____

City__Columbus ___ State_ohio_____ Zip Code 43221

Phone ____614 293 3600_____Fax _____6142934399_____E-mail____thomas.best@osumc.edu_____

Specialty Area/Discipline: _____sport medicine_____

Work setting: _____Credentials: ____Director, Division of Sports Medicine; Department of Family Medicine, Pomerene Chair of Family Medicine, Co-Medical Director, OSU Sports Medicine Professor of Biomedical Enjineering, Team Physician, OSU Athletic Department_____

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	Disagree / Somewhat Disagree / Somewhat Agree / Agree
1. The recommendations are clearly stated	Somewhat Agree: X
2. There is an explicit link between the recommendations and the supporting evidence	Somewhat Disagree: X
3. Given the nature of the topic and the data, all clinically important outcomes are considered	Somewhat Disagree: X
4. The guideline's target audience is clearly described	Somewhat Agree: X
5. The patients to whom this guideline is meant to apply are specifically described	Agree: X
6. The criteria used to select articles for inclusion are appropriate	Somewhat Agree: X
7. The reasons why some studies were excluded are clearly described	Somewhat Disagree: X
8. All important studies that met the article inclusion criteria are included	Somewhat Agree: X
9. The validity of the studies is appropriately appraised	Somewhat Agree: X
10. The methods are described in such a way as to be reproducible.	Somewhat Agree: X
11. The statistical methods are appropriate to the material and the objectives of this guideline	Somewhat Agree: X
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	Somewhat Disagree: X
13. Health benefits, side effects, and risks are adequately addressed	Somewhat Agree: X
14. The writing style is appropriate for health care professionals.	Somewhat Agree: X
15. The grades assigned to each recommendation are appropriate	Somewhat Agree: X

COMMENTS

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I feel medical care should always be based on a physician's expert judgment and the patient's circumstantial preferences. I typically do not recommend performing arthroscopy with lavage and/or debridement in patients with a primary diagnosis of symptomatic osteoarthritis of the knee.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

Strongly recommend

Recommend (with provisions or alterations)

X Would not recommend

Unsure

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American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
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- **Your conflicts of interest will be published on the AAOS website with your review.**

Reviewer Information:

Name of Reviewer Ron Bowman MD

Address 9445 SW Locust St

City Tigard State OR Zip Code 97223

Phone 503.352.1313 Fax 503 352.1314 E-mail ron@tigardortho.com

Specialty Area/Discipline: knee/shoulder sports medicine

Work setting: private practice Credentials: ABOS recert to 2023
CAQ Sports Medicine

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☑ Yes ☐ No

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Are you reviewing this guideline as a representative of a professional society? ☐ Yes ☑ No

If yes, may we list your society as a reviewer of this guideline? ☐ Yes ☐ No

Society Name: _____

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Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☑ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☑ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☑ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☑ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☑ No
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Guideline: "We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee"

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	☑
2. There is an explicit link between the recommendations and the supporting evidence	☑	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☑	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☐	☑
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	☑
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	☑
7. The reasons why some studies were excluded are clearly described	☑	☐	☐	☐
8. All important studies that met the article inclusion criteria are included	☑	☐	☐	☐
9. The validity of the studies is appropriately appraised	☑	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☑	☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☑	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☑	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☑	☐	☐	☐
15. The grades assigned to each recommendation are appropriate	☑	☐	☐	☐

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COMMENTS

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I could not find the body of literature used to support the Academy's proposed stance on visco-supplementation. My clinical experience with visco-supplementation has been positive and I think it benefits numerous patients who are poor candidates for an arthroplasty. Many of those who are candidates for TKA can forestall the invasive procedure for several years. The recommendation as stated will likely be used by insurance companies to deny payment for the procedure/series and create a hardship for patients who might otherwise benefit. I urge the Academy to not adopt this statement.

Ron Bowman.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

- ☐ Strongly recommend
- ☐ Recommend (with provisions or alterations)
- ☑ Would not recommend
- ☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

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Reviewer Information:

Name of Reviewer__Dr. Emily Casey_____

Address__805 ST. Vincent's Dr. _____

City_Birmingham_____ State__AL_____ Zip Code_35205_____

Phone __205-939-3699_____Fax __205-484-2661_____E-mail_____

Specialty Area/Discipline: Sports Medicine_____

Work setting: Clinic Credentials: ___M.D._____

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☒ Yes ☐ No
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	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☐	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	☐
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	☐
9. The validity of the studies is appropriately appraised	☐	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	☐
15. The grades assigned to each recommendation are appropriate	☐	☐	☐	☐

COMMENTS

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My comments and my interests are for viscosupplementation only. My patients respond well and get relief from their osteoarthritis pain with viscosupplementation. I recommend continue using these products.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☒ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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Reviewer Information:

Name of Reviewer: Michael J. Daley Ph.D.

Address: 7044 Ely Road
City: New Hope State PA Zip Code 18938

Phone: 484-678-8563 Fax: 484-840-5597 E-mail: michaeljdaley@comcast.net

Specialty Area/Discipline: Consulting – musculoskeletal diseases

Work setting: Consulting practice; no present contract with any HA company

Credentials: Former Medical Director Hyalgan (1998-2006) and Member of ACR, OARSI, ORS

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Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier: OrthogenRx, Inc.	☒ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
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	Disagree	Somewhat Disagree	Somewhat Agree	Agree
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2. There is an explicit link between the recommendations and the supporting evidence	☒	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☒	☐	☐	☐
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6. The criteria used to select articles for inclusion are appropriate	☒	☐	☐	☐
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9. The validity of the studies is appropriately appraised	☐	☐	☒	☐
10. The methods are described in such a way as to be reproducible.	☐	☒	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☒	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☒	☐
13. Health benefits, side effects, and risks are adequately addressed	☒	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	☒
15. The grades assigned to each recommendation are appropriate	☒	☐	☐	☐

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Recommendation #9: *"We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee."*

I understand that the AAOS has performed a meta-analysis and while a statistically significant differences between saline injections and HA was found an additional analysis on MCIS was also performed for which none of the studies were prospectively powered as an outcome to achieve. I believe that the methodology may be flawed and certainly at odds with well conducted meta-analyses previously published (Bannuru, 2011; Bellamy, 2006; Wang, 2004) with contrary findings.

I believe by changing a recommendation from neutral to negative that this may have a significant impact on safe treatment options available to orthopedic surgeons to treat patients with OA of the knee, and thus exposing these patients to the well-known potentially life threatening adverse effects associated with systemic medications used to control pain. This is especially true for the elderly population which is the predominate demographic for this disease state. The level of evidence to support a neutral versus negative recommendation for a class of FDA approved products should be the highest level of evidence and irrefutable given the potential consequences. Otherwise there may be significant legal consequences to the Academy, especially in light of significant body of evidence supporting the contrary opinion, in adopting a 'negative' opinion.

It would be most judicious of AAOS to reconsider this recommendation in the best interest of their membership and to carefully consider the final decision given the totality of the facts and potential consequences of their action.

Here are several bulleted points that should be considered in your full deliberation:

Study Selection and Comparators

- The analysis includes studies on products not approved in the U.S. No meta-analysis to determine the effectiveness of a class of products can justify inclusion of products that have not been approved for the indication.
- Saline injections are a positive clinical intervention and not a 'placebo' and need to be considered as such
- Mock needle injections have been exhibited less pain relief then the actual saline injection
- All studies with saline injections first require arthrocentesis if fluid is present and is an accepted clinical intervention
- The injection of Saline following the arthrocentesis significantly dilutes out pain and inflammatory mediators
- All patients in these clinical studies were allowed prn acetaminophen (up to 4 gr/d) a known analgesics
- In many studies 3-5 weekly Saline injections have demonstrated a robust and durable pain-relieving effect from baseline that exceeds the pain relief reported in the pivotal studies with a non-flare design for Vioxx or Celebrex taken bid for 6 months
- So achieving a statistically significant benefit over saline has established amongst the highest standards to achieve to which most of the approved pain relief medications used in OA could not fulfill. Significantly calling into question a negative recommendation.
- The indication for HAs is for mild-moderate OA. Some of the data analyzed populations which included grade IV Kellgren-Lawrence X-rays, or severe OA.

Clinically Significant Effects

- Calculated effect sizes for HAs have been reported in several analyses to be greater than that of NSAIDs and two-fold greater that the additive benefit of NSAIDS over acetaminophen which would be the correct comparator given the study designs
- Minimum clinically significant improvement (MCII) has been inappropriately applied as per published reports such as Angst et al By these standards most NSAIDs would be considered not significantly different from acetaminophen or saline injections. The MCCI should be calculated from Baseline improvement as this is the true benefit a patient experiences. Unless patient level data was available to exclude these patients these studies are inappropriate to include.
- A MCII is not appropriate when evaluating individual patient responsiveness. A more appropriate evaluation as established by ACR, OARSI and EULAR is patient responder analysis.

Clinical Safety Considerations

- The recommendation fails to consider the significant safety benefit of local HA therapy over systemic NSAID or analgesic treatments with known life threatening adverse events. Based upon post-marketing safety reports HAs clearly have a superior safety profile especially in an elderly population. The AAOS clearly ignores the significant benefit to risk assessment.
- No product associated death has been reported in the FDA MAUDE reports since the first HA approval back in 1997 with what is estimated to be a total of 30,000,000 injections administered.
- As a matter of example, the first hyaluronan approved in the U.S. was Hyalgan in 1997. Since the time of initial approval to date approximately 9,000,000 injections to have been administered over the 16 year period, and there have only been approximately 250 adverse events reported to the FDA MAUDE post-marketing safety database. Similar results are reported for the other products.
- Chronic NSAID use has been associated with an estimated 16,500 deaths per year due to GI bleeds, patients following their first MI are 60% more likely to die of a second MI if they take NSAIDs, patients with a history of heart disease have a 80% higher incidence of death with the use of NSAIDs.
- Potentially eliminating HA as a treatment option will expose the over 1MM patients treated to HAs to these serious adverse effects which will clearly be associated with significant adverse events and even death

References

Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis Cartilage. 2011 Jun;19(6):611-9.

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Campbell J, Bellamy N, Gee T. Differences between systematic reviews/meta-analyses of hyaluronic acid/hyaluronan/hylan in osteoarthritis of the knee. Osteoarthritis Cartilage. 2007 Dec;15(12):1424-36

Dworkin RH et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain. 2009; Vol. 146, 238-244.

Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. J Bone Joint Surg Am. 2004 Mar;86-A(3):538-45.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
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ALL REVIEW COMMENTS, OUR RESPONSES AND REVIEWER COI WILL BE AVAILABLE FOR REVIEW ON OUR WEBSITE FOLLOWING BOD APPROVAL OF THIS DOCUMENT.

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Please note that if you return a review:

- **Your comments will be published on the AAOS website with our explanation of why we did nor did not change the draft document in response to your comments.**
- **Your conflicts of interest will be published on the AAOS website with your review.**

Reviewer Information:

Name of Reviewer_Vinod Dasa_____

Address___5424 camp st _____

City_____New Orleans_____ State____LA_____ Zip Code_____70115_____

Phone _____5048994233_____Fax _____E-mail_____vdasa@lsuhsc.edu_____

Specialty Area/Discipline: _____Total joint replacement_____

Work setting: __LSU health Sciences Center_____Credentials: _____MD_____

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☒ Yes ☐ No
PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your public comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? ☐ Yes ☒ No

If yes, may we list your society as a reviewer of this guideline? ☐ Yes ☐ No

Society Name: _____
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If the boxes below are not checked and/or the reviewer does not attach his/her conflicts of interest, the reviewer's comments will not be addressed by the AAOS nor will the reviewer's name or society be listed as a reviewer of this GL. If a committee reviews the guideline, only the chairperson/or lead of the review must declare their relevant COI.

☐ **I have declared my conflicts of interest on page 2 of this form.**

☒ **I have declared my conflicts of interest in the AAOS database; my customer # is ___323157_____**

☒ **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.**

REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

Each item below requires an answer. Please report information for the last 12-months as required by the Accreditation Council for Continuing Medical Education (ACCME) guidelines.

Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes ☒ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company:Bioventus	☒ Yes ☐ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Bioventus	☒ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes ☒ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify:	☐ Yes ☒ No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify:	☐ Yes ☒ No

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Please complete and return this form electronically in **WORD format** to Song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **March 8, 2013.**

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☒	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☒	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☒	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☐	☒
5. The patients to whom this guideline is meant to apply are specifically described	☒	☐	☐	☐
6. The criteria used to select articles for inclusion are appropriate	☒	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☒	☐
8. All important studies that met the article inclusion criteria are included	☐	☐	☒	☐
9. The validity of the studies is appropriately appraised	☒	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☒	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	☒
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☒	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☒	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☒	☐	☐
15. The grades assigned to each recommendation are appropriate	☐	☐	☒	☐

COMMENTS

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Recommendation 6

1) Most studies used KL classification which is 1 standing AP knee xray as in clegg et al. 1 standing AP knee xray is not sufficient to appropriately diagnose the severity of knee oa. Most surgeons who are familiar with "cartilage" surgery usually obtain an AP, lateral, Notch, and merchant view. Can this committee confidently comment on the effectiveness of these treatments when most studies do not include appropriate imaging to appropriately diagnose knee OA severity?

Recommendation 7

1) AE's surrounding NSAID's did not include hypertension- should that be considered?
2) Some primary care physicians consider NOT prescribing PPI's or H2 blocker's w nsaid's as malpractice. They also recommend all patients should take nsaid's on a full stomach. This recommendation makes no mention of this additional prescribing info. The AE section sounds like this is not an issue.

Recommendation 8

1) No comments on safety of steroid injections. Transient systemic hyperglycemia especially in diabetics is well known and well established.
2) No Comment on the chondrotoxcity of steroids given the abundance of basic science literature.
3) No acknowledgments that "steroid injections" often include numerous additional analgesics which have been found to be extremely chondrotoxic (i.e. ropivicaine, bupivacaine…).
4) While I understand that only well done clinical studies are allowed to be reviewed, the practical nature and usefulness of a practice guideline is diminished when you do not acknowledge the abundance of science surrounding the biologic effects of steroid and analgesic injections.
5) Does the potential harm from a basic science perspective outweigh the clinical effectiveness of these injections given your clinical findings are inconclusive (downgraded from 2008 guidelines)?

Recommendation 9

1) Some studies included products which are not FDA approved In the US. Should this review be limited to FDA/US approved products?
2) Most studies are European- applicability to US population?
3) Many studies used patient with KL 3+ OA which is bone on bone OA. Most orthopedic surgeons would consider bone on bone oa as severe. Clinical studies have found decreasing efficacy with increasing OA severity. I'm not surprised HA and saline were comparable in bone on bone OA. . Please give us guidance as to which patients will benefit instead of making a blanket statement that it does not work in anyone. This recommendation eliminates this treatment option for all patients based on improper diagnosis and poorly designed trials.
4) No mention of the basic science research. chondroprotective properties, reduction in inflammatory cytokines such as tnf α, IL-6, IL-1…
5) Most of trials were done by rheumatologists. I do not think their interpretation/diagnosis of OA, its significance, and treatment are the same as orthopedists.

6) Orthopedic surgeons would be better served if the AAOS would create guidelines that are applicable based on orthopedic surgery insight. I'm worried that our treatment of OA is being driven by rheumatologists and the rheumatology literature and not orthopedic surgeons. An example of a well done study from an orthopedic clinical perspective is Leopold et al. JBJS 2006. In this study 4 views of the knee were taken to ensure that they were adequately diagnosing knee OA. None of the rheumatology papers included in these guidelines did this.
7) In our effort to find RCT's which are methodologically sound from a statistical perspective (randomized, blinded, placebo controlled…) we've lost sight of the clinical analysis, significance, and applicability.

Recommendation 13

1) Is there a potential liability issue for surgeons who perform arthroscopy for meniscal pathology in the face of knee OA (almost every knee scope in anyone over the age of 40). If there is a complication following surgery, will lawyers use these guidelines to challenge the appropriateness of surgery?
2) The recommendations are inconclusive in the benefit of arthroscopy for a meniscal tear in patients w OA. Does the location of the OA impact the benefit of the arthroscopy (i.e. patella femoral vs med tibio femoral vs lateral tibio femoral)? Does location of the meniscus tear (med vs lat) w respect to the location of OA matter? I think many surgeons would agree of the questionable benefit when the meniscus tear is in the same compartment as the severe OA, but when the OA is in a different compartment (or not severe) will arthroscopy will be of benefit? The study referenced (herrlin et al) does not correlate the meniscal pathology and success of surgery w OA severity or OA location. Although this may be a nice study design, it does not give any helpful clinical evidence.
3) Unsure how to interpret this. Arthroscopy to help relieve OA related knee pain in the face of a meniscus tear is inconclusive? In other words arthroscopy will help relieve the "meniscus tear pain" but not the "OA pain"?

Recommendation 14

1) There is no mention of a varus producing distal femoral osteotomy for valgus knee oa.

In general

1) Are studies chosen purely on the study design (i.e. randomized, blinded, placebo control…) or are they also assessed for their clinical usefulness? A well designed study may still not be a useful and valid study from a clinical perspective and thus may potentially provide wrong information.
2) Most studies only used 1 standing AP xray . Those of us that do cartilage work know the importance of the notch view, merchant view, and lateral view in adequately diagnosing articular cartilage pathology such as OA. How can you diagnose the extent of disease on 1 xray? From a scientific and clinical perspective why would this work group accept studies which are inadequate in diagnosing OA? I would think those studies would be excluded?
3) What the payors will take away from this review is that they will only pay for weightloss, nsaid's, and osteotomy for knee OA. The practical consequences of this review will drive more patients to use nsaid's and more invasive surgery. I think we've taken a step backwards with this guideline.
4) Should title of this CPG be labeled a little differently? Maybe treatment of mild and mod knee OA? Including surgeries like osteotomy opens the door for a discussion of UKA and TKA which doesn't seem to be the focus of this CPG. The treatment algorithm changes greatly based on disease severity. If the next work group on surgical management is examining treatments for severe OA then should this work group focus only on early OA treatments?

5) Can you add a section of what this work group thinks would be an ideal study design for any future studies? Type and number of xrays, length of follow up, randomization, blinding… this may help to standardize data moving forward to help make this process more fruitful in the future.
6) Language is confusing "can not recommend" vs "unable to recommend" vs "can not suggest using"…
7) My clinical experience is not consistent w many of the findings. I suspect many surgeons will feel the same way. Why does the work group think that is? Does the research not reflect the clinical reality or are we as physicians not objective enough in assessing our results?
8) Case example. This is a typical case we see every day in our practice. The xrays below would be consistent with KL grade 1 OA using only the standing AP knee xray and thus included in most studies looking at mild and moderate OA that this committee reviewed. When looking at other views such as the merchant view, there are subtle signs of osteophytes which indicate more severe disease. The arthroscopy pictures below verify complete cartilage loss consistent w severe OA. This patient would have been erroneously enrolled in any number of the studies which only required the KL grading system (1 standing AP knee xray) to assess OA severity thus giving the impression of poor treatment efficacy in these "mild" OA patients. I'm surprised this committee included studies which did not adequately diagnose knee OA severity.

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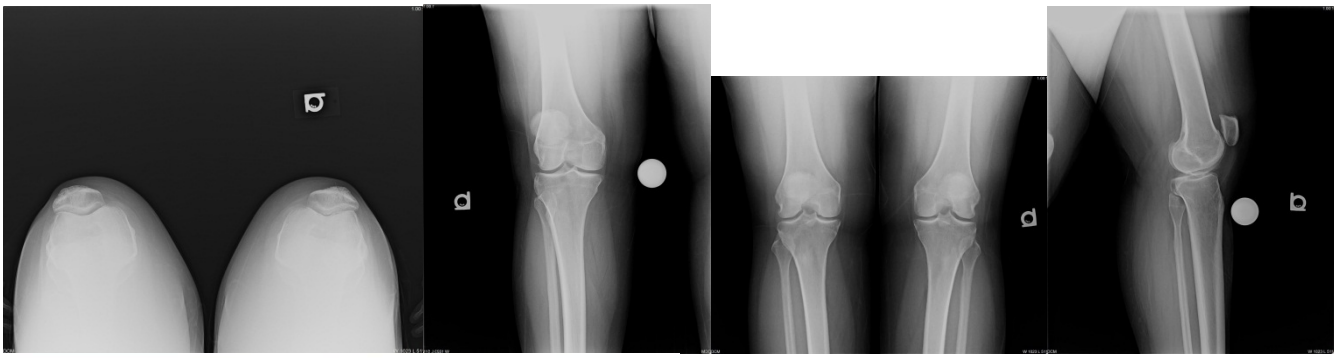

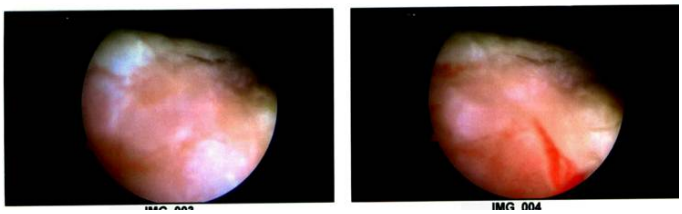

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

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Reviewer Information:

Name of Reviewer_____David Jacofsky, MD_____

Address_____3030 W. Agua Fria Freeway_____

City Phoenix _____State____AZ_____ Zip Code 85027_____

Phone _____623-4743421_____Fax _____E-mail____ David.jacofsky@thecoreinstitute.com _____

Specialty Area/Discipline: ____Arthroplasty_____

Work setting: _____Credentials: ___Chairman, The CORE Institute_____

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☒ Yes ☐ No
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Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Stryker, Biomet, Depuy, VQ Orthocare, Bacterin	☒ Yes ☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
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Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify:	☐ Yes ☒ No
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	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	☒
2. There is an explicit link between the recommendations and the supporting evidence	☒	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☒	☐	☐	☐
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9. The validity of the studies is appropriately appraised	☐	☒	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☒	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☒	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☒	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☒	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	☒
15. The grades assigned to each recommendation are appropriate	☐	☒	☐	☐

COMMENTS

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My comments are limited to recommendation #9. Although I did have financial disclosures, for clarity, neither I nor any family member has any financial interest in any product or company that makes a product discussed in this recommendation (I actually could argue that as a royalty designer of implants, I have a financial incentive to eliminate effective non-operative modalities). Our hospital system and our group has an evidence-based Quality Department whose sole purpose is standardization through evidence based best practice. We, as a group, are fully standardized and have done so based on the quality of the research and recommendations put forth by our Quality and Peer Review Committees. These groups have spent innumerable hours reviewing both our internal data and the published data regarding HA injections for knee arthritis. We have one of the largest orthopedic practices in the nation and all our orthopedic surgeons have a consensus based approach to the use of this treatment due to our understanding of the literature as it relates to a specific treatment in specific patients. Our research has indicated, as has that published, that there are dramatic differences in the available preparations of HA for injection. We have had our statistician review the FDA submissions for many, if not all, of these products as well. Differences in MW, dose, dosing intervals, and formulation have been CLEARLY proven to create very different effects on efficacy in multiple studies. For AAOS to combine multiple patient groups, multiple categories of disease severity, multiple and very different HA products, and multiple dosing regimens into one combined catch-all recommendation is reckless and not based on the available clinical and basic science data. Supartz, for example, has over 20 prospective randomized studies that have shown efficacy established across multiple measurable data points within both Lequesne, WOMAC and VAS Indexes whereas some formulations such as Synvisc One have shown, even in their own FDA data, no statistical difference from placebo when the proper statistical measures are used (of note, they used an incorrect method in their FDA submission which allowed the false demonstration of a slight benefit). To universally make a blanket recommendation that will almost certainly lead to changes in covered services for multiple products, while making no stratification of effect based on product type, patient characteristics, injection technique, or disease extent seems both unfair and unfounded. I have never felt obligated on behalf of patients to respond to any draft recommendation from AAOS in the past, but this blanket recommendation is unfounded, and will effectively eliminate from the armamentarium of the physician, certain proven treatments with benefits that clearly outweigh risks, in certain patient populations. Below are some of the more recent studies our quality team of statisticians, physicians, and QA experts used in standardizing our system to Supartz and in creating algorithms to help define what patients are the most appropriate candidates for such treatment.

Cochrane Database Syst Rev. 2006 Apr 19;(2):CD005321. Viscosupplementation for the treatment of osteoarthritis of the knee. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G.
Conclusion: "Based on the aforementioned analyses, viscosupplementation is an effective treatment for OA of the knee with beneficial effects: on pain, function and patient global assessment; and at different post injection periods but especially at the 5 to 13 week post injection period. It is of note that the magnitude of the clinical effect, as expressed by the WMD and standardized mean difference (SMD) from the RevMan 4.2 output, is different for different products, comparisons, timepoints, variables and trial designs."

Acta Ortop Mex. 2011 Jul-Aug;25(4):208-15. [Effectiveness of sodium hyaluronate in patients with gonarthrosis: randomized comparative study]. Pérez-Serna AG, Negrete-Corona J, Chávez-Hinojosa E, López-Mariscal C.
Conclusion: Intraarticular sodium hyaluronate is more effective for pain and function than methylprednisolone.

Osteoarthritis Cartilage. 2012 Jul;20(7):791-5. doi: 10.1016/j.joca.2012.03.020. Epub 2012 Apr 4. Acute inflammation with induction of anaphylatoxin C5a and terminal complement complex C5b-9 associated with multiple intra-articular injections of hylan G-F 20: a case report. Dragomir CL, Scott JL, Perino G, Adler R, Fealy S, Goldring MB.
Conclusion: "This present study is indicative of a pseudo-septic acute inflammatory reaction in response to local accumulation of hylan G-F 20 (Synvisc) with the activation of complement and local invasion of pro-inflammatory cells". There are a number of studies pointing out this unique and severe complication with Synvisc."

Ann Rheum Dis. 2012 Sep;71(9):1454-60. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. Berenbaum F, Grifka J, Cazzaniga S, D'Amato M, Giacovelli G, Chevalier X, Rannou F, Rovati LC, Maheu E.
Conclusion: This was a randomised, controlled, double-blind, parallel-group, non-inferiority trial with the possibility to shift to superiority and showed "Treatment with 3-weekly injections of intermediate MW HA may be superior to low MW HA on knee OA symptoms over 6 months, with similar safety.". Hyalgan and Supartz are the two brands with low MW formulations.

J Orthop Res. 2012 May;30(5):679-85. doi: 10.1002/jor.21580. Epub 2011 Oct 24. Early effect of hyaluronic acid intra-articular injections on serum and urine biomarkers in patients with knee osteoarthritis: An open-label observational prospective study.

Conrozier T, Balblanc JC, Richette P, Mulleman D, Maillet B, Henrotin Y, Rannou F, Piroth C, Hilliquin P, Mathieu P, Walliser-Lohse A, Rousselot I, Plattner V, Maillefert JF, Vignon E, Chevalier X; Osteoarthritis Group of the French Society of Rheumatology.
Conclusions: "This study showed that 90 days after HA IA injections, U-CTX II levels significantly decrease compared to baseline, suggesting a slowdown of type II collagen degradation." One of many newer studies showing a probable DISEASE MODIFYING EFFECT of the hyaluronans."

BMC Musculoskelet Disord. 2011 Aug 24;12:195. doi: 10.1186/1471-2474-12-195.Effects of Hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: a two-year single-blind clinical trial.Wang Y, Hall S, Hanna F, Wluka AE, Grant G, Marks P, Feletar M, Cicuttini FM.
Conclusions: "…intra-articular injections of Hylan G-F 20 administered to patients with symptomatic knee OA have a beneficial effect on knee cartilage preservation measured by both cartilage volume and cartilage defects"

Ann Rheum Dis. 2011 Nov;70(11):1957-62. doi: 10.1136/ard.2011.152017. Epub 2011 Aug 17. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, de la Serna AR, Naranjo A, Gimeno M, Herrero-Beaumont G; AMELIA study group.
Conclusions: This multicenter, randomized, patient and evaluator-blinded, controlled study showed that "The results of AMELIA offer pioneer evidence that repeated cycles of intra-articular injections of HA not only improve knee osteoarthritis symptoms during the in-between cycle period but also exert a marked carry-over effect for at least 1 year after the last cycle. In this respect, it is not possible to establish if this carry-over effect reflects true osteoarthritis remission or just a modification of the disease's natural course."

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

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Reviewer Information:

Name of Reviewer M. E. KERK

Address 2537 LARKIN ROAD

City LEXINGTON State KY Zip Code 40503

Phone (859) 277-5703 Fax _____ E-mail _____

Specialty Area/Discipline: ORTHOPAEDIC SURGERY

Work setting: _____ Credentials: MD

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☑ Yes ☐ No

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Are you reviewing this guideline as a representative of a professional society? ☐ Yes ☑ No

If yes, may we list your society as a reviewer of this guideline? ☐ Yes ☐ No

Society Name: _____

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Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	☑
2. There is an explicit link between the recommendations and the supporting evidence	☑	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☑	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☐	☑
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	☑
6. The criteria used to select articles for inclusion are appropriate	☑	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	☑	☐	☐	☐
8. All important studies that met the article inclusion criteria are included	☑	☐	☐	☐
9. The validity of the studies is appropriately appraised	☑	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☑	☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☑	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☑	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☑	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☑	☐
15. The grades assigned to each recommendation are appropriate	☑	☐	☐	☐

COMMENTS

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OVERALL ASSESSMENT

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☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☑ Would not recommend

☐ Unsure

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bioventus

Bioventus LLC
4721 Emperor Blvd., Suite 100
Durham, NC 27703
USA

1-919-474-6700
1-800-396-4325
www.BioventusGlobal.com

Dear Doctor,

Back in 2009, The American Academy of Orthopaedic Surgeons (AAOS) published an update of their Clinical Practice Guidelines (CPG) on *Treatment of Osteoarthritis of the Knee.* At that time they revised their position on the use of hyaluronic acid (viscosupplement) products from "...we recommend..." to "...we cannot recommend for or against..." Their decision was based on an existing AHRQ technology assessment.

The AAOS is now preparing to publish an update of the 2009 CPG and currently is seeking public comment on a draft version. In this draft the recommendation (Recommendation #9) on HA treatment has been revised downward once again to, **"We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee. Strength of recommendation: Strong"**. This new, negative, recommendation is based on a review of 14 studies chosen by the Review Committee measured against a new metric that AAOS has now arbitrarily created called Minimum Clinically Important Improvement (MCII). The Review Committee acknowledged that overall, there was a statistically significant difference between HA and saline but because the difference was not strong enough to meet the MCII threshold, the recommendation was changed from neutral to negative. If these guidelines are finalized the consequence is that health insurers could begin to pull back coverage for HA products making patient and physician access far more difficult or impossible. This is especially concerning for patients who are not candidates for surgery, NSAIDs and corticosteroids.

We believe that the basis for the AAOS draft Recommendation #9 is flawed for the following reasons:

- Study Selection:
  - The selection process failed to account for product differences – dosing schedule, dose size, formulation, concentration, source material, etc. The studies utilized several different HA products yet were treated as if they were all the same.
  - Two studies included were on products that are not approved for use in the US.

- Study Results:
  - Only two studies (Huang and Maheu) have been published since the last review. Both concluded that HA improved function and relieved pain. This begs the question, what new evidence is there to change the 2009 recommendation?
  - The AAOS analysis concluded *"...WOMAC pain, function and stiffness subscales scores all found statistically significant treatment effects..."* Based on this outcome overall, there does not seem to be justification to change a neutral recommendation to a negative.

- Control:
  - Saline is not a placebo but rather an active control due to the lavage/dilution effect - however HA was still significantly superior in the AAOS analysis.
  - In the real world, patients feel the difference from baseline, not from active control.

- Patient Inclusion:
  - Kellgren-Lawrence grade I-III patients were included in the studies used for the meta-analysis. That is a heterogeneous patient population.

- It is widely recognized that some patients are responders and others are not. These are difficult to pre-identify. Inclusion of both in clinical trials can result in a small mean change although many individual patients are helped significantly.

- MCII Effectiveness Measure
  - The MCII may help standardize the review process however there is no apparent correlation to the treatment of real world patients in a clinical setting. The MCII lens therefore may not be the best tool for developing clinical practice guidelines

WHAT YOU CAN DO

If you too are concerned about the impact of these guidelines on your ability to access HA treatment for your patients there is something you can do about it. The AAOS is accepting public comment through **March 8**. You can respond to Recommendation #9 on the attached "structured response form" and email to **song@aaos.org** or you can request the full set of draft guidelines by contacting:

Sharon Song, Ph.D.
Manager, Clinical Practice Guidelines Unit
Department of Research and Scientific Affairs
American Academy of Orthopaedic Surgeons
6300 North River Road
Rosemont, Illinois 60018
T: (847) 384-4328
Email: song@aaos.org

Please take note of the short timeline for response. If you need any further information please contact your Bioventus representative.

Best regards,

Peter Heeckt, MD, PhD
Chief Medical Officer

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
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Reviewer Information:

Name of Reviewer Dominic J Kleinhenz MD

Address 1821 NE 25th St

City Lighthouse Pt State FL Zip Code 33064

Phone 954 942 0321 Fax 954 946 7018 E-mail domklhp@gmail.com

Specialty Area/Discipline: General

Work setting: Hospital Based Credentials: Board Certified ABOS

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Society Name: ACOS

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4. The guideline's target audience is clearly described				X
5. The patients to whom this guideline is meant to apply are specifically described	X			
6. The criteria used to select articles for inclusion are appropriate	X			
7. The reasons why some studies were excluded are clearly described	X			

8. All important studies that met the article inclusion criteria are included	disagree
9. The validity of the studies is appropriately appraised	disagree
10. The methods are described in such a way as to be reproducible.	disagree
11. The statistical methods are appropriate to the material and the objectives of this guideline	No opinion
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14. The writing style is appropriate for health care professionals.	No opinion
15. The grades assigned to each recommendation are appropriate	No opinion

1

02.10 Rev 3

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Reviewer Information:

Name of Reviewer Philip Lavin, PhD, FASA, FRAPS

Address 3 Cahill Park Drive

City Framingham State MA Zip Code 01702

Phone 508 816 7231 Fax E-mail phil_lavin@hotmail.com

Specialty Area/Discipline: Biostatistics, regulatory, reimbursement, hyaluronic acid

Work setting: Public health Credentials: 20+ years designing and analyzing OA knee studies; 4 HA PMA approvals

---

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14. The writing style is appropriate for health care professionals.	☒	☐	☐	☐
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I am concerned that AAOS, as a surgical society, passes judgment on a safe and accepted therapeutic modality which, if eliminated, will promote NSAIDs use and knee replacement surgery for the treatment of knee OA; this is a clear conflict of interest. This will lead to increased incidence of GI toxicity as well as the morbidities associated with knee replacement surgery. The economics of this recommendation will accelerate knee replacement surgeries which will further burden our stressed health care system.

I also believe that the data analyses favor group-level endpoints expressed as means as opposed to patient-level success which uses the patient as their own control. The analyses presented do not acknowledge the efficacy of placebo as really being arthrocentesis which is consistently shown to be an effective treatment. Finally, the meta analyses are disappointing in that they ignore the baseline Kellgren-Lawrence score, the degree of baseline pain, and the administration of prior HA therapy.

Cost Benefit:

- If HA therapy is discontinued as a therapeutic option, a million patients would need to find other treatments. I estimate 50% would be K-L 3's who would be knee replacement candidates over the next five years. At $10,000 per surgery, we would face $1 billion per year (500,000 OA knee patients x $10,000 / 5 years) vs. $0.5 billion per year (500,000 OA knee patients x $10,000 / 10 years). The annualized cost of additional NSAIDs, braces, physical therapy, and orthopedic consults would approximately match the cost of single-injection OA knee HA therapy.

AAOS Data Analyses:

- Despite recommendations expressed in publications regarding patient-specific measures (Dworkin et al (2009) [1]), AAOS analyses (Tables 175-178) overly focus on group outcome measures as opposed to patient-specific measures like percent change from baseline in pain.
- The IMMPACT recommendations further state that individual-level as well as group-level outcomes both matter. More emphasis needs to be placed on the patient as their own control.
- The multi-dimensional benefit, evident from the AAOS summary tables (Tables 175-178), is not addressed. This is a generic flaw of meta-analysis.
- There is broad acceptance that the proportion benefitting as well as the onset time and duration of benefit are informative measures. No data are presented on these clinically meaningful outcomes.
- The OA knee population is quite heterogeneous given prior HA use, the degree of baseline pain, patient age, and baseline K-L score. The MCID also must be context-specific relative to the target population; this is different for a K-L 2 population than for a K-L 3 population. Again, this is not addressed by the meta-analyses.
- The AAOS analyses should try to identify which patients benefit from arthrocentesis. Please note that single-injection "placebo" control efficacy has steadily improved to resemble the efficacy of approved multi-injection regimens.
- No consensus exists with respect to the MCID to be detected per endpoint; over the last 20 years, the mean WOMAC pain MCID has been steadily dropping to reflect improving "placebo" outcomes.
- Finally, any negative recommendation regarding HA treatment can lead to more limited injection options for OA knee patients, thus forcing patients to consider more invasive and costly knee replacement surgery.

Thus I recommend that AAOS address the following:

- **Conduct a cost benefit analysis of the impact of their recommendation**
- **Conduct patient-specific analyses to balance the presentation.**
- **Address multi-dimensionality of OA knee HA therapy**
- **Comment on the efficacy of arthrocentesis.**

Reference:

1. Dworkin RH et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain. 2009; Vol. 146, 238-244.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

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- Your conflicts of interest will be published on the AAOS website with your review.

Reviewer Information:

Name of Reviewer Colleen Linehan
Address 4701 Towne Centre, Bldg. 2. Suite 301
City Saginaw State MI Zip Code 48604
Phone 989-921-3500 Fax _____ E-mail drColleenLinehan@gmail.com

Specialty Area/Discipline: Orthopaedic Surgeon
Work setting: Hospital Credentials: MD

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☒ Yes ☐ No
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Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
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Please complete and return this form electronically in **WORD format** to Song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **March 8, 2013.**

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	☒
2. There is an explicit link between the recommendations and the supporting evidence	☒	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☒	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☐	☒
5. The patients to whom this guideline is meant to apply are specifically described	☒	☐	☐	☐
6. The criteria used to select articles for inclusion are appropriate	☒	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	☐	☒	☐	☐
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	☐
9. The validity of the studies is appropriately appraised	☒	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	☒
11. The statistical methods are appropriate to the material and the objectives of this guideline	☒	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☒	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☒	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	☒
15. The grades assigned to each recommendation are appropriate	☒	☐	☐	☐

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OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

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As both a patient and board-certified orthopaedic surgeon, I completely disagree with your statement to "**not** recommend using highly uric acid for patients with **symptomatic** osteoarthritis of the knee." I have mild arthritis in my knee, and am under the age of 40. I am not comfortable having steroids placed in my knee on a regular basis for the next 20 years. When I have had Supartz injected, I have felt relief within one day. After my most recent knee surgery, which involves autologous chondrocyte implantation over the majority of my femur and patella, it was Supartz which allowed me to regain my final range of motion. The pain relief provided by Visco supplementation lasts in my knee, and the most of my patient's knees, for 6-12 months. I believe it would be a travesty to not recommend this to my patients. I completely disagree with your statement, and hope that this does not affect the ability of my patients to receive Visco supplementation into the knee. I do believe that Visco supplementation does not play a role in moderate to severe osteoarthritis of the knee. I reserve this medication only for early or mild arthritis. Perhaps a better recommendation would be to add a descriptor different than "symptomatic" osteoarthritis. I do agree that Visco supplementation does not play a role in bone-on-bone arthritis. However, your statement is very broad, and will likely be a detriment to my patients with early arthritis.

In addition, your selection process failed to account for product differences. I do not believe that all highly uric acid products are the same. I also do not believe that saline is an adequate placebo. Placing a needle into the joint and not injecting anything would have been a better placebo. Furthermore, the patient population used in this meta-analysis is too heterogeneous. It needs to be broken down further into a more discrete degrees of arthritis.

Sincerely,

M.D.

Colleen Linehan, M.D.
Board certified orthopedic surgeon

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Reviewer Information:

Name of Reviewer___Peter Loescher MD_____

Address_____12 Shippee Lane_____

City_____Sharon_____ State_____VT_____ Zip Code_____05065_____

Phone _____802-763-8000_____Fax _____763-8090_____E-mail_____

Specialty Area/Discipline: _____sports medicine_____

Work setting: _____clinic_____Credentials: _____MD, FAAFP_____

May we list you as a Peer Reviewer in the final Guidelines (GL)? x☐ Yes ☐ No
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	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	x☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	x☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	x☐	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	x☐	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	x☐	☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	x☐	☐
7. The reasons why some studies were excluded are clearly described	☐	x☐	☐	☐
8. All important studies that met the article inclusion criteria are included	x☐	☐	☐	☐
9. The validity of the studies is appropriately appraised	☐	x☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	x☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	x☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	x☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	x☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	x☐	☐	☐	☐
15. The grades assigned to each recommendation are appropriate	x☐	☐	☐	☐

COMMENTS

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I have used HA in my clinical practice for over 15 years. I use it primarily in knees, but also in hips, shoulders, ankles, primarily for moderate to severe OA. I find it to be effective in 80% of patients that I use it for. Many of the patients that I use HA on come back for repeat injections, and recommend the use of HA to their families and friends. I had a few cases of pseudosepsis back when I used rooster comb based product, but since switching to a synthetic product 3 years ago, I have had no such complications. I find HA to be a safe, effective and well tolerated treatment option for joint OA. I would like to see FDA approval for HA expanded to use in hips and shoulders and ankles in this country in addition to knees. It works well in all large joints, and should be continued to be recognized as an important part of our armamentarium against OA.

Thank you,

Peter Loescher, MD
Sharon Sports Medicine
12 Shippee Lane
Sharon, VT 05065

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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Reviewer Information:

Name of Reviewer__David J Mansfield_____

Address_____1720 Murchison_____

City___El Paso_____ State___TX_____ Zip Code___79902_____

Phone __915 533 7465_____Fax _____E-mail__mansfieldmd@me.com

Specialty Area/Discipline: __Orthopaedic Sports Medicine_____

Work setting: _Group Practice_____Credentials: __MD_____

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If yes, may we list your society as a reviewer of this guideline? **Yes** No

Society Name: ____AAOS_____
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Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	Yes No
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	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated			X	
2. There is an explicit link between the recommendations and the supporting evidence				X
3. Given the nature of the topic and the data, all clinically important outcomes are considered			X	
4. The guideline's target audience is clearly described				X
5. The patients to whom this guideline is meant to apply are specifically described				X
6. The criteria used to select articles for inclusion are appropriate				X
7. The reasons why some studies were excluded are clearly described			X	
8. All important studies that met the article inclusion criteria are included				\X
9. The validity of the studies is appropriately appraised			X	
10. The methods are described in such a way as to be reproducible.			X	
11. The statistical methods are appropriate to the material and the objectives of this guideline				
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed				X
13. Health benefits, side effects, and risks are adequately addressed		X		
14. The writing style is appropriate for health care professionals.				X
15. The grades assigned to each recommendation are appropriate		X		

COMMENTS

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First of all, congratulations to the work group for the huge amount of effort and exceptional finished product. Many of my questions have been addressed in the previous comment responses. There were two issues that I feel may be inadequately addressed.

1) The response to Dr Kennedy's comment did not address his comment. Multiple studies have shown that errors occur in needle placement when giving "blind" injections. I believe Dr Kennedy was trying to point out that the efficacy of injections may be improved by the use of Ultrasound Guidance. The response to his comment concerned diagnostic imaging within the studies.

2) Unfortunately, experience has shown us that Guidelines put forth by Medical Associations become rules by which payment and access decisions are made. I am extremely pleased that a very thorough and clear explanation of the terminology used in the recommendations was included. The corresponding tables and definitions of the varying degrees of strength of recommendation are extremely helpful. That being said, I have a hard time understanding the Strong recommendation against ALL viscosupplementation. Much time is spent discussing the fact the higher molecular weight Hyaluronic Acid was associated with a clinically significant decrease in pain. This is a common finding in many of our clinical practices. as decreasing pain is a vital component in the treatment of osteoarthritis. My concern is that this Strong recommendation againt HA use will be used to take away a modality that may practitioners, including myself, have used successfully in many patients.

Thanks again for the hard work and excellent product

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

Strongly recommend

Recommend (with provisions or alterations)

Would not recommend

Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

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Reviewer Information:

Name of Reviewer: Jason A. Reed, DO

Address: 75 Hospital Drive; Suite 380

City: Athens State: OH Zip Code: 45701

Phone: 740-566-4657 Fax: 740-566-4641 E-mail: jreed1111@hotmail.com

Specialty Area/Discipline: Orthopedic Surgeon

Work setting: Office Credentials: DO

May we list you as a Peer Reviewer in the final Guidelines (GL)? X☐ Yes ☐ No
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Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes X☐ No
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Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	X☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	X☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	X☐
4. The guideline's target audience is clearly described	☐	☐	☐	X☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	X☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	X☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	X☐
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	X☐
9. The validity of the studies is appropriately appraised	☐	☐	☐	X☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	X☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	X☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	X☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☐	X☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	X☐
15. The grades assigned to each recommendation are appropriate	☐	☐	☐	X☐

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OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

X☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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Reviewer Information:

Name of Reviewer….Jay Robert Seebacher_____

Address 24 Saw Mill River Road Suite 206

City Hawthorne_____ State New York ____ Zip Code __10532____

Phone 914 631 7777_____Fax _____E-mail jrbacher@optonline.net _

Specialty Area/Discipline: joint replacement/knee arthritis_____

Work setting: private office _____Credentials: hospital attending, board certified ABOS, clinical instructor

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May we list you as a Peer Reviewer in the final Guidelines (GL)? XX☐ Yes ☐ No
PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your public comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? ☐ Yes XX☐ No

If yes, may we list your society as a reviewer of this guideline? ☐ Yes ☐ No

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	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	XX☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	XX☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	XX☐	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☐	XX☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	XX ☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	XX☐
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9. The validity of the studies is appropriately appraised	xx☐	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	xx☐	☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	xx☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	xx☐	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	xx☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	xx ☐
15. The grades assigned to each recommendation are appropriate	xx☐	☐	☐	☐

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As a busy joint replacement surgeon trained at **HSS**, I have utilized some type of non-operative suppression program or schema for osteo-arthritic knees throughout my 3-decade career, during which I have nevertheless replaced over 2000 of them as well.

For the **last 7 years** I have employed a **unique program** on over 600 individuals with what I consider to be both excellent success and extreme safety. Three **Categories** of osteoarthritic knees are so served: **Category 1** /Those beyond the help of arthroscopy (which I never employ for osteoarthritic knees), whom I feel are not severely afflicted enough to warrant knee replacement but are suffering enough for them to consider surgery, **Category 2** / Those whom I deem as appropriate candidates for knee replacement based on symptoms, physical findings, and severe (bone on bone) x-ray evidence, who refuse the surgery for personal reasons and **Category 3** / Those who would benefit from a knee replacement but are strongly medically contraindicated to undergo one.

All practicing knee replacement surgeons are aware of patients with severe joint wear, who still function well without pain. The goal of my program is to reduce the pain caused by inflammation so that the patient can exercise and function, gaining strength and flexibility of the surrounding and supporting muscles and joints….so as to cushion, protect and off-load their damaged knees. With time, they may enter a positive cycle…often regaining strength, sometimes losing weight, maintaining extension and flexion. The overwhelming majority of patients so treated have at least focal bone on bone or more on their standing x-rays….many have generous bone on bone, or even bone erosion. *I*f a patient under treatment begins to physically deteriorate towards a point where operating would be more difficult or more risky, surgery is always recommended and discussed with the PCP as well.

Three critical features of the program, **about which I am busily assembling presentable data**, make it **unique** and are:
1/ Hyaluronic acid, a single low dose vial is injected *if and only if* the knee is acutely & as fully suppressed of inflammation firstly & **always by** a **water insoluble steroid injection** administered 3-7 days earlier and if then or still needed by 1-2wks of a **potent continuous acting NSAID** always accompanied by a **PPI** (the NSAID not usually required).
2 /Physical therapy for strengthening the quads, buttocks, abdominals & triceps surae is **required**, followed by an indefinite home program of 30 mins performed 4-6X/wk. NSAIDS are available and monitored for safety with the approval of the patient's PCP (only 30% of patients use NSAIDS)
3/The **two injections** (water insoluble steroid and then sodium hyaluronate) are **repeated back-to-back every 12 weeks.** All injections are performed with the knees in full or maximum extension behind the mid-patella. Ultra-sonic guidance is used on about 66% of the knees based on difficulty.

All patients (particularly those with less than 50% narrowing) are offered the opportunity to stop the injections after the first two cycles of shots (6 months). All patients grade their arthritic pain on a **0**(none) to **10(**severe) **scale**, recorded at each visit. They also indicate how many of the 12 weeks (during each interval) the shots remain **highly effective**. If the positive effect of the two shots is less than 8 weeks, surgery is encouraged for all **Category 2** patients. If the pain level does not drop below a level 4 after each round of shots, surgery is encouraged for all **Category 2** patients. Any **Category 2** patients who develop fixed flexion contractures above 5 degrees are encouraged to undergo surgery.

As I will be presenting preliminarily on this approach, as a fellow of and at the current AAOS meeting, I believe these are new facts meritorious of serious consideration and am happy to discuss them, and make my experiences with these ministrations known.

Respectfully Submitted

Jay Robert Seebacher

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

XX☐ Would not recommend

☐ Unsure

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Reviewer Information:

Name of Reviewer ___Adolph J. Yates, Jr., MD_____

Address _Suite 415, 5200 Centre Ave._____

City Pittsburgh_____ State PA_____ Zip Code____15232_____

Phone 412-802-4105 _____Fax 412-802-4120_____E-mail yatesas@upmc.edu___

Specialty Area/Discipline: Adult Reconstruction _____

Work setting: _____ Academic _____Credentials: Associate Professor University of Pittsburgh_____

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The work-group for this CPG should be congratulated for the considerable effort demonstrated by its proposed product. I am appreciative of the opportunity to provide public comment. After my review of the product as a whole, it would be appreciated if the group would address two minor suggestions regarding Recommendations 7 and 9 and then give attention to a more in depth issue concerning Recommendation 9.

Similar to previous comments made during this comment period, it does not seem appropriate to combine two very different classes of drugs in Recommendation 7A. Tramadol and NSAID's are different drugs with different biological targets. It is strongly suggested that the creation of a separate third subcategory for Recommendation 7 in which to address Tramadol would better match the practice patterns of most practitioners.

One minor concern regarding Recommendation 9 is that the derivations of the values given on the forest plots from the stated MCII's on page 17 are not demonstrated. It would be helpful to the membership of AAOS to know how values on the axis are determined, especially given its importance in the Recommendation's determination.

The major concern with Recommendation 9 is the actual determination of the MCII's used to adjudge the utility of HA injections for OA of the knee. Multiple previous reviewers during this public review process have expressed being uncomfortable with the "strong" recommendation about not being able to recommend this practice. The defense of this has been primarily the inability of this intervention to move to even an indeterminate level to the left of the offered MCII's on the forest plots provided. This reviewer does not feel that the less than robust literature regarding HA necessarily supports anything but an indeterminate response. My reasoning relies on specific concerns over the repeated stated reliance on the offered MCII's to justify this recommendation.

The given MCII's are borrowed from other studies assumed to be "closely related populations". The critical MCII values are from three studies from only two authors (1,2,3).

The MCII values for the WOMAC Pain, Function, Stiffness and Total Scores are derived from a population evaluated in two of the studies, both by Angst; the group consists of patients who have been admitted for inpatient rehabilitation for osteoarthritis (1,2). It is highly probable that such a population, given the need for inpatient admission, would have a higher baseline of pain and dysfunction with higher expectations and greater needs for adequate improvement, especially in comparison to the outpatient population usually receiving HA injections.

The paper by Tubach, used to determine the MCII's for pain VAS and global assessment, is a review article that references a previous study by the same author that evaluated a cohort of patients and their response to NSAID's (3); that population is not fully described in the citation as given, and comparison to the studies being evaluated regarding HA is not possible.

The data being evaluated consists of patient reported outcome scores, not dichotomous events and their incidence. The process for establishment of an MCII for such patient reported outcomes is not straightforward. In a 2008 review article from the Journal of Clinical Epidemiology, Revicki, et al recommend that the MID

(closely related to the MCII) for a patient reported outcome not be based from a single patient population and that it should be based on multiple approaches and triangulation (4).

In a different paper than used for this CPG, Tubach, et al state that, "no consensus exists on the methods that should be used to determine the MCID/MCII"; in that same paper, more than half of a polled group of rheumatologists recommend WOMAC MCII values effectively one half or less than the ones suggested for the CPG in question (5). The concept of MCII itself is debated, with this paper being one of many that raise the question of the greater utility of using the PASS (Patient Acceptable Symptom State) (5).

One recent paper on OA resorted to using three different MCII's to capture the potential variability (6). For the purpose of brevity, other reviewed papers will not be cited; there is, however, a greater literature on this topic available through Medline review.

None of this commentary is meant to prove or disprove the clinical efficacy of HA injections of the knee. The reviewer does not claim expertise in the fields of epidemiology or statistics. This review does, however, point out that the basic assumptions regarding the MCII's used to justify the stronger level of recommendation in Recommendation 9 are potentially debatable. If, after further clarification and possible utilization of a range of MCII's, the target is still not reached, the recommendation will be made more defensible. If, after further review, it is determined that the assumption of singular values for the MCII's in this study could be questioned, it would be best to assign an indeterminate finding or one with less strength. The patient population from which the current set of MCII's is derived is very different than those populating the papers being reviewed in the network meta-analysis.

To use a football analogy, this is a question as to where the goal post should be set, and the rules for such a determination do not appear to be set in stone. Please also keep in mind that the use of HA rarely occurs in isolation from other treatments such as NSAID's, exercise, etc., all with the patient's hopes of pain relief and avoidance of surgery. To finish the sports analogy, if HA injections act in part to move the ball into the "red zone" and some other intervention kicks the ball through the uprights wherever they might be set, there is an element of synergistic success.

Again, thank you for the opportunity for providing input.

1.) Angst F, Aeschlimann A, Michel BA, Stucki G. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. J Rheumatol 2002 January;29(1):131-8.

2.) Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum 2001 August;45(4):384-91.

3.) Tubach F, Wells GA, Ravaud P, Dougados M. Minimal clinically important difference, low disease activity state, and patient acceptable symptom state: methodological issues. J Rheumatol 2005 October;32(10):2025-9.

4.) Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. Journal of Clinical Epidemiology 61 (2008) 102e109

5.) Tubach F, Ravaud P, Beaton D, Boers M, Bombardier C, Felson DT, van der Heijde D, Wells G, Dougados M. Minimal Clinically Important Improvement and Patient Acceptable Symptom State for Subjective Outcome Measures in Rheumatic Disorders. J Rheumatology, 2007; 34: 1188-93.

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OVERALL ASSESSMENT

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☐ Strongly recommend

x☐ Recommend (with provisions or alterations)

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1. The recommendations are clearly stated	☐	☐	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	x☐	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	x☐	☐	☐	☐
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8. All important studies that met the article inclusion criteria are included	x☐	☐	☐	☐
9. The validity of the studies is appropriately appraised	☐	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	☐
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I strongly disagree with changing wording for Recommendation #9 to "Cannot Recommend" the use of viscosupplementation. I have found this to be an extremely important option in treating osteoarthritis of the knee. Most patients get very good, long-lasting relief. Many patients are not candidates for TKA for one reason or another, cortisone can have detrimental effects and rarely gives more than 3-4 weeks of relief, many patients cannot tolerate NSAIDS or Tylenol.

Viscosuplementation has provided patients with one more alternative to manage debilitating knee arthritis pain. I would fear that changing the wording would lead insurance companies to no longer cover this option any longer. I believe that by changing the wording, AAOS is doing a serious disservice to all patients with knee arthritis by giving insurance companies another reason not to cover certain treatments.

I would urge you to strongly reconsider the arbitrary changing of this wording with no good science behind it as many patients will suffer unnecessarily because of it.

OVERALL ASSESSMENT

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☐ Strongly recommend

☐ Recommend (with provisions or alterations)

x☐ Would not recommend

☐ Unsure

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	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	x☑	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☑x	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	x☑	☐	☐
4. The guideline's target audience is clearly described	☐	☐	x☑	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	x☑	☐
6. The criteria used to select articles for inclusion are appropriate	☐	x☑	☐	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	x☑	☐
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11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	x☑	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	x☑	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	x☑	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	x☑	☐
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While HA does not show large differences in benefit over saline vehicle, patients still receive benefit from HA. It is a mistake to equate saline injections with a placebo, they do offer therapeutic benefit. I have many patients who receive 6-12 months of pain relief from a series of HA. I do not support a negative recommendation.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☒ Strongly recommend

☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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1. The recommendations are clearly stated	☐	☐	XX	☐
2. There is an explicit link between the recommendations and the supporting evidence	XX	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	XX	☐	☐	☐
4. The guideline's target audience is clearly described	☐	XX	☐	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	XX	☐
6. The criteria used to select articles for inclusion are appropriate	☐	XX	☐	☐
7. The reasons why some studies were excluded are clearly described	XX	☐	☐	☐
8. All important studies that met the article inclusion criteria are included	XX	☐	☐	☐
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11. The statistical methods are appropriate to the material and the objectives of this guideline	XX	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	XX	☐	☐	☐
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As a physician who utilizes viscosupplementation with Hyaluronic Acid (HA) on a weekly basis, I have to strongly disagree with the recommendations. Many studies assessing the efficacy of HA injections used saline as a placebo, although it has been demonstrated that many patients receive a temporary benefit from the presence of saline in the joint such that this is not a true placebo and has the effect of diminishing the apparent benefit of HA. A true placebo would involve injecting nothing into the joint and comparing that to HA. Meta-analyses are by their nature are also fraught with statistical pitfalls such that a recommendation of this nature with such potentially far-reaching effects should not be based on anything short of rock-solid evidence.

A further concern I have is that this recommendation is being generated by a panel of orthopedists and one could argue that they have a conflict of interest in that HA therapy has the potential to reduce the need for knee replacements, which could negatively impact their surgical income.

Over the course of the last year and a half, I have witnessed first-hand the benefits of HA injections as patient after patient has had a return to normal function and life-altering improvements in pain. This proposed recommendation threatens to reduce the availability of a therapy that I can offer my patients with osteoarthritis of the knee.

In summary, I strongly oppose this recommendation as I feel that its conclusion is erroneous and the motives of the individuals behind the recommendation are suspect.

OVERALL ASSESSMENT

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☐ Strongly recommend

☐ Recommend (with provisions or alterations)

XX Would not recommend

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	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	xx	☐
2. There is an explicit link between the recommendations and the supporting evidence	x	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	x	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	x	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	x	☐	☐
6. The criteria used to select articles for inclusion are appropriate	x	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	☐	x	☐	☐
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9. The validity of the studies is appropriately appraised	☐	x	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	x	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	x☐	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	x☐	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	x☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	x☐	☐	☐	☐
15. The grades assigned to each recommendation are appropriate	x☐	☐	☐	☐
16. The recommendations reflect your clinical experience.	x☐			

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Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

xx Would not recommend

☐ Unsure

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13. Health benefits, side effects, and risks are adequately addressed	x☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	x☐
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Cannot believe that anyone who has been using HA products could say that it isn't beneficial to most of their patients! Definitely not all but the majority.

OVERALL ASSESSMENT

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- ☐ Strongly recommend
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1. The recommendations are clearly stated	X☐	☐	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	X☐	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	X☐	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☐	X ☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	X ☐
6. The criteria used to select articles for inclusion are appropriate	X☐	☐	☐	☐
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12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	X☐	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	X☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	X ☐
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☐ Strongly recommend

☐ Recommend (with provisions or alterations)

X☐ Would not recommend

☐ Unsure

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1. The recommendations are clearly stated	☐	☐	xx	☐
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6. The criteria used to select articles for inclusion are appropriate	x	☐	☐	☐
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9. The validity of the studies is appropriately appraised	☐	x	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	x	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	x☐	☐	☐	☐
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13. Health benefits, side effects, and risks are adequately addressed	x☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	x☐	☐	☐	☐
15. The grades assigned to each recommendation are appropriate	x☐	☐	☐	☐
16. The recommendations reflect your clinical experience.	x☐			

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My main concern is the benefit of intra-articular hyaluronic acid injections. My patients get improvement from these injections. If no harm is done and patients get improvement in symptoms then I would continue these injections. If one can show no benefit or show risk factors then I would agree to discontinue these HA injections.

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☐ Strongly recommend

☒ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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I find this concerning because use of hyaluronic acid injections has been a significant part of my treatment regiment for knee arthritis during the past 16 years.

I am a fellowship trained hip and knee surgeon in private practice in Illinois. I do not claim to be a researcher nor will I argue statistics with you, but I would have to say that 16 year of experience and thousands of injections would give a little credibility in my point of view.

I offer the injections to my patients who do not have any significant flexion contracture or alignment deformity. I do not recommend the injections to people with evidence of "bone on bone "arthritis on radiographs. I apologize that I am not a researcher and cannot give detailed statistical results on my patients but I would say that > 50% of the patients I give viscosupplementation to receive relief for at least 6 months. I have seen a significant difference between the various types of hyaluronic acid injections, marcaine injections, and steroid injections on the amount of pain relief and the duration of the pain relief in patients with arthritis. I cannot say anything about saline because I have never injected it in my patients. However, occasionally I find arthritis in patients that have meniscal tears. These patients have their knees flushed with at least 3 liters of saline during arthroscopy. By 6 weeks patients with significant arthroscopically identified arthritis are in pain. In these patients I perform viscosupplementation injections and the vast majority has significant relief lasting more than 6 months.

I have a number of patients who have returned to repeat the injection series more than once. These patients tell me that the injections were very effective in relieving their pain and improving their function. After a few series of injections in the time frame of a couple of years they tell me the injections no longer provided relief and they want to proceed with surgery.

Many cardiologists have restricted our use of NSAIDS in patients with arthritis, cortisone injections that provide short term relief infrequently have some systemic side effects. If the viscosupplemenation injections were removed from our treatment options I think many of my patients would suffer from the loss of a very safe and effective treatment option.

Thank you for your time.

OVERALL ASSESSMENT

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☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Public Comment Review Form

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Reviewer Information:

Name of Reviewer: **ANONYMOUS – Name and identifying information withheld upon request**
Address:
City: State: Zip Code:
Phone: Fax: E-mail:
Specialty Area/Discipline:
Work setting: Credentials:

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☐ Yes x☐ No
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Are you reviewing this guideline as a representative of a professional society? ☐ Yes x☐ No

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Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes x☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes x☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes x☐ No
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Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	X
2. There is an explicit link between the recommendations and the supporting evidence	X	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	X	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☐	X
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	X
6. The criteria used to select articles for inclusion are appropriate	X	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	X	☐	☐	☐
8. All important studies that met the article inclusion criteria are included	X	☐	☐	☐
9. The validity of the studies is appropriately appraised	☐	☐	X	☐
10. The methods are described in such a way as to be reproducible.	X	☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	X	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	X	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☐	X
14. The writing style is appropriate for health care professionals.	☐	☐	☐	X
15. The grades assigned to each recommendation are appropriate	☐	☐	☐	X

COMMENTS

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I believe that the basis for the AAOS draft Recommendation #9 is flawed for the following reasons:

- **Study Selection:**
  - **The selection process failed to account for product differences – dosing schedule, dose size, formulation, concentration, source material, etc. The studies utilized several different HA products yet were treated as if they were all the same.**
  - **Two studies included were on products that are not approved for use in the US.**

- **Study Results:**
  - **Only two studies (Huang and Maheu) have been published since the last review. Both concluded that HA improved function and relieved pain. This begs the question, what new evidence is there to change the 2009 recommendation?**
  - **The AAOS analysis concluded *"...WOMAC pain, function and stiffness subscales scores all found statistically significant treatment effects..."* Based on this outcome overall, there does not seem to be justification to change a neutral recommendation to a negative.**

- **Control:**
  - **Saline is not a placebo but rather an active control due to the lavage/dilution effect - however HA was still significantly superior in the AAOS analysis.**
  - **In the real world, patients feel the difference from baseline, not from active control.**

- **Patient Inclusion:**
  - **Kellgren-Lawrence grade I-III patients were included in the studies used for the meta-analysis. That is a heterogeneous patient population.**
  - **It is widely recognized that some patients are responders and others are not. These are difficult to pre-identify. Inclusion of both in clinical trials can result in a small mean change although many individual patients are helped significantly.**

- **MCII Effectiveness Measure**
  - **The MCII may help standardize the review process however there is no apparent correlation to the treatment of real world patients in a clinical setting. The MCII lens therefore may not be the best tool for developing clinical practice guidelines**

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)
☐ X I strongly would not recommend

☐ Unsure

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Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Merck (wife)	x☐ Yes ☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:Depuy	x☐ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes x☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier: Biogen, Merck	x☐ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes x☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes x☐ No
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Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	x☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	x☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	x☐	☐	☐
4. The guideline's target audience is clearly described	☐	x☐	☐	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	x☐	☐	☐
6. The criteria used to select articles for inclusion are appropriate	☐	x☐	☐	☐
7. The reasons why some studies were excluded are clearly described	☐	x☐	☐	☐
8. All important studies that met the article inclusion criteria are included	☐	x☐	☐	☐
9. The validity of the studies is appropriately appraised	☐	x☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	x☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	x☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	x☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	x☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	x☐	☐
15. The grades assigned to each recommendation are appropriate	☐	x☐	☐	☐

COMMENTS

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After reviewing the proposed guidelines regarding "Treatment of Osteoarthritis of the Knee", I would have to disagree with some of the recommendations as they are stated. As an extremely busy practicing Sports Medicine physician at the Rothman Institute for the past 12 years, I feel more than qualified to express my concerns over certain recommendations that have been proposed by the AAOS. While I agree with the majority of these recommendations, I have concerns specifically in reference to #1, #2, #7A and 7B, #8, and, especially, #9.

I agree with the STRONG recommendation (#1) that patients participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education; and engage in physical activity consistent with national guidelines. However, I am not in agreement with only a MODERATE recommendation (#2) for weight loss in patients with symptomatic OA of the knee and a BMI>25. I do not understand why a STRONG recommendation for weight loss has not been proposed. Obesity is a significant risk factor for knee OA and its progression. I am quite sure that the overwhelming majority of clinicians that treat patients with knee OA would agree with this statement. I feel that this recommendation needs to be revisited.

I am having a difficult time understanding why the AAOS has made such a STRONG recommendation (#7A) regarding the use of NSAIDs and only an INCONCLUSIVE recommendation (#7B) for the use of acetaminophen for knee OA pain management. Furthermore, why has acetaminophen been categorized with narcotic medications and given an INCONCLUSIVE recommendation? The medical journals are filled with the potential negative effects of NSAIDs and I am certain that most physicians have seen these potential detrimental effects first hand and have tried to avoid them as much as possible, especially for chronic OA pain management. Therefore, if the justification of applying a STRONG recommendation is because "the benefits of the recommended approach CLEARLY exceed the potential harm" then I cannot agree with this recommendation. I (and I am sure most clinicians would agree) do not feel that the benefits of NSAIDs CLEARLY exceed the potential harm they can cause. This recommendation needs to be revisited and discussed further in my opinion. Regarding the use of acetaminophen for knee OA, I do not understand why the AAOS would not endorse this as a STRONG recommendation. In this case (as opposed to NSAID use) I could see the justification of applying a STRONG recommendation (benefits outweigh risks). Furthermore, almost every guideline that has ever been proposed has always endorsed the use of acetaminophen as a first-line agent to treat knee OA pain. I am not sure why the AAOS is not in favor, or not sure, of its use at this time.

Lastly, as a extremely experienced hyaluronic acid injection user, I am adamantly opposed to the STRONG recommendation (#9) against using hyaluronic acid for patients with symptomatic knee OA. Once again, I cannot understand this STRONG recommendation. I do not see how in this case the "potential harm CLEARLY exceeds the benefits" of using HA injections to treat knee OA pain. I would like a much clearer explanation has to how this was determined by the AAOS. Even though both HA and corticosteroid injections are minimally invasive, the risk involved with administration of and potential infection is minimal, at best. These products have been studied and approved by the FDA for use in treating knee OA. They offer, in my opinion, a safer alternative for knee OA pain treatment over chronic NSAIDs or corticosteroid use, especially in patients with mild to moderate pathology. I would like to know if this recommendation stems directly from the systematic review and meta-analysis titled "Viscosupplementation for Osteoarthritis of the Knee" published in the Annals of Internal Medicine (June 12, 2012, volume 157). In this article Rutjes et al concluded "that the benefit of viscosupplementation on pain and function in patients with symptomatic osteoarthritis of the knee is minimal or nonexistent" and that "the administration of these preparations should be discouraged". A major flaw with the methods used to calculate effect size is that the authors did not take into account the fact that saline injections can also be therapeutic. If this benefit of intra-articular saline is not taken into account, the effect size for viscosupplementation will appear smaller than it actually would be if measured against a true placebo. Since intra-articular saline does have an effect, it should be considered a control rather than as no treatment. Essentially, they equate saline injections with no therapy. The meta-analysis did not differentiate between efficacy results measured at different time points, nor were these results stratified by type of hyaluronic acid product injected. Regarding adverse effects, again Rutjes et al did not differentiate between different hyaluronic acid products in terms of purity, crosslinking, and other aspects, so it is impossible to know if the treatment-related adverse events were all caused by one type of product or were distributed evenly among all the products. Furthermore, several serious adverse effects, such as GI problems, cardiovascular events, and cancer, were listed, but no mention was made of whether the investigators in the reported trials deemed these events to be related to treatment or coincidental. The authors, in discussing limitations of their analysis, wrote "many reports did not provide adequate data on adverse events…the low quality of reporting safety data means that we could not understand the probable causes of serious adverse events." Based on my years of clinical expertise using these HA products, I STRONGLY feel that this recommendation needs to be revisited on many levels. In reviewing all 15 of these recommendations, I am deeply concerned that the pain management options for patients afflicted with and suffering from knee OA (especially mild to moderate) would be greatly compromised if these recommendations were to ALL go through as currently proposed.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

x☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

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Reviewer Information:

Name of Reviewer: Bioventus LLC - Peter Heeckt, MD

Address: 4721 Emperor Boulevard Suite 100

City: Durham State: NC Zip Code: 27703

Phone: (901) 277-6974 Fax: (901) 474-6893 E-mail: ChiefMedicalOfficer@BioventusGlobal.com

Specialty Area/Discipline: Distributor Medical Device

Work setting: Clinical Credentials: Medical Doctor

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Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Bioventus LLC and Smith & Nephew	☒ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier: Bioventus LLC and Smith & Nephew	☒ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
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12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☒	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☒	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☒	☐
15. The grades assigned to each recommendation are appropriate	☒	☐	☐	☐

COMMENTS

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Thank you for the opportunity to provide commentary on the draft AAOS guideline on *Treatment of Osteoarthritis of the Knee.* Specifically our comments are around Recommendation #9 which reads, *"We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee."* We understand how the AAOS has performed the analysis, however we believe that the AAOS erred in the application of the MCII analysis leading to an incorrect result. Further, we disagree with the conclusion and recommendation for this and other reasons that we will address below.

Study Selection:
The study selection process assumed that all Hyaluronic Acid products are the same when in fact there are substantial differences in the products approved for use in the US. The dosing schedule, dose size, formulation, concentration and source material are just a few of those differences. The studies utilized several different HA products yet they are treated as though they were all identical. Please note that intra-articular HA products are classified by the FDA CDRH division as class III medical devices. To gain approval in the US, each must demonstrate safety and effectiveness via randomized, controlled clinical trials. The FDA has reviewed many HA products that have not met the agency's safety and effectiveness criteria and therefore have not been approved in the US. This underscores the differences in HA products.

In addition, two of the studies reviewed include HA products which are NOT approved in the US. Because this review is the basis of a recommendation for US physicians, we are concerned this will confuse and mislead many readers.

Study Results:
Only two new studies (Huang and Maheu) have been published since the last review. Both concluded that HA improved function and relieved pain. This brings up the question, what new evidence has surfaced since the last AAOS review to prompt a negative change from the 2009 recommendation? Further, the analysis concluded *"...WOMAC pain, function and stiffness subscales scores all found statistically significant treatment effects…"* Based on this outcome, there does not seem to be adequate justification to change a neutral recommendation to a negative.

Control:
In the analysis and the clinical studies reviewed, saline injections were considered a "placebo". In fact saline is an **active control** and not an inert substance which is at least partially due to the lavage/dilution effect. By removing the effusion and diluting inflammatory cytokines patients will experience a degree of relief that exceeds a "placebo" effect. It is important to note that compared to this active control HA was still statistically significantly superior in every one of the four analyses (WOMAC pain, VAS weight bearing pain, function, WOMAC stiffness) that AAOS reviewed.

Patient Inclusion:
Kellgren-Lawrence grade I-IV patients were included in the studies reviewed as part of the meta-analysis. This is not a homogeneous patient population. It is commonly known that HA products are not as effective in late stage osteoarthritis. As such grade IV patients should not have been included in the analysis.

MCII Effectiveness Measure:
The AAOS has chosen to apply minimum clinically important improvement (MCII) criteria to measure the treatment effects of hyaluronic acid. In the draft guideline document it states, *"Analysis of statistical significance is limited without consideration of clinical importance to patients. Whenever the data was available, we identified minimum clinically important improvement (MCII) treatment effects in addition to statistical significance. The MCII reflects the smallest clinical change **that is important to patients** and recognizes that there are some treatment-related statistically significant improvements that are too small to matter."*

Angst et al. developed an algorithm for measuring the minimum clinically important difference of conservative OA treatments against baseline and provided standards for measurement that AAOS has utilized in their analysis of HA therapy. We believe that measuring MCII in the manner Angst et al. and others described can be a valuable and valid tool to detect small clinically important treatment effects, however, we also believe AAOS applied the standard incorrectly and ultimately came to an incorrect conclusion.

The true clinical improvement, that is important to a patient, should measure the change between the baseline assessment and the treatment effect. AAOS instead measured the delta between patients who received saline treatment and patients who received HA treatment. According to Dworkin et.al.[1.] "meaningful change in individual patients reflects any effects of the active treatment, placebo and other non-specific effects of the clinical setting, natural history and spontaneous resolution, and statistical regression to the mean. Differences between treatment and placebo groups, however, reflect the incremental benefits of active treatments that contribute to improvement after subtracting out placebo and other non-specific effects, natural history, and regression to the mean…" Therefore, Dworkin concludes that "given their critical differences, evaluations of the clinical meaningfulness of group differences in chronic pain trials **should not** be based on criteria for evaluating clinically meaningful changes in individual patients".

When this analysis is done correctly, we conclude that the clinical effectiveness scores are 2 to 3 times the MCII value depending on the individual study. This is the difference ***that is important to patients***.

Alternative Treatments

One of the only four (out of 15) treatments that received a positive recommendation in the draft guideline was NSAID treatment. Given that there were so few positive recommendations overall, we are concerned that the consequence will be increased usage, and perhaps overuse of NSAID treatment. With well documented safety issues around NSAIDs we believe this could lead to an increase in patient harm. A 1999 study in the New England Journal of Medicine states, *"It has been estimated conservatively that 16,500 NSAID-related deaths occur among patients with rheumatoid arthritis or osteoarthritis every year in the United States."* [2.]
Alternatively, HA products, have a stellar safety record, yet received a negative recommendation leading us to wonder how much weight was given to patient safety when each recommendation in the guidance was made.

The AAOS Clinical Practice Guidelines are referenced by orthopaedic surgeons and other health care providers and have generally been held in high regard. It's important to point out that they are also referenced by health insurers who may wholly or partially, base coverage decisions on the AAOS Clinical Practice Guidelines. The effect of a negative recommendation can easily result in coverage limitations thereby reducing, or eliminating patient and physician access to treatment options. For this to occur based on an incorrect CPG conclusion would be disastrous for many patients, especially those who do not tolerate NSAIDs, wish to avoid or delay knee replacement surgery, or are unsuitable candidates for arthroplasty.

Eliminating effective, non-surgical treatments by recommending against their use will result in a significant increase in arthroplasty procedures in younger patients, or will leave those patients who are poor surgical candidates with virtually no options at all. With the aging baby boomer population and the issues around rising health care costs overall, we believe that AAOS must very carefully consider the real world impact of their CPG recommendations. Before recommending against any treatment option, we believe that AAOS has a responsibility to be certain that no one will benefit from that treatment.

In summary, we are convinced of HA's benefit to a large percentage of patients suffering from knee OA. This has been established by scientifically valid trials demonstrating superiority over active controls which have resulted in peer reviewed FDA approvals. Additional MCII analysis confirms the efficacy of HA. Though not all patients respond to HA treatment the preponderance of patients do and they enjoy substantial benefit. On this basis we request that Recommendation #9 be changed to "We recommend the use of HA for the treatment of knee osteoarthritis".

1. Dworkin RH et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain. 2009; Vol. 146, 238-244.

2. Wolfe M. MD, Lichtenstein D. MD, and Singh Gurkirpal, MD, "Gastrointestinal Toxicity of Nonsteroidal Anti-inflammatory Drugs", The New England Journal of Medicine, June 17, 1999, Vol. 340, No. 24, pp. 1888-1889.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

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Dear Doctor,

Back in 2009, The American Academy of Orthopaedic Surgeons (AAOS) published an update of their Clinical Practice Guidelines (CPG) on *Treatment of Osteoarthritis of the Knee.* At that time they revised their position on the use of hyaluronic acid (viscosupplement) products from "...we recommend..." to "...we cannot recommend for or against..." Their decision was based on an existing AHRQ technology assessment.

The AAOS is now preparing to publish an update of the 2009 CPG and currently is seeking public comment on a draft version. In this draft the recommendation (Recommendation #9) on HA treatment has been revised downward once again to, **"We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee. Strength of recommendation: Strong"**. This new, negative, recommendation is based on a review of 14 studies chosen by the Review Committee measured against a new metric that AAOS has now arbitrarily created called Minimum Clinically Important Improvement (MCII). The Review Committee acknowledged that overall, there was a statistically significant difference between HA and saline but because the difference was not strong enough to meet the MCII threshold, the recommendation was changed from neutral to negative. If these guidelines are finalized the consequence is that health insurers could begin to pull back coverage for HA products making patient and physician access far more difficult or impossible. This is especially concerning for patients who are not candidates for surgery, NSAIDs and corticosteroids.

We believe that the basis for the AAOS draft Recommendation #9 is flawed for the following reasons:

- Study Selection:
  - The selection process failed to account for product differences – dosing schedule, dose size, formulation, concentration, source material, etc. The studies utilized several different HA products yet were treated as if they were all the same.
  - Two studies included were on products that are not approved for use in the US.

- Study Results:
  - Only two studies (Huang and Maheu) have been published since the last review. Both concluded that HA improved function and relieved pain. This begs the question, what new evidence is there to change the 2009 recommendation?
  - The AAOS analysis concluded *"...WOMAC pain, function and stiffness subscales scores all found statistically significant treatment effects..."* Based on this outcome overall, there does not seem to be justification to change a neutral recommendation to a negative.

- Control:
  - Saline is not a placebo but rather an active control due to the lavage/dilution effect - however HA was still significantly superior in the AAOS analysis.
  - In the real world, patients feel the difference from baseline, not from active control.

- Patient Inclusion:
  - Kellgren-Lawrence grade I-III patients were included in the studies used for the meta-analysis. That is a heterogeneous patient population.

- It is widely recognized that some patients are responders and others are not. These are difficult to pre-identify. Inclusion of both in clinical trials can result in a small mean change although many individual patients are helped significantly.

- MCII Effectiveness Measure
  - The MCII may help standardize the review process however there is no apparent correlation to the treatment of real world patients in a clinical setting. The MCII lens therefore may not be the best tool for developing clinical practice guidelines

WHAT YOU CAN DO

If you too are concerned about the impact of these guidelines on your ability to access HA treatment for your patients there is something you can do about it. The AAOS is accepting public comment through **March 8**. You can respond to Recommendation #9 on the attached "structured response form" and email to **song@aaos.org** or you can request the full set of draft guidelines by contacting:

Sharon Song, Ph.D.
Manager, Clinical Practice Guidelines Unit
Department of Research and Scientific Affairs
American Academy of Orthopaedic Surgeons
6300 North River Road
Rosemont, Illinois 60018
T: (847) 384-4328
Email: song@aaos.org

Please take note of the short timeline for response. If you need any further information please contact your Bioventus representative.

Best regards,

Peter Heeckt, MD, PhD
Chief Medical Officer

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Public Comment Review Form

ALL REVIEW COMMENTS, OUR RESPONSES AND REVIEWER COI WILL BE AVAILABLE FOR REVIEW ON OUR WEBSITE FOLLOWING BOD APPROVAL OF THIS DOCUMENT.

Review of any AAOS confidential draft allows us to improve the overall guideline but does not imply endorsement by any given individual or any specialty society who participates in our review processes. The AAOS review process may result in changes to the documents; therefore, endorsement cannot occur until the AAOS Board of Directors officially approves the final guideline.

Please note that if you return a review:

- **Your comments will be published on the AAOS website with our explanation of why we did nor did not change the draft document in response to your comments.**
- **Your conflicts of interest will be published on the AAOS website with your review.**

Reviewer Information:

Name of Reviewer_____Mitek Sports Medicine, DePuy Synthes, Johnson & Johnson_____

Address_____325 Paramount Drive_____

City___Raynham_____ State_____MA_____ Zip Code_____02767_____

Phone ____508-977-6475_____Fax _____E-mail____sbhatta6@its.jnj.com_____

Specialty Area/Discipline: _____Sports medicine_____

Work setting: _____ Credentials: ___PhD, MD, MPH, MBA_____

May we list you as a Peer Reviewer in the final Guidelines (GL)? X Yes ☐ No
PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your public comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? ☐ Yes ☒ No

If yes, may we list your society as a reviewer of this guideline? ☐ Yes ☐ No

Society Name: _____
(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

If the boxes below are not checked and/or the reviewer does not attach his/her conflicts of interest, the reviewer's comments will not be addressed by the AAOS nor will the reviewer's name or society be listed as a reviewer of this GL. If a committee reviews the guideline, only the chairperson/or lead of the review must declare their relevant COI.

☒ **I have declared my conflicts of interest on page 2 of this form.**

☐ **I have declared my conflicts of interest in the AAOS database; my customer # is** _____

☒ **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.**

REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

Each item below requires an answer. Please report information for the last 12-months as required by the Accreditation Council for Continuing Medical Education (ACCME) guidelines.

Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes ☒ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company:	☐ Yes ☒ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Mitek Sports Medicine, DePuy Synthes, Johnson & Johnson	☒ Yes ☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier: Johnson & Johnson	☒ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes ☒ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify:	☐ Yes ☒ No
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American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Public Comment Review Form

Reviewer Instructions
Please read and review this Draft Clinical Practice Guideline and its associated Technical Report with particular focus on your area of expertise. Your responses are confidential and will be used only to assess the validity, clarity and accuracy of the interpretation of the evidence. If applicable, **please specify the draft page and line numbers in your comments**. Please feel free to also comment on the overall structure and content of the guideline and Technical Report.

Please complete and return this form electronically in **WORD format** to Song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **March 8, 2013.**

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☒	☐
2. There is an explicit link between the recommendations and the supporting evidence	☒	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☒	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☒	☐	☐
5. The patients to whom this guideline is meant to apply are specifically described	☒	☐	☐	☐
6. The criteria used to select articles for inclusion are appropriate	☒	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	☒	☐	☐	☐
8. All important studies that met the article inclusion criteria are included	☐	☒	☐	☐
9. The validity of the studies is appropriately appraised	☒	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☒	☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☒	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☒	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☒	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	☒
15. The grades assigned to each recommendation are appropriate	☒	☐	☐	☐

COMMENTS

PLEASE RETURN ALL COMMENTS IN WORD FORMAT

This Draft Clinical Practice Guideline has already completed peer review and has been reviewed by content experts. The feedback provided during this process is attached in the PDF. If you have any other brief additional comments, please feel free to provide them here. If applicable, please specify the draft page and line numbers in your comments.

RECOMMENDATION 9
We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee.
Strength of Recommendation: Strong

While we applaud the effort of AAOS to evaluate intra-articular HA therapy on the basis of clinical relevance, we respectfully take issue with Recommendation 9. Our primary objections are with the strength of the recommendation, and with the methodology and application of the Minimum Clinically Important Improvement (MCII). These and other concerns are detailed below.

2. There is an explicit link between the recommendations and the supporting evidence: DISAGREE
AND
10. The methods are described in such a way as to be reproducible: DISAGREE
AND
11. The statistical methods are appropriate to the material and the objectives of this guideline: DISAGREE

Recommendation 9 hinges largely on the use of the MCII as developed in publications by Angst and by Tubach. According to Angst, MCID is defined as the following: *"The minimal clinically important difference (MCID) can be defined generally as the smallest difference in score (i.e., the effect) that patients perceive as beneficial and which would then mandate, in the absence of troublesome side effects and excessive costs, a change in the patient's management."* It is critical to note that Angst established the MCID as a difference between pre- and post-therapy scores, ***not the difference between a therapy group and a control group***, which is how AAOS is using this analysis.

Dr. Robert H. Dworkin, PhD [Professor of Anesthesiology, Neurology, Oncology, and Psychiatry; Professor of Neurology in the Center for Human Experimental Therapeutics; Director, Anesthesiology Clinical Research Center] as our consultant has provided comments on the determination of the clinical importance of group differences. His letter can be found at the end of our comments section in its entirety but some of his comments are provided below.

> This critical distinction was clearly described in a pivotal article by Guyatt et al. (1998), and has been discussed by numerous others, including renowned biostatisticians (Kraemer et al., 2003; Kraemer and Kupfer, 2006), the IMMPACT consortium (Dworkin et al., 2008, 2009), the OMERACT organization (Beaton et al., 2001; Goldsmith et al, 1993), and most recently by Tubach herself and her colleagues (Ruyssen-Witrand et al., 2011) in an important systematic review and applied to prospective studies (Tubach et al., 2012).
>
> Unfortunately, there is no accepted and evidence-based approach for setting thresholds for the clinical importance of *group differences*. The literature cited above emphasizes that the magnitude of group differences that should be considered clinically important depends on a careful consideration of the condition being treated, the availability of other treatments for the condition, and the safety and tolerability of the treatment in view of other available treatments. ***As such, the use of a single study to establish MCII for comparing intra-articular HA against placebo is not supported by the literature.***

Even if the use of the Angst MCII were valid, we have concerns about the methodology used to determine it. Angst states: "the difference between the mean effects . . . of the "slightly better" group and the "equal" group was defined as the MCID *(i.e. MCII)* of improvement . . . ". The questionnaire used by Angst to segment physical therapy patients according to their reported "health status" contained only two choices for improvement: "slightly better" and "much better". The average WOMAC scores from the "slightly better" group were used to establish the MCII. While WOMAC is a widely

accepted and validated tool for assessing improvement in OA patients, we believe that the condensed scoring system of the Angst questionnaire lacks sufficient resolution to establish a meaningful MCII. It is further limited by its reliance on patient memory of their pre-therapy health status, and could be influenced by many health factors other than pain. Angst acknowledges these weaknesses in the study, which are borne out by the very large standard deviations within each group (+/- 100% in most cases).

3. Given the nature of the topic and the data, all clinically important outcomes are considered: DISAGREE
The working group identified the following outcomes as important:

> "Performance based physical function, serious GI bleed, ability to perform recreational activities, survival, treatment side effects, surgical complications, night time pain affecting sleep, major surgery complications, revision surgery, ability to earn income, ability to drive, social role function, joint stiffness, stability, range of motion, minor GI bleed, avoidance of need for knee replacement, strength, limpness, prevention of disease progression, deformity, joint alignment and stability, and joint swelling/effusion."

In addition to the outcomes listed above, we believe that Responder Rate should be considered as a clinically relevant outcome, as population averages can sometimes mask differences in the percentage of patients who respond to a therapy.

Even though many of the clinically important outcomes cited by AAOS are related to the safety of the therapy, Recommendation 9 was based entirely on conventional pain measures (e.g. WOMAC, VAS). As a class, HA viscosupplements have proven to be extremely safe, with negligible risk to patients. We believe that the safety profile of hyaluronic acid addresses several important clinical outcomes cited by AAOS, and has not been sufficiently factored into Recommendation 9.

5. The patients to whom this guideline is meant to apply are specifically described: DISAGREE
AND
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed: DISAGREE

- The Angst study included both knee (59%) and hip (41%) OA patients. HA is not approved by the FDA to treat hip osteoarthritis. Moreover, the inclusion criteria and baseline patient data indicate that all grades of OA were included. As clinical studies for HA viscosupplements have been tested in knee OA patients with K-L (Kellgren-Lawrence) grades II-III, the Angst study is not relevant because it included a broader group of OA patients than the studies included in this analyses.
- The variability in WOMAC pain reduction reported by Angst is also quite high (+/- 100% or more). Factoring in the high baseline variability, it is not clear whether the improvements in this study were even statistically significant, clinical significance aside.
- The Angst study patients were treated with more than one therapy, including " . . . passive physical therapy, such as electrotherapies, hydrotherapies, thermotherapies, massage, and others, and of especially active physical therapy to strengthen and stretch the musculature and passive structures, and to reestablish regular joint mobility". It is troubling that the MCII used in the AAOS analysis was determined using such a heterogeneous therapy regimen, when AAOS exclusion criteria do not allow studies that incorporated "treatment of interest and another treatment".

6. The criteria used to select articles for inclusion are appropriate: DISAGREE
AND
7. The reasons why some studies were excluded are clearly described: DISAGREE
AND
9. The validity of the studies is appropriately appraised: DISAGREE

> We disagree with the exclusion of studies having a duration less than 4 weeks. OA patients suffer from chronic pain, and it is important to include therapies that can mitigate pain quickly after the treatment (e.g. NSAID therapy, which AAOS recommends as a knee OA therapy) as well as long term (e.g weight loss and exercise, which are

also recommended). Moreover, the requirement of efficacy greater than four weeks dictated the exclusion of a highly recognized and widely cited Cochrane Review of 2009 and the therapeutic trajectory of benefit meta-analysis (Bannuru RR et al., 2011).

The only FDA approved products on the US market are Supartz, Orthovisc, Hyalgan, Synvisc/Synvisc 1, Gel-One, and Euflexxa. As these are class III products in the US, FDA has mandated that companies perform robust, statistically powered clinical studies to demonstrate safety and efficacy over saline placebo. FDA has not approved all HA products that have gone through their review (i.e. Durolane) because FDA treats these products individually recognizing that all the HA's are not the same in terms of efficacy. The papers used in the CPG included Durolane [Altman (2009)], Suplasyn [Petrella (2006)] and Adant [Navarro-Sarabia (2011)]. Durolane did try to get approval in the US but did not after an FDA panel meeting. Suplasyn and Adant have not presented any data to the FDA and are only commercialized outside US, in countries that do not require Level 1 clinical evidence for regulatory approval. If this is a recommendation for practice of medicine in the US, the analyses should be based on data from products that have been through the **rigorous FDA approval process**.

By definition, FDA approved hyaluronic acid products are commercially available due to the high strength of their clinical data. The narrow study selection criteria utilized by AAOS resulted in the analysis of only 14 papers, compared to over 100 papers utilized by Bellamy et al. in the cited Cochrane Review of 2009. Perhaps the recommendation by AAOS should be to require improvements in the quality of the reporting of clinical trial results to be able to facilitate this type of meta-analyses. The most recent studies that were included in this analyses (Huang 2011, Maheu 2011) demonstrate efficacy of the HA over placebo.

The CPG's selection criteria states that *"Case series studies that gave patients the treatment of interest and another treatment were excluded."* However, the Heybeli (2008) paper is referenced in Figure 79 and this study was focused only on patients receiving arthroscopic debridement *and* HA injections. Per CPG's selection criterion stated above, this study should have been excluded from the analyses as these patients received another treatment. The effect of the arthroscopic debridement may confound any analyses on just the HA injection. In addition, thie Heybeli reference was not listed as one of the 14 studies that was used, yet it is shown in the analyses.

HA molecular weight/concentration
We acknowledge the paucity of clinical data comparing HA products of differing molecular weights. However, a large body of *in vitro* and *in vivo* evidence suggests that the molecular weight, as well as the concentration, of HA can significantly impact its therapeutic effects at the cellular level. In particular, evidence suggests an optimum range of HA molecular weight for impacting cellular function. These studies have further shown that the cellular impact of HA increases strongly with concentration. Unfortunately, the clinical trials used in the AAOS analysis are dominated by HA products with very low (Hyalgan) and very high molecular weights (Hylan G-F 20), and relatively low concentrations (8-10 mg/ml). Only one study (Altman 2009) in the AAOS analysis incorporated an intermediate molecular weight HA product (BioHA, 2.4 million Da), and only one HA product with a concentration greater than 10 mg/ml was included. As such, we believe that the efficacy of HA as a class has been underestimated by the AAOS analysis.

13. Health benefits, side effects, and risks are adequately addressed: DISAGREE
AND
15. The grades assigned to each recommendation are appropriate: DISAGREE

As defined in the CPG, a STRONG recommendation is warranted when "benefits of the recommended approach clearly exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a strong negative recommendation), and/or that the quality of the supporting evidence is high." AAOS recognizes that there is very little safety impact for these products. **We believe the STRONG recommendation is inconsistent with this definition.**

SUMMARY

Based on our review of the supporting literature for Recommendation 9, we propose that AAOS alter its recommendation on hyaluronic acid to reflect the recommendation made in 2008. We further propose that the strength of the recommendation be changed from STRONG to LIMITED or INCONCLUSIVE.

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Letter from Dr. Dworkin:

March 5, 2013

Brad Bisson, MPH
Manager Clinical/Medical Affairs
DePuy Synthes
325 Paramount Drive, M-60
Rayham, MA 02767

Dear Mr. Bisson:

I am writing in response to your request to prepare comments on the American Academy of Orthopedic Surgeons (AAOS) draft "Evidence-Based Guideline on Treatment of Osteoarthritis of the Knee" focusing on issues involving the determination of the clinical importance of group differences in randomized clinical trials of intrarticular hyalorunic acid (HA). Although I have only carefully reviewed those sections of the AAOS draft Guideline directly relevant to these issues, it is important to emphasize that my comments on the determination of the clinical importance of group differences involve general methodologic and statistical issues and could therefore be applicable to other sections of the AAOS draft Guideline.

It is important to begin by emphasizing that before determining whether the group difference between an active treatment and a placebo control (or an active comparator) is clinically important, there should be evidence that the group difference is statistically significant. Specifically, chance must be excluded as an explanation for the difference between groups in the primary endpoint using a pre-specified and conventionally accepted level of statistical significance. Once the statistical significance of the group difference has been established, the clinical importance of the effect can be evaluated.

The AAOS draft Guideline states that for the WOMAC pain scale, "the HA group reported significantly lower pain scores than the control group;" that for pain on weight bearing as assessed by the Visual Analogue Scale (VAS), "the results were statistically significant;" and that for the WOMAC function scale, "HA did produce statistically significant improvement in function" (page 783; Figures 79-81). Given the statistically significant differences found in favor of HA, the AAOS draft Guideline then evaluates the clinical importance of these differences. For WOMAC pain, VAS pain on weight bearing, and WOMAC function, the AAOS draft Guideline concludes that none of the group differences between HA and placebo were clinically important (page 783).

These assessments of clinical importance are based on the results of studies that determined the minimum clinically important improvement (MCII) treatment effects, which the AAOS draft Guideline states "reflects the smallest clinical change that is important to patients and recognizes that there are some treatment-related statistically significant improvements that are too small to matter" (page 17). Studies by Angst et al. (2001, 2002) and by Tubach et al. (2005b; see also Tubach et al., 2005a, 2007) were cited as providing the values for determining the MCIIs used in evaluating whether statistically significant treatment group differences were clinically important (page 18).

However, these studies determined MCIIs for *within-patient improvements*, not criteria for clinically important *treatment group differences*. For example, Tubach et al. (2005b) concluded that pain reductions of 19.9 mm on a 100 mm VAS scale would be considered an MCII by patients, but they did not conclude that 19.9 mm is the minimum difference between an active treatment and placebo that is clinically important.

There is an evidence-based consensus that improvements in pain of this magnitude are important to patients (e.g., Dworkin et al., 2008; Tubach et al., 2007). However, it is essential to recognize that there is also a consensus among clinical epidemiologists, clinical trialists, and biostatisticians that the magnitude of clinically important improvements for individual patients should *not* be used as a basis for determining the magnitude of the group difference that should be considered a clinically important difference between an active treatment and placebo. This critical distinction between the interpretation of the clinical importance of individual patient improvements and of group differences was clearly described in a pivotal article by Guyatt et al. (1998), and has been discussed by numerous others, including renowned

biostatisticians (Kraemer et al., 2003; Kraemer and Kupfer, 2006), the IMMPACT consortium (Dworkin et al., 2008, 2009), the OMERACT organization (Beaton et al., 2001; Goldsmith et al, 1993), and most recently by Tubach herself and her colleagues (Ruyssen-Witrand et al., 2011) in an important systematic review. In this literature, it has been emphasized that the determination of what magnitude of group difference should be considered clinically important depends on a careful consideration of the condition being treated, the availability of other treatments for the condition, and the safety and tolerability of the treatment in view of other available treatments.

Several quotations making these critical points appear in the Appendix following the text of this letter. Consistent with the conclusions of these other investigators, the IMMPACT consensus recommendations for interpreting the clinical importance of group differences in chronic pain trials (Dworkin et al., 2009) emphasize that although the clinical importance of individual patient improvements can be determined by assessing what patients themselves consider important, the clinical importance of group differences "must be determined by a multi-factorial evaluation of the benefits and risks of the treatment and of other available treatments for the condition in light of the primary goals of therapy. Differences in mean reductions in pain between active treatment and placebo groups do not adequately describe the potential benefits of a treatment in the population of individuals with chronic pain." The IMMPACT consensus recommendations concluded that "because this multi-factorial evaluation must consider the benefits and risks of the treatment and of other available treatments for the condition, it is impossible to provide specific guidelines for determining whether or not a specific group difference is clinically meaningful. Such determinations must be conducted on a case-by-case basis, and are ideally informed by patients and their significant others, clinicians, researchers, statisticians, and representatives of society at large."

There is therefore a clear consensus that thresholds for the clinical importance of group differences should not be based on the magnitude of improvement that patients consider important. From this perspective, the approach taken in the AAOS draft Guideline of basing evaluations of the clinical importance of osteoarthritis treatments on WOMAC or VAS thresholds of clinically important patient improvements is not appropriate. This is not only because of the unwarranted extrapolation of individual patient MCIIs to group differences, but also because there is no accepted and evidence-based approach for setting thresholds for the clinical importance of group differences. Indeed, the critical distinction between what patients consider important improvement and what group difference is clinically important has been widely misunderstood (e.g., Bjordal, 2007). As Tubach and her colleagues (Ruyssen-Witrand et al., 2011) conclude on the basis of a careful systematic review of pain trials, there is great variability not only in published thresholds for MCIIs for individual patient improvements but also for the clinically important group differences used in calculating statistical power, and they emphasize that the confusion among these definitions can be misleading when interpreting the results of clinical trials. Most importantly, Tubach and her colleagues (Ruyssen-Witrand et al., 2011) also emphasize that criteria for clinically important group differences are often inappropriately based on what is considered clinically important at the individual patient level; they illustrate this with seven examples in which "the authors confused the application of the reference value at the individual or group level" (page 463, also Table 2), highlighting one trial that for sample size calculation "used the value of 20mm as a meaningful difference between groups and justified such a cutoff with a reference … that defined the value of 20 mm as the threshold of imprecision at the individual level" (page 466).

Sincerely,
Robert H. Dworkin, PhD
Professor of Anesthesiology, Neurology, Oncology, and Psychiatry
Professor of Neurology in the Center for Human Experimental Therapeutics
Director, Anesthesiology Clinical Research Center

Appendix: Relevant quotations from the literature (in chronological order)

Guyatt GH, Juniper EF, Walter SD, et al. (1998): "Clinicians and investigators tend to assume that if the mean difference between a treatment and a control is appreciably less than the smallest change that is important, then the treatment has a trivial effect. This may not be so. Let us assume that a randomized clinical trial shows a mean difference of 0.25 in a questionnaire in which the minimal important difference is 0.5. It might be concluded that the difference is unimportant and that the result does not support giving the treatment. This interpretation assumes that every patient treated scored 0.25 better than they would have done had they received the control and ignores the possibility that treatment might have a heterogeneous effect."

Beaton D, Bombardier C, Katz JN, et al. (2001): "Research has shown that the interpretation of change may vary depending on whether we are thinking at a group level (where smaller changes may be interpreted as important) or at an individual level, where larger changes are required before they are confidently accepted as indicating a meaningful change."

Kraemer HC, Morgan GA, Leech NL, et al. (2003): "The clinical significance of a treatment is based on external standards provided by clinicians, patients, and/or researchers. Unfortunately, to date there is little consensus about the criteria for these efficacy standards… We have provided some general guidelines for interpreting measures of clinical significance. It is not possible, however, to present more than a tentative recommendation for which effect size to use, or to provide any fixed standards for any such effect size that a clinician could universally use to conclude that an effect size was clinically significant. It makes a difference whether the treatment is for a deadly disease like polio, or the common cold, and whether the treatment is risky and costly or perfectly safe and free. The context in which an effect size is used matters in interpreting the size of the effect; the choice of effect size is only to facilitate consideration of the effect in the context of its use."

Kraemer HC, Kupfer DJ (2006): "The most challenging and urgent task remains unsolved: developing the principles that underlie the thresholds of clinical significance in different clinical contexts. This is a task with which biostatisticians have long struggled in designing RCTs, because they need such a threshold to do power calculations, but in the absence of clinical knowledge of the field, they can only arbitrarily set one. On the other hand, clinical researchers have the clinical knowledge of the field necessary to set the threshold but have not to date had the language to translate this knowledge to a form usable for power computations."

Ruyssen-Witrand A, Tubach F, Ravaud P (2011): "A lot of studies proposed values at the individual level for the CID (clinically important difference) with anchor-based approaches. At the group level, such important CID has not been proposed, because it can only be established on the broader context of the disease being treated, the currently available treatment, and the overall risk-benefit ratio of the treatment."
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OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
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Review of any AAOS confidential draft allows us to improve the overall guideline but does not imply endorsement by any given individual or any specialty society who participates in our review processes. The AAOS review process may result in changes to the documents; therefore, endorsement cannot occur until the AAOS Board of Directors officially approves the final guideline.

Please note that if you return a review:

- **Your comments will be published on the AAOS website with our explanation of why we did nor did not change the draft document in response to your comments.**
- **Your conflicts of interest will be published on the AAOS website with your review.**

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Work setting: Industry Credentials: MD, Orthopaedic Surgeon

May we list you as a Peer Reviewer in the final Guidelines (GL)? x☐ Yes ☐ No
PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your public comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? ☐ Yes x☐ No

If yes, may we list your society as a reviewer of this guideline? ☐ Yes ☐ No

Society Name: _____
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Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

If the boxes below are not checked and/or the reviewer does not attach his/her conflicts of interest, the reviewer's comments will not be addressed by the AAOS nor will the reviewer's name or society be listed as a reviewer of this GL. If a committee reviews the guideline, only the chairperson/or lead of the review must declare their relevant COI.

X☐ **I have declared my conflicts of interest on page 2 of this form.** ☐ **I have declared my conflicts of interest in the AAOS database; my customer # is** _____
X☐ **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.**

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Each item below requires an answer. Please report information for the last 12-months as required by the Accreditation Council for Continuing Medical Education (ACCME) guidelines.

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Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes X☐ No
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Reviewer Instructions
Please read and review this Draft Clinical Practice Guideline and its associated Technical Report with particular focus on your area of expertise. Your responses are confidential and will be used only to assess the validity, clarity and accuracy of the interpretation of the evidence. If applicable, **please specify the draft page and line numbers in your comments**. Please feel free to also comment on the overall structure and content of the guideline and Technical Report.

Please complete and return this form electronically in **WORD format** to Song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **March 8, 2013.**

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	x ☐	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	x☐	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	X☐	☐	☐	☐
4. The guideline's target audience is clearly described	X☐	☐	☐	☐
5. The patients to whom this guideline is meant to apply are specifically described	X☐	☐	☐	☐
6. The criteria used to select articles for inclusion are appropriate	X☐	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	X☐	☐	☐	☐
8. All important studies that met the article inclusion criteria are included	X☐	☐	☐	☐
9. The validity of the studies is appropriately appraised	X☐	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	X☐	☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	X☐	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	X☐	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	X☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	X☐	☐
15. The grades assigned to each recommendation are appropriate	X☐	☐	☐	☐

COMMENTS

PLEASE RETURN ALL COMMENTS IN WORD FORMAT

This Draft Clinical Practice Guideline has already completed peer review and has been reviewed by content experts. The feedback provided during this process is attached in the PDF. If you have any other brief additional comments, please feel free to provide them here. If applicable, please specify the draft page and line numbers in your comments.

Recommendation # 9: Comments on the use of Hyaluronic Acid

Ferring Pharmaceuticals Inc. is a research-driven biopharmaceutical company devoted to developing and marketing innovative products for the treatment of osteoarthritis and the manufacturer of EUFLEXXA® (1% sodium hyaluronate), a highly purified, non-avian derived, high molecular weight hyaluronic acid indicated for treatment of osteoarthritis knee pain in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics (e.g., acetaminophen). We appreciate the opportunity to comment on the proposed AAOS Clinical Practice Guidelines for treatment of osteoarthritis of the knee.

The Work Group is to be commended for their efforts to use an evidence based approach for making recommendations on current therapies, however, Ferring would like to provide further clarification as to the Recommendation #9 which proposes a strong recommendation be made against the use of hyaluronic acid for patients with symptomatic osteoarthritis of the knee.

Specifically, Recommendation #9 currently states:

> **RECOMMENDATION 9**
> We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee.
> **Strength of Recommendation: Strong**
> Description: A **Strong** recommendation means that the benefits of the recommended approach clearly exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a strong negative recommendation), and/or that the quality of the supporting evidence is high.
> Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

Ferring, however, supports the Arthroscopy Association of North America position that AAOS has overlooked a large body of literature on the use of HA for the treatment of osteoarthritis of the knee and would encourage further assessment of the data generated with more recent products including EUFLEXXA.

The 2009 Cochrane Review of Viscosupplementation for the Treatment of Osteoarthritis of the Knee, included 40 trials that compared HA with a either saline or arthrocentesis (through 2005, therefore not including the strong EUFLEXXA FLEXX study). The conclusions of the Cochrane Review dramatically differ from the revised draft AAOS Recommendation #9 that was based on 14 studies with apparent study design and population variability.

Three “high quality” studies heavily impacting Recommendation #9 (Lundsgaard et al 2008; Huang et al 2011 and Puhl et al 1993), have considerable variability in study population and design, therefore, raising question as to their “poolability” or clinical appropriateness within the AAOS meta-analysis. Lundsgaard et al patient population was > 60 years of age, predominantly female and had severe osteoarthritis (Kellgren–Lawrence grade 3 or 4). Huang et al concluded the study Taiwanese population, again, lending question to the generalizability of this Asian population based data to the American population. Puhl et al used the Lequesne Index criterion, which is not well-accepted by FDA or utilized in more recent trials (study conducted in early 1990’s).

The Recommendation #9 states that the meta-analyses of WOMAC pain, function, and stiffness subscales scores all found statistically significant treatment effects, but none of the improvements met the minimum clinically important improvement (MCII) thresholds.

The new MCII definition was based on Armitage et al and reflects "*the smallest clinical change that is important to patients and recognizes that there are some treatment-related statistically significant improvements that are too small to matter*." As stated within the draft document itself, it appears that the main basis for the recommendation against HA seems to be the inability to meet the pre-specified MCII thresholds that were derived from the published literature. The Work Group used the effect sizes reported by Angst et al. to compute the MCII of pain (0.39), the primary indication for this therapeutic class.

Though Ferring disputes the appropriateness of this MCII definition, given the complexity of pain measures, EUFLEXXA meets the MCII for pain (100mm VAS), WOMAC Function, and Patient's Global Assessment.

- The MCII for a 100 mm VAS pain scale is -19.9 mm (Tubach et al., 2005).
    - In the FLEXX Trial (Altman et al. 2009), the change from baseline in pain (100 mm VAS) at 26 weeks was -25.7 mm for EUFLEXXA and -18.5 mm for placebo (saline). Thus, EUFLEXXA demonstrated MCII and saline did not in this study.

- The MCII for WOMAC function is -9.1 mm or a -26% change from baseline (Tubach et al., 2005).
    - In the FLEXX Trial (Altman et al. 2009), the change from baseline in WOMAC function at 26 weeks was -19.5 mm for EUFLEXXA and -14.6 mm for placebo (saline). Thus, both EUFLEXXA and saline achieved MCII for WOMAC function.
    - Results from a 12 week clinical trial comparing EUFLEXXA to Synvisc (Kirchner and Marshall, 2005) show that reduction from baseline for WOMAC function was -26.9% for EUFLEXXA and -25.2% for Synvisc. Thus, in this study, EUFLEXXA achieved MCII and Synvisc did not.

While Ferring recognizes the need to apply a criteria for the Working Group analysis, associations between changes in pain scores and patient definitions of clinical significance are not absolute. This approach is problematic because it does not assess whether a group-determined change in pain is meaningful for any given individual. The individual's subjective experience is disregarded by considering patient needs as a group, inappropriately applying group-derived findings to the individual.

There are several effective pain therapeutics reporting effect sizes lower than 0.39 (Angst et al) and there is a great deal of current literature indicating differing approaches towards MCII. The IMMPACT Recommendations provide benchmarks for clinically important differences in pain related treatment outcomes and distinguish clinical meaningfulness of a) what change in the outcome measure represents a clinically important difference for patients and b) establishing the difference in the magnitude of response between the treatment and control groups that will be considered large enough to establish the scientific or therapeutic importance of the results. It is crucial to recognize that criteria for clinically important change in individuals cannot be directly applied to the evaluation of clinically important group differences.

Table 1. Provisional Benchmarks for Interpreting Changes in Chronic Pain Clinical Trial Outcome Measures

Outcome Domain and Measure	*Type of Improvement**	*Method†*	*Change*
Pain intensity			
0–10 numerical rating scale	Minimally important	Anchor	10–20% decrease
	Moderately important	Anchor	≥30% decrease
	Substantial	Anchor	≥50% decrease

Based on these recommendations, EUFLEXXA clearly has a clinically significant effect with respect to reduction of knee pain. With respect to the difference in the magnitude of response between HA treatment and IA saline control, recent FDA Advisory Committee Panel (CDRH December 9, 2008) unanimously supported the finding of efficacy and clinical relevance for 100mm VAS score treatment differences of ~3mm (equivalent of treatment effect size of 0.15 reported for SynviscOne). This group difference is meaningful since IA saline cannot be regarded simply as inactive placebo, but rather an active comparator – making any such comparisons statistically and clinically rigorous. As reflected in multiple clinical trials of OA, group differences between HA treatment and IA saline controls are consistently smaller than what patients perceive as MCII. Group differences reflect the incremental benefit associated with the HA treatment that contributes to improvement. In 1997, Kirwan and Rankin reported that joint aspiration alone improves knee pain in

patients with OA. More recent data has demonstrated that simple knee aspiration provides acute and sustained lasting OA knee symptom relief. Zang et al reported that placebo is effective in the treatment of OA pain, stiffness and self-reported function, and the size of effect is influenced by the route of delivery (among other considerations). Authors went on to state that among the various OA paint therapies, the placebo effect was the greatest in clinical trials of IA HA.

Therefore, Ferring believes the data supporting EUFLEXXA clearly supports its efficacy and provides clinically meaningful knee pain reduction in the indicated OA patient population.

We also contend that the potential harm of viscosupplementation with hyaluronic acid for treatment of OA knee pain does not exceed the potential benefits as stated in the current draft of the clinical practice guidelines and respectfully suggest that this language be revised to more accurately reflect the basis for the committee's recommendation. The potential for adverse events with repeat injection cycles has been documented for one cross-linked avian based product available in the United States, but this risk is not generally applicable for all HA preparations.

In the case of EUFLEXXA, results of the FLEXX Trial showed no differences from saline in terms of adverse events and no joint effusions (Altman et al, 2009). The 26-week Extension Study of the FLEXX Trial showed no significant increase in adverse events and no joint effusions among patients who received a second course of 3 weekly injections of EUFLEXXA (Altman et al., 2011). Results from the AMELIA trial also indicated no significant increase in adverse events with repeated series of intra-articular HA injections over 40 months. (Navarro-Sarabia et al. 2011).

There are currently no available treatments for osteoarthritis knee pain that provide equivalent, prolonged pain relief similar to intra-articular hyaluronic acid. It is an effective and safe option for patients who have not achieved adequate pain relief with other interventions or who cannot tolerate adverse events associated with acetaminophen, NSAIDS, or intra-articular corticosteroid injections, or are unwilling to accept the well-known risks associated with these drugs. It is our position that the current analysis does not substantiate the strong recommendation against use of hyaluronic acid products for the treatment of osteoarthritis, and that certainly data for EUFLEXXA support clinically meaningful improvements in pain.

References:

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- Navarro-Sarabia et al. *Ann Rheum Dis.* 2011;70:1957-1962.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

X☐ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

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- **Your conflicts of interest will be published on the AAOS website with your review.**

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2. There is an explicit link between the recommendations and the supporting evidence	X			
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4. The guideline's target audience is clearly described		X		
5. The patients to whom this guideline is meant to apply are specifically described		X		
6. The criteria used to select articles for inclusion are appropriate		X		
7. The reasons why some studies were excluded are clearly described		X		
8. All important studies that met the article inclusion criteria are included	X			
9. The validity of the studies is appropriately appraised	X			
10. The methods are described in such a way as to be reproducible.	X			
11. The statistical methods are appropriate to the material and the objectives of this guideline		X		
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed		X		
13. Health benefits, side effects, and risks are adequately addressed		X		
14. The writing style is appropriate for health care professionals.			X	
15. The grades assigned to each recommendation are appropriate	X			

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OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

X☐ Would not recommend

☐ Unsure

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Reviewer Information:

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Specialty Area/Discipline: _____

Work setting: Pharmaceutical company Credentials: MD

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1. The recommendations are clearly stated	☒	☐	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	☒	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☒	☐
4. The guideline's target audience is clearly described	☐	☐	☐	☒
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	☒
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☒	☐
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9. The validity of the studies is appropriately appraised	☐	☒	☐	☐
10. The methods are described in such a way as to be reproducible.	☒	☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☒	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☒	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☒	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☒	☐
15. The grades assigned to each recommendation are appropriate	☐	☒	☐	☐

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Letter to be pasted in here.

Dear 2012 OA of the Knee Work Group,

Thank you for the opportunity to review the American Academy of Orthopaedic Surgeons' draft Guidelines for the Treatment of Osteoarthritis (OA) of the Knee. Clearly, a lot of time and effort went into developing these guidelines and we applaud AAOS for undertaking this significant and important task. We certainly appreciate the importance of providing treatment guidelines for the more than 10 million people in the U.S. estimated to have OA in one or both knees. The objective of this letter is to respectfully call your attention to our concerns surrounding AAOS' strong recommendation against the use of hyaluronic acid (HA), which was deemed safe by your review. We urge you to reconsider and revise the current designation for HA.

While there is no cure for OA, we believe that physicians and patients should have a wide range of treatment options available to manage OA knee pain. However, the current guidelines will limit treatment options for these patients. In addition to its recommendation against HA, the work group also recommended against 11 treatments, including acetaminophen, opioids, pain patches, and intra-articular steroid injections. Noteworthy, is the fact that NSAID's and tramadol are now the only pharmacologic options before surgery that AAOS strongly recommends. This shortened treatment pathway to total knee replacement is a disservice to patients, especially for those who do not wish to undergo surgery, or those that are not acceptable surgical candidates.

We would like to call attention to a few issues that may require further review prior to finalizing the treatment recommendations. In the short time we have had to review the extensive document, we have defined some major points of concern. We also agree with many of the comments made by other reviewers. In the interest of brevity, we will focus on three major points:

I. Lack of conformity to generally accepted principles of minimum clinically important improvement (MCII),
II. Application of the study selection criteria, and
III. High molecular weight HA differentiation

I. Lack of conformity to generally accepted principles of minimum clinically important improvement (MCII)

Multiple experts agree that MCII in pain studies is defined as the magnitude of pain reduction (from baseline to follow up within a treatment group) that patients consider clinically important.[1] The distinction between the clinical significance of patient-level improvements and between-group differences is often confused, and can be inaccurately applied to the results of pain studies.[2] In the proposed guidelines, the MCII was inappropriately applied to compare change between placebo and treatment groups, when it should only be used as a benchmark

for the magnitude of improvement that is important to patients. Applying patient-level MCII to determine between-group differences leads to an unrealistic high bar for therapies to be considered clinically meaningful.[3]

The level of improvement patients consider clinically important is typically greater than the difference between treatment and placebo. Meaningful change for individual patients reflects treatment effects, placebo effects, and other non-specific effects of the clinical setting, including natural history, spontaneous resolution, and regression to the mean. However, differences between active treatment and placebo groups reflect the incremental benefit of the active treatment.

In the case of intra-articular interventions, a substantial placebo group response has been documented.[4] Potential reasons for these large placebo effects are the invasiveness of the treatment (compared with oral or topical medication) and the use of rescue and concomitant analgesic medications. Given this placebo effect, by focusing only on the delta between treatment and placebo to demonstrate meaningful clinical improvement, the benefit of intra-articular HA therapies for treating OA pain has been obfuscated. Thus, we request that you apply MCII as a change within treatment groups, reflecting patient-level improvements.

Clinically meaningful changes from baseline have been defined by many in the medical literature. The cited sources of Angst et al. and Tubach et al. (which are not clinical studies) define an 8.3-mm WOMAC pain (18%) and 19.9-mm VAS pain (41%)[5-7] change from baseline to follow up as a clinically important change within group. Dworkin et al., on behalf of IMMPACT, report a 10-20% improvement from baseline as a conservative MCII for OA pain, with a moderate improvement being at least a 30% change.[8] Similarly, Farrar and colleagues published a 30% improvement from baseline as clinically important in pain studies.[9]

Of the 14 HA studies included in the AAOS guidelines analysis (see below), 9 studies showed statistical significance with treatment versus placebo.[10-18] Of those 9 studies, 8 had data to calculate change or improvement from baseline, which ranged from 36% to 64% (Table 1).[10-17] These mean percent changes from baseline[8,9] exceed MCII for a meaningful patient improvement as defined by pain experts.

Table 1. Change from baseline of the 9 statistically significant studies for HA treatment

Study	Mean % improvement from baseline	Endpoint
Altman 2009[10]	53	WOMAC pain
Chevalier 2010[11]	36	WOMAC pain
Day 2004[12]	52	WOMAC pain
Huang 2011[13]	64	WOMAC pain
Kahan 2003[17]	50	WOMAC pain
Lohmander 1996[14]	36	WOMAC total
Navarro-Sarabia 2011[18]	NR	WOMAC pain
Puhl 1993[15]	50	VAS global pain
Wobig 1998[16]	51	VAS weight bearing pain

NR: Data not reported or not reported adequately enough to calculate

In fact, the percent improvements from baseline with HAs were similar to those reported with NSAIDs and tramadol, which are strongly recommended by the work group. Improvements from baseline reported with NSAIDs and tramadol range from 18% to 45% (Table 2).[19-32]

Table 2. Change from baseline for statistically significant NSAID/tramadol treatment

Drug	Study	Mean % improvement from baseline	Endpoint
Celecoxib	Bingham 2007[19]	37	WOMAC pain
	Birbara 2006[20]	40	WOMAC pain
	Gibofsky 2003[21]	42	WOMAC pain
	Lehmann 2005[22]	41	VAS pain
	McKenna 2001[23]	38	WOMAC pain
	Pincus 2004[27]	18	WOMAC total
	Rother 2007[24]	37	WOMAC pain
Diclofenac	Case 2003[25]	27	WOMAC pain
	McKenna 2001[23]	40	WOMAC pain
	Schnitzer 2004[26]	35	WOMAC pain
Diclofenac topical	Bookman 2004[28]	43	WOMAC pain
	Grace 1999[29]	37	WOMAC pain
Tramadol/acetaminophen	Emkey 2004[30]	30	WOMAC pain
	Silverfield 2002[31]	43	WOMAC pain
Tramadol	Babul 2004[32]	45	WOMAC pain

II. Application of the study selection criteria

The manner in which selection criteria were applied is another major limitation of this guideline. While we applaud the use of primary studies as evidence, many studies recalled for full text review were not considered in the analysis. The Attrition chart for the identified studies (lines 3806 to 3807) illustrates this point. Of the 2,222 articles recalled for full text review, only 218 (less than 10%) of the studies were considered for all treatments examined.

Fourteen HA studies were identified for analysis by the work group.[10-18,33-37] Given the large body of HA literature, this is not likely an accurate representation of the evidence. For example, the Cochrane review published in 2006, well recognized for its rigorous methodology, evaluated 76 trials on HA.[38] In the Cochrane review, pooled analyses from the studies selected supported the efficacy of VS and this review should not be discounted. Additionally, the recommendation of the working group for HA is not consistent with the latest OA treatment guidelines published by the American College of Rheumatology[39]and the Osteoarthritis Research Society International.[40]

We identified 13 additional studies[41-53] that seem to have met the work group's inclusion criteria, yet they were excluded for reasons that are not apparent. Of the 13 studies, 8 reported statistically significant efficacy of HA compared with placebo.[41,43-46,49,52,53] All of these studies reported HA treatment improvement from baseline, which ranged from 30% to 69% (Table 3). These studies continue to reinforce the efficacy of VS in the treatment of OA of the knee.

Table 3. Change from baseline of the 8 additional studies for statistically significant HA treatment

Study	Mean % improvement from baseline	Endpoint
Altman 1998[41]	67	VAS pain
Brandt 2001[53]	31	WOMAC pain
Dickson 2001[43]	44	WOMAC pain
Dixon 1988[44]	NR	VAS pain
Dougados 1993[45]	57	VAS pain
Huskisson 1999[46]	40	VAS pain
Petrella 2008[49]	69	VAS pain
Strand 2012[52]	30	WOMAC pain

NR: Data not reported to calculate

III. High molecular weight HA differentiation

Lastly, we were interested in the evaluations between different molecular weight HA products. Heterogeneity within the HA class has been noted in several meta-analyses.[38,54-60] Differences between compositions of the HAs may contribute to this heterogeneity. In lines 2835 to 2837, the AAOS analysis suggested "statistically and possibly clinically important differences in favor of Hylan G-F 20." Based on the group's findings, hylan G-F 20 should not be included in the strong recommendation against use of the HA class.

Summary

Thank you for considering our comments. Again, we appreciate the significant undertaking required to formulate these draft recommendations, as well as the opportunity for response. Taking away several treatment options is not beneficial to patients without providing alternative options, especially when no new class of treatments has been approved for knee OA pain in the last decade. Patients and physicians deserve to have more, not fewer, treatment options to manage pain and improve function before arthroplasty. Osteoarthritis affects people differently and over the course of a patient's disease progression successful treatment regimens may include a combination of therapies.

Prior to finalizing these recommendations, we ask that you carefully consider the implications the proposed recommendations will have on patient care. Based on our comments, we encourage you to reconsider your recommendation against the use of HA, and support its inclusion in the knee OA treatment paradigm.

Respectfully,

Richard Toselli, MD
Vice President of Global Medical Affairs
Sanofi Biosurgery

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OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
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ALL REVIEW COMMENTS, OUR RESPONSES AND REVIEWER COI WILL BE AVAILABLE FOR REVIEW ON OUR WEBSITE FOLLOWING BOD APPROVAL OF THIS DOCUMENT.

Review of any AAOS confidential draft allows us to improve the overall guideline but does not imply endorsement by any given individual or any specialty society who participates in our review processes. The AAOS review process may result in changes to the documents; therefore, endorsement cannot occur until the AAOS Board of Directors officially approves the final guideline.

Please note that if you return a review:

- **Your comments will be published on the AAOS website with our explanation of why we did nor did not change the draft document in response to your comments.**
- **Your conflicts of interest will be published on the AAOS website with your review.**

Reviewer Information:

Name of Reviewer SEIKAGAKU CORPORATION

Address 6-1, Marunouchi 1-chome Chiyoda-ku

City Tokyo, Japan State_____ Zip Code 100-0005

Phone (81) 3-5220-8974 Fax (81) 3-5220-8975 E-mail shigeru.kawahara@seikagaku.co.jp

Specialty Area/Discipline: Research, Development and Manufacture of Hyaluronic Acid Products

Work setting: Industry Credentials: Hyaluronic Acid Product Research, Development and Manufacture

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May we list you as a Peer Reviewer in the final Guidelines (GL)? ☒ Yes ☐ No
PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your public comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? ☐ Yes ☒ No

If yes, may we list your society as a reviewer of this guideline? ☐ Yes ☒ No

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☒ **I have declared my conflicts of interest on page 2 of this form.**

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☒ **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.**

REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

Each item below requires an answer. Please report information for the last 12-months as required by the Accreditation Council for Continuing Medical Education (ACCME) guidelines.

Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device: *Seikagaku is a pharmaceutical/device manufacturer.*	☐ **Yes** ☐ No
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Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: *Seikagaku is a pharmaceutical/device manufacturer.*	☐ **Yes** ☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: *Seikagaku is a pharmaceutical/device manufacturer.*	☐ **Yes** ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: *Seikagaku is a pharmaceutical/device manufacturer.*	☐ Yes ☐ **No**
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier: *Seikagaku is a pharmaceutical/device manufacturer.*	☐ Yes ☐ **No**
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: *Seikagaku is a pharmaceutical/device manufacturer.*	☐ Yes ☐ **No**
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier: *Seikagaku is a pharmaceutical/device manufacturer.*	☐ Yes ☐ **No**
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher: *Seikagaku is a pharmaceutical/device manufacturer.*	☐ Yes ☐ **No**
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify: *Seikagaku is a pharmaceutical/device manufacturer.*	☐ Yes ☐ **No**
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify: *Seikagaku is a pharmaceutical/device manufacturer.*	☐ Yes ☐ **No**

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
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Reviewer Instructions
Please read and review this Draft Clinical Practice Guideline and its associated Technical Report with particular focus on your area of expertise. Your responses are confidential and will be used only to assess the validity, clarity and accuracy of the interpretation of the evidence. If applicable, **please specify the draft page and line numbers in your comments**. Please feel free to also comment on the overall structure and content of the guideline and Technical Report.

Please complete and return this form electronically in **WORD format** to Song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **March 8, 2013.**

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☒	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☒	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☒	☐	☐
4. The guideline's target audience is clearly described	☒	☐	☐	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☒	☐	☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☒	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☒	☐
8. All important studies that met the article inclusion criteria are included	☐	☒	☐	☐
9. The validity of the studies is appropriately appraised	☐	☒	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☒	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☒	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☒	☐
13. Health benefits, side effects, and risks are adequately addressed	☒	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☒	☐	☐	☐
15. The grades assigned to each recommendation are appropriate	☐	☒	☐	☐

COMMENTS

PLEASE RETURN ALL COMMENTS IN WORD FORMAT

This Draft Clinical Practice Guideline has already completed peer review and has been reviewed by content experts. The feedback provided during this process is attached in the PDF. If you have any other brief additional comments, please feel free to provide them here. If applicable, please specify the draft page and line numbers in your comments.

We are deeply concerned that the basis used for assessment of clinical importance given in the AAOS draft Recommendation #9 has serious scientific flaws from the statistical point of view, rendering the subsequent AAOS conclusion and recommendation scientifically invalid. The key issue is how the MCII Effectiveness Measure was defined and used for assessment of clinical importance in using HA for patients with symptomatic osteoarthritis of the knee.

MCII Effectiveness Measure

- Scientific principles in psychometrics dictate that in order for a measurement instrument to retain its validity, it must be applied to the same scientific context in which the measurement instrument was originally defined and derived. Otherwise, the measurement instrument loses its validity and a measure based on that instrument cannot be properly interpreted.
- The MCII measures that AAOS draft uses have been derived from within-group patient data and defined with respect to baseline at the individual patient level. Despite recommendations expressed in publications regarding patient-specific measures (Dworkin et al (2009) [Ref. 1]), AAOS analyses (Tables 175-178) misapply the MCII as group outcome measures.
- This means that the MCII measure that AAOS uses should be applied only to the assessment of clinical importance for change from baseline within each patient. However, AAOS inappropriately uses the said MCII measure for the assessment of clinical importance for group differences in change from baseline between the treatment and placebo groups.
- In clinical statistics, those two measures are clearly distinguished and used differently. Togo et al. (2011) [Ref. 2] calls the measure of clinical importance derived with change from baseline within each patient (such as those used in the AAOS draft) “Minimal Clinically Important Change from Baseline” (MCIC) and the measure of clinical importance derived with change from baseline between treatment groups “Minimal Clinically Important Difference between Groups” (MCID). They state that MCIC is to be used to evaluate individual change and to calculate percentage of responders who achieve MCIC, whereas MCID is to be used for the comparison between treatment groups.
    - The same point was made in IMMPACT recommendation by Dworkin et al. [Ref. 1], stating “it is crucial to recognize that criteria for clinically important changes in individuals cannot be extrapolated to the evaluation of group differences.” The scientific reason is that “meaningful change in individual patients reflects any effects of the active treatment, placebo and other non-specific effects of the clinical setting, natural history and spontaneous resolution, and statistical regression to the mean. Differences between treatment and placebo groups, however, reflect the incremental benefits of active treatments that contribute to improvement after subtracting out placebo and other non-specific effects, natural history, and regression to the mean…” Therefore, the IMMPACT group concludes that “given their critical differences, evaluations of the clinical meaningfulness of group differences in chronic pain trials should not be based on criteria for evaluating clinically meaningful changes in individual patients”. The IMMPACT recommendations further state that one must consider individual-level outcomes as well as group-level outcomes such as the proportion of subjects benefiting and the onset time and duration of benefit as informative measures.

- Another relevant explanation came from Dr. Marc Hochberg (one of the co-authors of Tubach et al. article that AAOS cites for its MCII measure) when he stated, in response to a question from a medical reviewer at CDRH during the FDA-sponsored public meeting on MCID in 2012 [Ref. 3], that a measure of minimal clinical importance determined at the individual level is meant for the purposes of determining the proportion of subjects who meet the standard in order to be able to compare that between treatment groups and it is not intended to be used to interpret group differences as to whether it exceeds or fails to exceed that measure in making decisions from a regulatory standpoint. Thus, we believe it is only natural and logical that AAOS should follow the guidance put forward by one of the researchers who developed the MCII measure used by AAOS regarding its proper use and interpretation.

- A potential reason for what we believe was inadvertent misapplication of the MCII measure in the AAOS draft may be due to the fact that measure for minimum clinical importance has been defined in different ways and called by different acronyms by various academics without fully describing the context in which each measure was defined and the purpose for which it was to be used. This has led to a great deal of confusion among clinical researchers and regulators with respect to what is meant by the MCII / MCID. In fact, we believe that this state of confusion has led FDA to remove all references to minimum important difference or minimum clinically important differences in the latest FDA guidance (issued in Dec, 2009) [Ref. 4] on patient reported outcome measures, a point duly noted by Dr. Kathleen Wyrwich during the FDA-sponsored public meeting on MCID in 2012 [Ref. 3].
- We wish to point out that, to the best of our knowledge, there has been no universal agreement with respect to the outcome measure or the corresponding minimum clinically important difference between groups in knee OA. We believe that any such definition must abide by the sound scientific principle espoused in the IMMPACT recommendation, such that "the clinical meaningfulness of group differences must be determined by a multi-factorial evaluation of the benefits and risks of the treatment and of other available treatments for the condition in light of the primary goals of therapy" [Ref. 1]. The MCID also must be context-specific relative to the target population.
- In fact, there is no consensus on how minimum clinically important difference between groups should be even used in designing and interpreting a clinical study, even if we assume such a measure can be defined and agreed upon. (For example, see Chuang-Stein et al. (2010) [Ref. 5]. Statistical experts such as Chuang-Stein argue that the most reasonable role for such a measure is to use it as a target for sample size and power calculation during study design, while cautioning against overuse and over-interpretation of the concept.)

We respectfully request that AAOS uphold the appropriate scientific standard in its evaluation of clinical meaningfulness of HA treatments, by:

- **Using the minimum clinically important improvement from baseline in the scientifically proper context, by applying it only to assess change from baseline in pain and function measures at the individual patient level.**
- **Following the recommendation given by the IMMPACT group in considering the multi-factorial dimensions of treatment characteristics in assessing clinically meaningful difference between HA and control treatment groups.**

References:

1. Dworkin RH et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain. 2009; Vol. 146, 238-244.
2. Togo K, Matsuoka N, Hashigaki S, Imai K, Moriya T. Clinically important effects in new drug development. Drug Information Journal. 2011; Vol. 45, pp 805-810.
3. Public transcript from "Minimum Clinically Important Difference (MCID): Defining Outcome Metrics for Orthopedic Devices – Public Meeting", held at FDA White Oak Campus on Nov 27-28, 2012.

4. US Department of Health and Human Services, FDA, CDER, CBER, CDRH. Guidance for industry, patient-reported outcome measures: use in medical product development to support labeling claims. Dec 2009.
5. Chuang-Stein C, Kirby S, Hirsch I, Atkinson G. The role of the minimum clinically important difference and its impact on designing a trial. Pharmaceutical Statistics. 2011; Vol. 10, 250-256.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

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Reviewer Information:

Name of Reviewer: ANONYMOUS – Name and identifying information withheld upon request Address:

City: State: Zip Code:

Phone: Fax: E-mail:

Specialty Area/Discipline:

Work setting: Credentials:

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☐ Yes ☒ No
PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your public comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? ☐ Yes ☒ No

If yes, may we list your society as a reviewer of this guideline? ☐ Yes ☒ No

Society Name: _____
(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

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Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Zimmer, Inc	☒ Yes ☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier: Zimmer, Inc	☒ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
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Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☒	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	☒
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☒	☐	☐
4. The guideline's target audience is clearly described	☒	☐	☐	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☒	☐	☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☒	☐
7. The reasons why some studies were excluded are clearly described	☐	☒	☐	☐
8. All important studies that met the article inclusion criteria are included	☒	☐	☐	☐
9. The validity of the studies is appropriately appraised	☐	☒	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☒	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☒	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☒	☐
13. Health benefits, side effects, and risks are adequately addressed	☒	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	☒
15. The grades assigned to each recommendation are appropriate	☐	☒	☐	☐

COMMENTS

PLEASE RETURN ALL COMMENTS IN WORD FORMAT

Zimmer would like to express serious concerns with the proposed guidance contained in Recommendation #9. We believe that there are scientific flaws contained in the analysis and that the guidance will have un-intended consequences for physicians who use Hyaluronic Acid injections and the thousands of patients who benefit from, or may benefit from this therapy.

We respectfully but strongly encourage the AAOS to change the current draft recommendation to maintain the neutral guidance language for Hyaluronic Acid therapy as it was in the previously published guidance from 2008 (and noted below):

Recommendation 16: We cannot recommend for or against the use of intra-articular hyaluronic acid for patients with mild to moderate symptomatic OA of the knee. Level of Evidence: I and II Grade of Recommendation: Inconclusive

The following areas will be addressed in our comments that follow:

- Definition and usage of MCII effectiveness measure for assessment of clinical importance
- Study selection
- Discussion of saline as a control and potential impact on results
- Patient Inclusion and length of therapy

- Un-intended payer audience – impact on access
- Un-intended connotation of "Strong" recommendation

MCII Effectiveness Measure

The issue at the heart of our concern is how the MCII Effectiveness Measure was defined and used for an assessment of clinical importance for patients with symptomatic osteoarthritis of the knee. This should also be viewed in the context that all meta-analysis results by AAOS showed statistically significant treatment effects across WOMAC pain, function and stiffness subscales scores. The following bullets explain the concerns with MCII:

- It is vital to good science that measurement instruments must be applied to the same scientific context in which the measurement instrument was originally defined.
- MCII measures have been derived from within-group patient data and defined with respect to baseline at the individual patient level.
- This means that the MCII measure that is used in the draft guidelines should only be applied to the assessment of clinical importance for change from baseline for each patient. However, the MCII measure in the proposal is being used for the assessment of clinical importance for group differences in change from baseline between the treatment and placebo groups.
- There has been substantial discussion of incorrect usage of the MCII measures some of which has been used by manufacturers to convince FDA to correctly apply these measures. Some important references include:
    - Togo et al. (2011) [Ref. 1] distinguishes minimal clinically important change from baseline from minimal clinically important difference between groups
    - Dworkin et al. (2009) [Ref.2], as made in IMMPACT recommendation, states that "it is crucial to recognize that criteria for clinically important changes in individual cannot be extrapolated to the evaluation of group differences." The conclusion is that "given their critical differences, evaluation of the clinical meaningfulness of group difference in chronic pain trials should not be based on criteria for evaluating clinically meaningful changes in individual patients."
    - Dr. Marc Hochberg stated in response to a question from a medical reviewer at CDRH during the FDA-sponsored public meeting on MCID in 2012 [Ref.3], that a measure of minimal clinical importance determined at the individual level is meant for the purposes of determining the proportion of subjects who meet the standard in order to be able to compare that between treatment groups and it is not intended to be used to interpret group differences as to whether it exceeds or fails to exceed that measure in making decision from a regulatory standpoint. As one of the researchers who developed the MCII measures, Dr. Hochberg's statement on proper use and interpretation should be taken as important guidance.
- The confusion over these methodologies and acronyms may have led FDA to remove all references to minimum important difference or minimum clinically important differences in the latest FDA guidance (issued in Dec. 2009) [Ref. 4] on patient reported outcome measures, a point duly noted by Dr. Kathleen Wyrwich during the FDA-sponsored public meeting on MCID in 2012 [Ref.3].

- At this time we are not aware of any validated study to determine the minimum clinically important differences between groups and believe that any such definition must abide by sound scientific principle such as those espoused in the IMMPACT recommendation.
- Chuang-Stein et al. (2010) [Ref. 5] argues that the most reasonable role for a minimum clinically important difference between groups measure is to use it as a target sample size and power calculation during study design, while cautioning against overuse and over-interpretation of the concept.

References (copies available upon request):

1. Togo K, Matsuoka N, Hashigaki S, Imai K, Moriya T. Clinically important effects in new drug development. Drug Information Journal. 2011; Vol. 45, pp 805-810.
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3. Public transcript from "Minimum Clinically Important Difference (MCID): Defining Outcome Metrics for Orthopedic Devices – Public Meeting", held at FDA White Oak Campus on Nov 27-28, 2012.
4. US Department of Health and Human Services, FDA, CDER, CBER, CDRH. Guidance for industry, patient-reported outcome measures: use in medical product development to support labeling claims. Dec 2009.
5. Chuang-Stein C, Kirby S, Hirsch I, Atkinson G. The role of the minimum clinically important difference and its impact on designing a trial. Pharmaceutical Statistics. 2011; Vol. 10, 250-256.

Study Selection

Zimmer is concerned with the study selection criteria applied by AAOS.

- The selection process failed to account for product differences such as number of injections, schedule of injections, dose size, formulation, concentration and source material, instead treating all HA products as if they were the same.
- Two studies included were on products that are not approved by FDA for use in the US.
- We feel that the selected studies do not represent the body of evidence on HA product and in fact, that some of the most rigorously designed studies, including those used to gain FDA approval for HA products were excluded.

Discussion of saline as a control and potential impact on results

Zimmer feels that treatment of a saline control as a placebo does not adequately portray the therapeutic nature of saline injection. Bradley et al.[1] showed that intraarticular irrigation of the knee with saline was superior to steroid injections in pain score improvement as early as 12 weeks, continuing beyond 26 weeks. The most relevant finding was not that saline was superior to steroids, but that saline injection was shown to provide lasting improvement over baseline. Failure to account for the real clinical benefit of saline injection may have skewed the current analysis and resulted in an under-estimation of the clinical benefits of hyaluronic acid therapy.

1. Bradely JD, Heilman DK, Katz BP, et al. Tidal irrigation as treatment for knee osteoarthritis: a sham-controlled, randomized, double-blinded evaluation. Arthritis Rheum 2002;46:100-8.

Patient Inclusion and length of therapy

The following concerns were noted relative to the selection and treatment of clinical data**:**

- Homogeneity was violated by selection of Kellgren-Lawrence grade I-IV patients in the studies reviewed as part of the meta-analysis.
- It is difficult to sort out individual benefits which may be much greater than indicated by measures because both responders and non-responders were included in the studies.
- Many of the measures factored in data that was well beyond a 6 month time horizon, which does not reflect the typical or expected therapeutic usage of these products. These predictably poorer long term results likely skewed overall conclusions of the meta-analysis.

Un-intended Audience – Impact on Access

Zimmer would like to point out that in publishing these clinical guidelines, they will likely be noticed and used by health insurance payers to define medical policies that may result in non-coverage of HA injections for many patients. This will impact the clinical practice of many orthopedic surgeons and will restrict access to a therapy that hundreds of thousands of patients currently benefit from or may

benefit from in the future. Non surgical options for patients with osteoarthritis are limited and are either plagued with compliance issues or have demonstrated potential adverse affects.

Additionally, it is important to point out that many payer medical policies, including some of the Medicare Administrative Contractors LCDs along with CMS guidance (MLN matters) currently require non-surgical therapy prior to approving joint arthroplasty procedures. This includes intra-articular injections which indicate that payers currently view HA injections as an important non-surgical therapy and clinical choice. This proposed AAOS guidance could impact or limit the therapeutic alternatives that physicians currently have to address pain relief and non-surgical management for their patients.

Un-intended Connotation of "Strong" Recommendation

Zimmer is concerned that the "Strong" recommendation will be interpreted by physicians and insurance payers as indicating that HA injections' harms out-weigh the benefits. This is clearly not true, as pointed out in AAOS responses to peer reviewers who identified this issue in the initial round of comments. As we described above, we think that the Strong recommendation is scientifically overstated. We also believe that AAOS will create a perception regarding this therapy that is clearly inappropriate and as such, we take a major issue with Recommendation #9 and request that it be addressed, by modifying the language as noted at the beginning of our comments.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Public Comment Review Form

ALL REVIEW COMMENTS, OUR RESPONSES AND REVIEWER COI WILL BE AVAILABLE FOR REVIEW ON OUR WEBSITE FOLLOWING BOD APPROVAL OF THIS DOCUMENT.

Review of any AAOS confidential draft allows us to improve the overall guideline but does not imply endorsement by any given individual or any specialty society who participates in our review processes. The AAOS review process may result in changes to the documents; therefore, endorsement cannot occur until the AAOS Board of Directors officially approves the final guideline.

Please note that if you return a review:

- **Your comments will be published on the AAOS website with our explanation of why we did nor did not change the draft document in response to your comments.**
- **Your conflicts of interest will be published on the AAOS website with your review.**

Reviewer Information:

Name of Reviewer: **ANONYMOUS – Name and identifying information withheld upon request**
Address:
City: State: Zip Code:
Phone: Fax: E-mail:
Specialty Area/Discipline:
Work setting: Credentials:

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☐ Yes ☒ No
PLEASE READ: If you do not wish to be listed, your name will be removed for identification purposes. However, your public comments, our responses and your COI will still be available for public review on our website with the posted Guideline if you complete this review.

Are you reviewing this guideline as a representative of a professional society? ☐ Yes ☒ No

If yes, may we list your society as a reviewer of this guideline? ☐ Yes ☒ No

Society Name: _____
(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

If the boxes below are not checked and/or the reviewer does not attach his/her conflicts of interest, the reviewer's comments will not be addressed by the AAOS nor will the reviewer's name or society be listed as a reviewer of this GL. If a committee reviews the guideline, only the chairperson/or lead of the review must declare their relevant COI.

☒ **I have declared my conflicts of interest on page 2 of this form.**

☐ **I have declared my conflicts of interest in the AAOS database; my customer # is** _____

☐ **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline on the AAOS website.**

REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

Each item below requires an answer. Please report information for the last 12-months as required by the Accreditation Council for Continuing Medical Education (ACCME) guidelines.

Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes ☒ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company:	☐ Yes ☒ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier: Fidia Pharma, USA	☒ Yes ☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier: Pfizer, Medtronic	☒ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☒ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes ☒ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify:	☐ Yes ☒ No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify:	☐ Yes ☒ No

American Academy of Orthopaedic Surgeons (AAOS) *Treatment of Osteoarthritis of the Knee*
Public Comment Review Form

Reviewer Instructions
Please read and review this Draft Clinical Practice Guideline and its associated Technical Report with particular focus on your area of expertise. Your responses are confidential and will be used only to assess the validity, clarity and accuracy of the interpretation of the evidence. If applicable, **please specify the draft page and line numbers in your comments**. Please feel free to also comment on the overall structure and content of the guideline and Technical Report.

Please complete and return this form electronically in **WORD format** to Song@aaos.org ; please contact Sharon Song at (847) 384-4328 if you have any questions. Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please return the completed form in **WORD format** by end of day **March 8, 2013.**

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☒	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	☒	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☒	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☒	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☒	☐
6. The criteria used to select articles for inclusion are appropriate	☒	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	☒	☐	☐	☐
8. All important studies that met the article inclusion criteria are included	☒	☐	☐	☐
9. The validity of the studies is appropriately appraised	☐	☒	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☒	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☒	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☒	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☒	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	☒
15. The grades assigned to each recommendation are appropriate	☒	☐	☐	☐

COMMENTS

PLEASE RETURN ALL COMMENTS IN WORD FORMAT

This Draft Clinical Practice Guideline has already completed peer review and has been reviewed by content experts. The feedback provided during this process is attached in the PDF. If you have any other brief additional comments, please feel free to provide them here. If applicable, please specify the draft page and line numbers in your comments.

OVERALL ASSESSMENT

Would you recommend these guidelines for use in clinical practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☒ Would not recommend

☐ Unsure

Note: Your answer to this question does not constitute an endorsement of this guideline. We ask this question as a means of monitoring the clinical relevance of our guideline.

March 7, 2013

Re: AAOS Treatment of OA of the knee – Public Commentary
RECOMMENDATION 9: "We recommend not using hyaluronic acid for patients with symptomatic osteoarthritis of the knee".

Dear Sirs/Madams,

Thank you for offering us the opportunity to review the current version of the AAOS OA Knee evidence based guidelines 2nd edition. We congratulate the authors on their efforts to prepare, interpret, analyse and review the literature set forth in these guidelines.

Hyalgan is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients that have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics. Hyalgan was approved by the Food and Drug Administration in May, 1997.

Hyalgan is a viscous solution of purified natural sodium hyaluronate extracted from rooster combs, the salt form of hyaluronic acid. Hyaluronic acid, by virtue of its viscosity, elasticity and other rheological properties acts as a lubricating and shock absorbing fluid in joints. Hyalgan is a viscous solution of molecular weight fraction (500-730 KDa) of purified natural sodium hyaluronate.

As per the American College of Rheumatology (ACR), European League Against Rheumatology (EULAR) and Osteoarthritis Research Society (OARSI) [1,2,3,4] use of HA is recommended for patients suffering from knee OA. As per EULAR and OARSI recommendations, intra-articular hyaluronic acid (IA HA) is considered as a Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOA) [5]; and there is evidence that SYSADOA (glucosamine sulphate, chondroitin sulphate, diacerein, and hyaluronic acid) may possess structure modification properties.

Hyaluronic acid and other SYSADOA are effective in the management of knee OA, its role in pain reduction, functional improvement, and disease modification in knee OA has been assessed. Many trials assessed the efficacy of hyaluronic acid in relation to the knee joint. Three randomised controlled trials, that allowed calculation of effect size (ES), recorded significant reductions in pain against placebo (ES 0.4, 0.49, 0.9) over time periods of 60 days to one year [6, 7, 8]. One study recorded functional improvements on Lequesne's index (ES 0.36) over one year [7]. A 12 month randomized controlled trial of 39 patients with knee OA showed that intra-articular hyaluronan delayed the structural progression of OA as assessed by arthroscopic assessment of articular cartilage. [9]

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The literature demonstrates how Hyaluronic acid (MW 500-730KDa) treatment is associated with structural changes in the knee, such as improvement of the cartilage surface layer (blinded arthroscopic examination), increase in chondrocyte density and metabolism (histomorphology and biochemical analysis), reduction of synovial inflammation, supporting that Hyaluronic acid (MW 500-730KDa) delays the progression of structural changes in articular cartilage associated with OA. [9, 10, 11, 12, 13, 14].

These studies are discussed in a recent meta-analysis where the authors stated that based on preclinical data; there is evidence to support the notion that all the approved HAs in the US may have some disease-modifying properties. Growing clinical evidence also indicates that Hyalgan sodium hyaluronate, (MW 500-730 kDa) may alter the progression of OA [15].

The literature base for the comparison of hyaluronans to placebo for the treatment of pain associated with OA of the knee is extensive.

In 2011, the most recent review of the hyaluronic acids was published by Bannuru et al [16] with the objective to evaluate the therapeutic trajectory of these agents versus placebo. Data sources included Medline, EMBASE, CINAHL, BIOSIS, Web of Science, Google Scholar, Cochrane database; hand searched reviews, manuscripts, and supplements; and, author contacts for unpublished data. Randomized trials that reported effects of intra-articular hyaluronic acids versus placebo on knee OA were selected based on inclusion criteria. The investigators computed effect sizes for change from baseline at 4, 8, 12, 16, 20 and 24 weeks, using Bayesian random effects model. Multivariate analysis was performed adjusting for correlation between time points. Meta-regressions were performed adjusting for potential confounders.

A total of 54 eligible trials that included 7545 participants were included. The conduct and quality of these trials varied in a number of aspects. The effect size (ES) favored hyaluronic acid by week 4 (0.31; 95% CI 0.17, 0.45), reaching the peak at week 8 (0.46; 0.28, 0.65), and then trending downwards, with a residual detectable effect at week 24 (0.21; 0.10, 0.31). This therapeutic trajectory was consistent with the subset of high-quality trials and on multivariate analysis adjusting for correlation between time points.

The investigators concluded that this meta-analysis highlighted the therapeutic trajectory of hyaluronic acid for knee OA pain over 6 months post-intervention. With this additional perspective, we are able to infer that hyaluronic acid is efficacious by 4 weeks, reaches its peak effectiveness at 8 weeks and exerts a residual detectable at 24 weeks [16].

In addition, the peak effect size (0.46; 0.28, 0.65), is greater than published effects from other OA analgesics [acetaminophen (ES=0.13; 0.04, 0.22) [17]; NSAIDs (ES=0.29; 0.22, 0.35) [18]; and COX-2 inhibitors (ES=0.44; 0.33, 0.55) [19]. An effect size above 0.20 is considered to be clinically relevant on an individual patient basis in chronic pain conditions such as knee OA. Thus, its

properties could have utility for certain clinical situations, or in combination with other therapies. According to the Imitative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) consensus [20], an effect size above 0.20 is considered to be clinically relevant on an individual patient basis in chronic pain conditions such as knee OA. Considering the effect sizes of Bannuru pooled analyses all the relative value were above 0.20 from weeks 4 to 24.

A 2009 Cochrane Review of the effects of viscosupplementation with hyaluronans for the treatment of OA of the knee has been reported [92]. In preparing this review, MEDLINE, EMBASE, PREMEDLINE, Current Contents up to July 2005, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched. The review identified 40 trials that included comparisons of hyaluronic acid with a placebo (either saline or arthrocentesis). The pooled analysis of the effects of viscosupplements against 'placebo' controls generally supported the efficacy of this class of intervention. The conclusions of the Cochrane Collaboration Review of Viscosupplementation are diametrically opposite to your current recommendation. In addition, failure to use the studies that compare intra-articular viscosupplementation to non-steroidal anti-inflammatory drugs (all of which seem to identify equal efficacy, with potential improved safety with the intra-articular injections versus oral non-steroidals) has resulted in a strong recommendation for oral non-steroidals, at the same time a strong recommendation against viscosupplementation, while in head-to-head comparison the two are equal with improved safety with the viscosupplementation (as per John C. Richmond, MD reviewer AAOS Treatment of OA of the knee second edition).

A 2003 meta-analysis of studies reported from 1966 to 2003 and the Cochrane Controlled Trials Register pooled the results of 22 trials of intra-articular hyaluronan versus intra-articular placebo injections. The authors concluded that hyaluronan injections were superior to the intra-articular saline injections [22].

In summary, as reported in the available literature, we believe IA HA has efficacy for knee OA pain. The magnitude of effect could be considered modest, but it exceeds a minimally clinically significant threshold.

These findings are in contrast to the AAOS proposed recommendations; therefore we think that AAOS guidelines do not help to clarify the debate concerning the efficacy of intra-articular therapy with hyaluronic acid. There is no known cure for OA and there are no specific pharmacologic therapies that can prevent the progression of joint damage secondary to OA.

In conclusion, we ask AAOS experts to reconsider their position on recommendation 9, since Hyaluronic acid evidence suggests its therapeutic value and it represents the only available pharmacological option for those patients who are not responsive to conservative pharmacological therapy or for which NSAIDs are contraindicated or finally for those patients who do not want to undergo total knee replacement surgery.

Some studies showed that using IA HA in older patients especially those who are inactive with limited household ambulation could improve WOMAC scores, increase patients' satisfaction and decrease consumption of selective COX-2 inhibitors. Moreover, this treatment can delay the need for surgical procedures within the 2-years follow-up period. [23] According to the results, 80% of patients responded to the IA HA treatment and the cost of this treatment in the response group was only 26.02% compared to 73.98% of other medication costs most of which are costs for selective COX-2 inhibitors. All the patients who responded did not need any surgical intervention for at least 2 years during the follow-up period. In the non-response group the cost of IA HA was only 6.44%. [23]

In fact data suggest that knee viscosupplementation with Hyaluronic Acid may be effective in delaying TKR due to its symptomatic action and consequently it may be considered as conservative treatment to be carried out before considering TKR, as OARSI recommendations suggest. [3,4]

At the same time, we strongly ask AAOS to avoid differentiating high versus low molecular weight viscosupplementation, since even if your analysis showed that most of the statistically significant outcomes were associated with high-molecular cross linked hyaluronic acid, the available published evidence does not clearly support the clinical superiority of one HA product over another.

There is limited evidence to suggest that one HA product is more efficacious than another. The HA category is characterized by scant head-to-head data, and by small studies generating dubious outcomes. Most published head-to-head comparative studies of HA preparations demonstrate equivalent efficacy or non-inferiority [24, 25, 20]. Additionally, a systematic review and meta-analysis of 13 randomized, controlled trials "found no robust evidence for a clinically relevant benefit of" hylan GF20, a chemically cross-linked, high-molecular-weight HA preparation, compared with sodium hyaluronate HA preparations in patients with knee OA [26]. While there are individual studies that purportedly demonstrate the superiority of one HA product over another, the evidence based medicine should consider whether to judge the clinical effectiveness or safety of one product versus another strictly on the basis of one clinical study whose conclusions may be the result of faulty trial design or the play of chance.

While there are no substantive differences among the available HA products in terms of major adverse events (AEs), there are differences in terms of localized, transient reactions (e.g., edema in knee, injection-site pain, severe acute inflammatory reactions [SAIRs]) that may raise significant issues for patients [27, 28, 29, 30, 31, 32, 33]. Although the mechanism for SAIRs remains unproven, these reactions tend to occur with cross-linked HA preparations. [34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46]. The differences in incidence of localized, transient reactions are particularly striking when comparing agents such as hylan G-F20 to Sodium hyaluronate, which has an extremely low rate of reported AEs.

Despite the lack of definitive data demonstrating the superiority of one product over another, evidence suggests that injectable HA products are useful in managing OA knee pain, and they may be underutilized among eligible patients. Many patients are managed on oral agents that provide insufficient pain relief and which may also cause significant, debilitating adverse events, such as hepatotoxicity with acetaminophen [47, 48], gastrointestinal toxicity with conventional NSAIDs2,3, and cardiotoxicity with the “coxib” subclass of NSAIDs [49, 50] and cardio-toxicity, with the “coxib” subclass of NSAIDs [51, 52].

Physicians often reserve HA therapy for patients who are in the more advanced stages of OA. That is a disservice to many patients living with OA, as currently available HA products offer a favorable risk-benefit profile for all levels of disease severity. Patients with mild to moderate forms of OA may derive significant benefit from HA therapy, particularly from agents with a well-documented safety and tolerability profile.

Yours sincerely,

Anonymous

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(973) 507-5120 ● www.fidiapharma.us

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