Washington State Health Care Authority

Hyaluronic Acid/Viscosupplementation and Platelet Rich Plasma for Knee or Hip Osteoarthritis

Topic nomination, Draft key questions and Peer review: Comments and Response

June 26, 2023

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Hyaluronic Acid/Viscosupplementation and Platelet Rich Plasma for Knee or Hip Osteoarthritis

Provided by:

Aggregate Analytics, Inc.

Topic nomination, Draft key questions and Peer review:
Public and Peer Review Comments and Response

June 26, 2023

Specific responses pertaining to peer reviewer comments are included in **Table 1**. Draft report peer reviewers include:

- Erek W. Latzka, MD, Orthopedics and Sports Medicine, Attending Physician and Assistant Professor, UW Sport Medicine Center, University of Washington
- Andre Abadin, DO, CAQSM, RMSK, Acting Assistant Professor - Department of Family Medicine, Primary Care Sports Medicine, University of Washington

Responses to public comments on the Key Question posting from medical and professional organizations may be found in **Table 2**. These include:

- Robert GR Lang, MD, FACS, FRCS(C)
- Ken Long, Vice President Market Access, Orthogenrx

Responses to public comments on the Topic Nomination posting from medical and professional organizations may be found in **Table 3**. These include:

- Ken Long, Vice President Market Access, Orthogenrx
- Noelle Redmond, PharmD, Manager, Clinical Pharmacy Operations, Regence Pharmacy Services

Full texts of peer reviews and public comments may be found in the Appendix at the end of the document following the list of individuals who provided general public comment.

Table 1. Responses to Clinical Peer Reviewers

Section	Comments	Response
Erek Latzka		
	Specific comments	
Introduction	Page ES-1: "PRP also shows promise for improving osteoarthritis symptoms for longer intervals than similar intra-articular treatments with a similar adverse event risk profile, particularly in younger patients, but the overall evidence base utilized for many reviews and recommendations may be outdated." Does PRP really show a similar adverse event risk profile to steroids? Not in my opinion. The only similar risk is infection. Steroid can raise blood pressure, suppress immune system, and raise blood sugar. We acknowledge these additional risks later on in page 13: "carry risk of adverse events such as pain flare and rapid destructive osteoarthritis of the joint as well as increased risk of post-operative surgical infection months following injection, transient increases in blood sugar and hypertension and transient decrease in immune response."	Thank you for the comment. We made changes to the material to address this.

Background	Page 11: "~~Inflammation caused by~~ these processes results in inflammation within the synovial fluid of the joint, known as synovitis, which disrupts production of hyaluronan and plasminogen activator production, causing thickening of synovial fluid." Might just cross out the line above to avoid redundancy.	Thank you for the comment. We removed this error.
	Page 13: "Current evidence suggests that platelet-rich plasma is able to lubricate the joint more effectively than similar treatments while also suppressing several inflammatory mechanisms and increasing cartilage production within the knee." Without a citation, it might be a stretch to say that PRP increases cartilage production within the knee.	Thank you for the comment. We adjusted the writing to make the citation for this sentence clearer.
Report Objectives & Key Questions	On page ES-2 (and Page 44), the Key questions are outlined 1 A-D and 2 A-D. Then in Results KQs are listed as KQ1 (ES-7), KQ2 (ES-15), KQ1 and 2 (ES-16). But then on page ES-17 suddenly there is "KQ 4. Cost effectiveness" which does not fit the prior outline, and additionally, there was never a KQ 4 listed in the ES.. Instead of KQ-4 this should be called KQ 1D and 2D. KQ3 is only addressed on pages 58, 92 and 144. Seems like it should be called KQ 1C and 2C.	Thank you for the comment. We changed key question numbering accordingly.
Methods	None	
Results	Efficacy / Effectiveness: Knees; I appreciate the summary results findings on pages ES-7 to ES-13 which list the major findings. As expected, PRP with no differences for short term results, but better for intermediate-long term vs HA; better at all times vs Saline; slightly better vs steroid (surprised PRP did not do better vs steroid; want to look at these 9 studies more). Inconclusive data PRP vs Exercise, vs PT, vs Prolo, for Lower vs Higher # of injections, and for LR vs LP. . Hips: Insufficient evidence for HA vs Saline, HA vs PRP, HA vs Steroid	Thank you for the comment.
	Adverse Events / Safety: Knees: ES 15 to 16. On ES 16 they list mild fever as an AE, but the maximum temp was not beyond 99.5. I	Thank you for the comment. The fever was just one component of the adverse event that was reported. Authors reported "severe

	would not consider this a fever; rather its within realm of normal temp.	swelling and mild fever (not >99.5)"; because the authors designated the swelling specifically as severe/serious, we classified it as such. Furthermore, one of these patients went on to need arthroscopy to treat the symptoms.
	Cost effectiveness: Unable to answer for PRP. For HA, cost effective at a willingness to pay of 50K/QALY	Thank you for the comment, we made revisions and additions to the economic analysis section.
	I love Table 9 comparing this re-review to prior report.	Thank you for the comment.
Summary	Some studies in the past have made the claim that saline is not necessarily a placebo. Do we want to change the term placebo to "saline" ? I am indifferent.	Thank you for the comment. We are aware that some may not consider saline a placebo, we checked each study for specific placebo type, and made edits where appropriate.
Overall Presentation & Relevancy	ES-16: The ES should at least include KQ 3(1d and 2d). It seems odd to not answer one of our Key questions within the ES.	Thank you. This was an omission on our part. Summary information for KQ 1c and 2c (differential efficacy and safety) has been added to the ES.
Other	I actually struggled a bit with this form. I am using a PC (Thinkpad). Tab would not take me from one textbox to the next. I had to manually use the mouse, and to enter any text within the grey boxes, I would have to double click and enter them within a popup (I've pasted the image below). Rather than do that, I just deleted the boxes and highlighted my text with a grey background.	Thank you for the feedback. The current Peer Review Form has not been updated in several years, and we will be revising it for future projects.
Andre Abadin		
	Specific comments	
Introduction	Page ES-1, line 2nd to last paragraph: PRP has less adverse events compared to corticosteroid and viscosupplementation injections. Would recommend rewording.	Thank you for the suggestion.
Background	Page 14: Would recommend highlighting American medical society of sports medicine (AMSSM) in the overview of guidelines from different organizations as it is the biggest organization of non-surgical orthopedics (primary care sports medicine physicians) with many of the leaders having years of experience with HA and PRP injections. Overall, literature review	Thank you for your comment. The AMSSM is included in the Phillips SR of clinical guidelines.

	and background of OA is thoroughly covered including recommendations of medical organizations.	
	Page 1: Overview of topic should include that once patient do not respond to corticosteroid injections, there are limited non-surgical options for the patients therefore HA and PRP can be alternative to repeat steroid injections and/or knee replacement .	Thank you for the suggestion. We've added material to address this.
Report Objectives & Key Questions	Page 44: Aims and objectives are clearly stated.	Thank you for the comment.
	Page 44: Key questions should include what is effectiveness and harm of HA and PRP in the intermediate term as well.	Thank you. The key questions should have said "long**er"** term, not just "long" term. We have edited the key questions accordingly.
Methods	Page ES-5: Unclear if the two independent reviewers that screened all records are the same reviewers that critical appraised primary outcomes of studies and evaluating the methodological quality, study limitations and potential for bias.	There was an overlap between reviewers who screened and critically appraised the studies. Sometimes a third independent reviewer was also involved. The point is that at least dual and always independent review was done for these processes.
Results	Page 66, 1st line under 5.1.1.2: Don't know if it is a typo, unclear if studies are comparing HA vs PRP or HA with PRP vs other treatments. Please clarify as it is written many times in the section, HA with PRP.	Thank you for the suggestion. We've changed all instances to "HA versus PRP"
	Figures under the HA vs PRP section should have lines between studies are more space in between studies as the HA and PRP category columns are cramped making it difficult to read.	Thank you for the suggestion. We've edited the figures to help with this.
	Page 80: Figure 12 is difficulty read as HA category is too close together.	Thank you for the suggestion. We've edited the figures to help with this.
	Page 61 and multiple pages: Function "success" is an unusual category. I would eliminate this section as most studies did not report this and success is subjective based on authors of the studies. Pain and functions scores, which were included, are more objective.	Thank you for the suggestion. We include both for transparency. "Success" or response as reported by trials included in our report was defined as the proportion of patients who achieved a certain threshold or cut-off on a validated outcomes measure, i.e., ≥30% or ≥50% on WOMAC pain or VAS pain scale; thus, it is not just a subjective measure of patients' improvement based on the investigators assessment.

		Response also typically tries to get at a clinically important/relevant degree of improvement. "Success" or response is often more intuitive to readers than the change scores, too.
Summary	Page ES-14: Overall, general conclusions described were accurate. A table for PRP vs PRP: greater vs fewer number of injections would have been helpful. Tables were clear on concise.	. Additional summary tables were added to the ES for the final and included both comparisons of PRP regimens (greater vs. fewer number of injections and LR vs. LP)
Overall Presentation & Relevancy	Page 52: The review is well structured and organized. I like how the executive summary is the first section. I am unclear why there is a section on "number of studies retained and comparison with prior reports." If anything this section should be at the end of the executive summary and not at the beginning of the result section.	Thank you for your suggestion.
Other	Unable to tab through the editable gray boxes, otherwise it was easy to use.	Thank you for the feedback. The current Peer Review Form has not been updated in several years, and we will be revising it for future projects.

Table 2. Responses to KQ Posting

	Comments	Response
Robert GR Lang, MD, FACS, FRCS(C)		
	I have recently changed my prescribing habits to favor Curcumin capsules as opposed to standard NSAIDS which I have prescribed at therapeutic doses for over 42 years. I am including two articles https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3327-2 quoted in Harvard Health: https://www.health.harvard.edu/blog/curcumin-for-arthritis-does-it-really-work-2019111218290, that piqued my interest to initially use Curcumin for those patients who "hate taking pills' as an alternative to NSAIDS. I am also including a consumer report https://www.consumerreports.org/turmeric-supplement/turmeric-inflammation-a1205144105/ that describes some potential pitfalls of using over the counter supplements that are less regulated than pharmaceuticals. Perhaps you would consider including curcumin in this study or in a separate study as a potentially safer and less expensive alternative to NSAIDS and	Thank you for your comment. This treatment is not within the scope of our review.

	injections, if it is indeed as effective as some claim. At least it has staying power – over 3000 years.	
Ken Long, Vice President Market Access, Orthogenrx		
	While the current HTCC Coverage Determination and corresponding Reimbursement Determination considers hyaluronic acid/viscosupplementation to be a covered benefit for the treatment of pain associated with osteoarthritis of the knee, when conditions are met, it only includes individuals who have a documented contraindication to **ALL** forms of non-surgical care. Given numerous supporting peer-reviewed evidence published over the past nine years, it would be prudent to ***include patients who are also refractory in addition to those contraindicated for other forms of non-surgical treatment as well as patients who are not candidates for surgical intervention due to obesity, medical co-morbidities, depression, or other prognostic indicators suggestive of non-response to TKA.***[iii]	Thank you for your comment. As the vendor we do not suggest nor evaluate policy.
KQ 1a	***Hyaluronic acid injections offer more durable pain relief and functional improvement over other commonly used conservative treatments and injections for a period of 4-26 weeks*** A systematic review by ***Altman et al (2018)*** of 7 RCTs and 10 cohort studies looked at the efficacy and safety of repeated courses of hyaluronic acid injections for knee OA. All studies reported pain reduction from baseline in the HA treatment group throughout the initial treatment cycle which was sustained or further reduced with additional injections. Common adverse events were transitory joint swelling and arthralgia with no serious adverse events and additional injections well tolerated. The authors conclude that repeated courses of HA are a safe and effective treatment for knee OA and demonstrate maintenance or further improvement in pain reduction with no increased safety risk.[iv] ***Vaishya et al (2017)*** found that HA seems to be better for pain relief and improved function in the short and mid-term period. This prospective study found that when comparing HA to intraarticular injection of triamcinolone hexacetonide, that up to 12 weeks there were no statistically significant between group difference in Knee Society Score (KSS) and VAS but that after 12 weeks, KSS and VAS in the steroid group deteriorated rapidly. At six months HA was significantly better than steroid.[v] ***Miller and Block (2013*)** conducted a systematic review and meta-analysis of randomized saline-controlled trials to determine the safety and efficacy of US-approved intra-articular HA injections	Thank you for your comment. All cited publications were reviewed per our final key questions and scope and those meeting inclusion criteria were included in our report. Additionally, the bibliographies of all cited systematic reviews and meta-analyses were hand-searched for publications that may fit our protocol and those publications were then evaluated as well.

	for symptomatic knee OA including 29 studies of 4,866 unique subjects. HA injections resulted in very large treatment effects between 4 and 26 weeks for knee pain and function compared to pre-injection values.[vi] ***Bannuru et al (2015)*** performed a meta-analysis on 137 studies to assess the relative efficacy of available treatments for knee OA. For pain, all interventions significantly outperformed oral placebo, with effect sizes from 0.63 (95% credible interval [CrI], 0.39 to 0.88) for the most efficacious treatment (hyaluronic acid) to 0.18 (CrI, 0.04 to 0.33) for the least efficacious treatment (acetaminophen). For function, all interventions except IA corticosteroids were significantly superior to oral placebo. For stiffness, most of the treatments did not significantly differ from one another.[vii].	
KQ 1b	***Hyaluronic acid injections present no significant safety or adverse harms compared to saline injection*** A systematic review of 29 studies including 4,866 patients by ***Miller and Block (2013***) found no statistically significant differences between HA and saline controls for any safety outcomes including serious adverse events.[viii] Given the favorable safety profile of HA injections over NSAIDS, HA may be a viable alternative for older patients at greater risks for systemic adverse events.[ix]	Thank you for your comment. All cited publications were reviewed per our final key questions and scope and those meeting inclusion criteria were included in our report. Additionally, the bibliographies of all cited systematic reviews and meta-analyses were hand-searched for publications that may fit our protocol and those publications were then evaluated as well.
KQ 1c	***Hyaluronic acid injections are more effective for improving pain, function, and stiffness than intra-articular steroid injection, NSAIDs, oral analgesics and placebo. Adverse events are more common among oral treatments than intra-articular injections which may result in similar transient local reaction for all therapy types (HA or steroid). The safety profile of HA over NSAIDs suggest HA is a better therapy option for older patients at greater risk for adverse events.*** A network meta-analysis by ***Bannuru et al (2015)*** examined the efficacy of treatments of primary knee OA using RCTs of adults with knee OA comparing two or more treatments: acetaminophen, diclofenac, ibuprofen, naproxen, celecoxib, intra-articular corticosteroids, IA hyaluronic acid, oral placebo, and IA	Thank you for your comment. All cited publications were reviewed per our final key questions and scope and those meeting inclusion criteria were included in our report. Additionally, the bibliographies of all cited systematic reviews and meta-analyses were hand-searched for publications that may fit our protocol and those publications were then evaluated as well.

	placebo. 137 studies comprising 33,243 subjects were identified. • Pain: All interventions were statistically significantly better than oral placebo (Table 1), with effect sizes ranging from 0.18 (CrI, 0.04 to 0.33) for the least efficacious treatment (acetaminophen) to 0.63 (CrI, 0.39 to 0.88) for the most efficacious treatment (IA hyaluronic acid). • Function: All interventions except IA corticosteroids were statistically significantly superior to oral placebo (Supplement Table 5), with effect sizes ranging from 0.15 to 0.45. Naproxen, ibuprofen, diclofenac, and celecoxib were statistically significantly better than acetaminophen. Intra-articular hyaluronic acid was statistically significantly better than IA placebo and IA corticosteroids. Intra-articular placebo was not significantly better than oral placebo (effect size, 0.15 [CrI, _0.22 to 0.53]). • Stiffness: Naproxen, ibuprofen, diclofenac, and celecoxib were statistically significantly better than oral placebo and acetaminophen. Intraarticular hyaluronic acid was statistically significantly better than IA placebo. Intra-articular placebo was not significantly better than oral placebo (effect size, 0.10 [CrI, _0.26 to 0.46]). • Safety: Adverse events were more common among oral treatments (acetaminophen, non-selective NSAIDs, and celecoxib) than intra articular therapies. Commonly reported IA events include transient local reactions and are similar between different IA therapies (HA and steroid). The safety profile of HA injections over NSAIDS, suggests HA may be a better alternative for older patients at greater risks for systemic adverse events.[x]	
KQ 1d	***Hyaluronic acid is more cost effective than PRP for the treatment of knee OA. HA injection in patients with knee OA is associated with an increase in time-to-TKA and significant cost savings to the health system.*** Outcome data regarding the use of PRP or hyaluronic acid injections for the treatment of symptomatic knee osteoarthritis were determined from the available literature published to 2015. Costs were determined by examining typical charges for patients	Thank you for your comment. All cited publications were reviewed per our final key questions and scope and those meeting inclusion criteria were included in our report. Additionally, the bibliographies of all cited

	undergoing a series of either PRP or HA injections with the health utility values and costs used to create an expected-value decision analysis model. The results of the model revealed that the cost per quality-adjusted life-year (QALY) of a series of PRP injections was $8,635.23/QALY and that of a series of HA injections was $5,331.75/QALY.[xi] A large retrospective analysis of 744,734 patients was conducted to examine the relationship between intra-articular hyaluronic acid treatment and delaying TKA in patients with knee OA compared with patients who did not receive HA. A delay to TKA was observed after IA-HA treatment for patients treated with IA-HA compared to those who did not receive IA-HA. At 1 year, the TKA-free survival was 85.8% (95% CI: 85.6%-86.0%) for patients who received IA-HA and 74.1% (95% CI: 74.0%-74.3%) for those who did not receive IA-HA. At 2 years, the TKA free survival was 70.8% (70.5%-71.1%) and 63.7% (63.5%-63.9%) in the 2 groups, respectively.[xii] In patients that eventually had TKA, the median knee OA-related costs were lower among those who received IA-HA before their TKA ($860.24, 95% CI: 446.65-1722.20), compared to those who did not receive IA-HA ($2659.49, 95% CI: 891.04-7480.38). For patients who did not have TKA, the median and interquartile range (IQR) knee OA-related costs per year were similar for patients who received IA-HA compared with those who did not.[xiii] Similarly, a French retrospective study of 14,782 patients treated for knee osteoarthritis found that of the 1,662 patients that had TKA, at each time point (1, 3, 5 and 7.5 years), restricted mean survival time without TKA was significantly higher for the patients who received HA, delaying TKA from +51 to +217 days at 1 and 7.5 years respectively. In addition, the study reported that ambulatory care costs were similar in both groups, i.e., €744 for the HA group and €805 for the non-HA group the year before TKR (p-value = 0.104).[xiv] A study by ***Ong et al*** sought to evaluate the treatment costs following knee OA diagnosis to determine differences between patients using HA and/or TKA based commercial claims data between 2011-2015. Non-arthroplasty therapies accounted for about one third of the costs of treating knee OA and despite the consideration of limiting the use of HA to reduce costs, HA only amounted to 3% of overall costs. Among patients who underwent TKA, those treated with HA experienced elevated costs from the surgery later than those without HA, which reflects their longer	systematic reviews and meta-analyses were hand-searched for publications that may fit our protocol and those publications were then evaluated as well.

	time to undergoing TKA. The ability to delay or avoid TKA altogether can have a substantial impact on the cost to the healthcare system.[xv]	
	The published evidence continues to support hyaluronic acid injections as a safe, efficacious, and cost-effective therapy for the treatment of OA knee pain. It should continue to be a covered benefit for Washington State Healthcare Authority members however restrictions severely limiting patient access to this important treatment should be reconsidered in light of the continually growing body of evidence that hyaluronic acid injections are both safe and effective for the treatment of OA knee pain.	Thank you for your comment. As the vendor we do not suggest nor evaluate policy.

Table 3. Responses to Topic Nomination

	Comments	Response
Ken Long, Vice President Market Access, Orthogenrx		
	While this therapy is currently restricted to patients who have a documented medical contraindication to other forms of non-surgical care including ALL of the following: NSAIDS, corticosteroid injections, and physical therapy/exercise, it is our expectation that given the numerous supporting peer-reviewed evidence published over the past nine years that these conditions will be adjusted to include patients who are refractory to or contraindicated for other forms of non-surgical treatment or not candidates for surgical intervention.	Thank you for your comment. As the vendor we do not suggest nor evaluate policy.
	Intra-articular injections of hyaluronic acid have been widely used in the US for almost three decades for the treatment of knee OA[iv]pain and have become an integral component of the standard of care. Most professional medical society clinical practice guidelines (CPGs) for the care of knee OA begin with conservative care including NSAIDs, weight loss, bracing or taping, 2and exercise. There are conflicting guidelines for the use of intraarticular injections of either intra-articular corticosteroids (ICS) or viscosupplementation with hyaluronic acid (HA) with the overwhelming majority of societies recommending HA injections.[v]	Thank you for your comment. All cited publications were reviewed per our final key questions and scope and those meeting inclusion criteria were included in our report. Additionally, the bibliographies of all cited systematic reviews and meta-analyses were hand-searched for publications that may fit our protocol and those publications were then evaluated as well.
	A recent systematic review of clinical practice guidelines by Phillips et al found that intra-articular hyaluronic acid was recommended by most professional society CPGs. In fact even the new AAOS CPG now suggests a specific subset of patients	Thank you for your comment. All cited publications were reviewed per our final key questions and scope and

	might benefit from IA-HA use, a much different position than their statement in their previous (2013) CPG. A systematic review conducted by Chavda et al of 39 studies included 5,025 patients from 2015-2020. All studies concluded that intra-articular injections of HA resulted in clinical improvement over baseline pain, stiffness, and function for up to three to six months.[vi]Another recently published systematic review by Pereira et al looked at 25 large placebo-controlled trials from 1983-2021. Unfortunately, only 8 of the trials included were from 2014-2021 and included 4 unpublished (non-peer reviewed) trials. This poses significant limitations to their study and severely weakens their conclusion that "strong evidence indicates that among patients with knee osteoarthritis, viscosupplementation is associated with clinically irrelevant reduction in pain intensity."[vii]Altman et al(2018) reviewed the efficacy and safety of repeated courses of hyaluronic acid injection for knee OA. This systematic review of 7 RCTs and 10 cohort studies reported that all studies reduced pain from baseline in HA treatment groups throughout the initial treatment cycle and either sustained or further reduced pain with repeated courses of treatment with no increased safety risk. [viii]A prospective randomized study, Vaishya et al, of 82 patients demonstrated statistically improved durability of HA over ICS as measured by function (KSS) and pain (VAS) beginning at 12 weeks post injection through 6 months.[ix]Suppan et al.[x]compared single dose vs. repeated doses of HA injections concluding no significant difference between groups for pain scores up to 12 months. Results of this study correlate with a 2019 meta-analysis of 28 studies, which also concluded that single HA injections produced results comparable to those of multiple injections.[xi]	those meeting inclusion criteria were included in our report. Additionally, the bibliographies of all cited systematic reviews and meta-analyses were hand-searched for publications that may fit our protocol and those publications were then evaluated as well.
	Commenter discusses several cost-effectiveness analyses and cites included data on general cost-effectiveness analyses as well as TKA-related cost.	Thank you for your comment. All cited publications were reviewed per our final key questions and scope and those meeting inclusion criteria were included in our report. Additionally, the bibliographies of all cited systematic reviews and meta-analyses were hand-searched for publications that may fit our protocol and those publications were then evaluated as well. Data included in this report was

		analyzed via our methodology.
	Commenter references efficacy data from cited sources	Thank you for your comment. All cited publications were reviewed per our final key questions and scope and those meeting inclusion criteria were included in our report. Additionally, the bibliographies of all cited systematic reviews and meta-analyses were hand-searched for publications that may fit our protocol and those publications were then evaluated as well. Data included in this report was analyzed to determine clinical significance.
	Based on the wide range of studies and publications demonstrating the safety and effectiveness of HA, the cost effectiveness role it has in the treatment of OA, as well as the overwhelming majority of CPGs supporting the use of HA, we request that Washington Health Care Authority continue to offer this benefit to members and strongly consider expanding the indications to include those who are refractory to or contraindicated for other non-surgical therapy or are otherwise avoiding or contraindicated for surgical intervention.	Thank you for your comment. As the vendor we do not suggest nor evaluate policy.
Noelle Redmond, PharmD, Manager, Clinical Pharmacy Operations, Regence Pharmacy Services		
	As the medical coverage administrator for Uniform Medical Plan, we are writing today to encourage reconsideration of the current HTCC position on intraarticular hyaluronic acid (IAHA) products. We recommend coverage of IAHA, at minimum, in patients that are not surgical candidates. However, we also strongly encourage consideration of a broader preferred product strategy. In October 2021, we (Regence BCBS) changed our commercial (non-UMP) coverage position from "not medically necessary (NMN)" to a preferred product step strategy. We previously held the NMN position since 2015 based on inconclusive evidence of safety and efficacy, as well as the lack of consistent support by evidence-based clinical guidelines.	Thank you for your comment. As the vendor we do not suggest nor evaluate policy.
	The net cost of IAHA therapy has decreased significantly. For most IAHA products, a course of therapy for one knee is <$300. Use of preferred IAHA products can be as low as $60.	Thank you for your comment.

	Coverage of IAHA therapy varies by other health plans, across markets	Thank you for your comment.
	Expert opinion from practicing providers disagreed with our NMN policy. Based on peer-to-peer conversations with providers (as part of the PA process): • Most patients seeking IAHA have exhausted conservative treatment options. • Surgery not an option in certain clinical situations and remaining treatment options generally are very limited. • Long-term use of intra-articular (IA) corticosteroids is not reasonable or sound due to the long-term risks. • Most were aware of AAOS guidelines but pointed to the lack of consensus across guidelines, including different guidelines or more recent meta-analyses.	Thank you for the comment.
	There are Health Equity concerns with non-coverage of IAHA therapy. Treatment alternatives include physical therapy (PT), opioids, and surgery, which may not be feasible for some of our members. While some members can afford to pay cash for IAHA treatment despite lack of insurance coverage, other members may not have the financial means to pursue this option. Real-world examples we've seen in our PA review include: • Members who would no longer be able to work their trade with knee replacement. • Members that are too young, so providers want to delay surgery as long possible and reduce the need for revision (repeat surgery). • Members denied coverage for knee replacement due to their high weight but cannot lose weight due to pain.	Thank you for the comment.
	Although evidence of efficacy for IAHA therapy remains conflicting, there is directional data supporting small improvements in pain with use of IAHA therapy. Most high-quality systemic reviews have concluded that IAHA injections modestly improve pain and mobility; however, improvements may or may not be clinically meaningful. • Most studies show a small, statistically significant improvement in pain and function that may or may not be clinically meaningful. • ACR evidence report: Endpoints favor IAHA but results are not clinically significant • Strand et al Systematic Review: IAHA is safe and efficacious through 26 weeks in patients with symptomatic knee OA.	Thank you for your comment. All cited publications were reviewed per our final key questions and scope and those meeting inclusion criteria were included in our report. Additionally, the bibliographies of all cited systematic reviews and meta-analyses were hand-searched for publications that may fit our protocol and those publications were then evaluated as well.
	Commenter provides a table of clinical guidelines.	Thank you for your comment. All cited publications were

		reviewed per our final key questions and scope and those meeting inclusion criteria were included in our report. Additionally, the bibliographies of all cited systematic reviews and meta-analyses were hand-searched for publications that may fit our protocol and those publications were then evaluated as well.

APPENDIX: Clinical/Peer Reviews and Public Comments Received

Introduction and Form

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for the **HA/PRP** HTA update. Your contribution and time are greatly appreciated.

The general time commitment ranges between 2 and 4 hours; we are able to pay a maximum of 6 hours.

The report and appendices are available at: Hyaluronic acid/viscosupplementation, platelet-rich plasma injections for knee or hip osteoarthritis: draft evidence report

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement. You may also provide a separate document covering the questions posed in this form

We will be going through the draft for typographical errors as well as grammatical and minor edits, allowing you to **focus on the substance/content of the report**.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to: [redacted] **please cc:** [redacted]

We will need your review by Tuesday, June 13, 2023 at the latest.

If you have questions or concerns, please contact [redacted]**. Thanks!**

Peer Reviewer #1

Reviewer Identification Information

Reviewer Name	**Erek Latzka**
Address	**Street:** [redacted] **City** [redacted] **State** [redacted] **Zip Code** [redacted]
Phone	[redacted]
Fax	
E-mail	[redacted]

- *INTRODUCTION Comments (pages 1-10)*

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate? **YES**
- Topic of assessment is important to address? **YES**
- Public policy and clinical relevance are well defined? **YES**

Page	Line

Page ES-1: “PRP also shows promise for improving osteoarthritis symptoms for longer intervals than similar intra-articular treatments with **a similar adverse event risk profile**, particularly in younger patients, but the overall evidence base utilized for many reviews and recommendations may be outdated.”

Does PRP really show a similar adverse event risk profile to steroids? Not in my opinion. The only similar risk is infection. Steroid can raise blood pressure, suppress immune system, and raise blood sugar. We acknowledge these additional risks later on in page 13: “carry risk of adverse events such as pain flare and rapid
destructive osteoarthritis of the joint as well as increased risk of post-operative surgical infection months following injection, transient increases in blood sugar and hypertension and transient decrease in immune response.”

Page	Line

- *Page*
- Lin e

Enter Comments Here

BACKGROUND Comments (pages 1, 11-38)

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient? **YES**

- *Page*
- Line

Page 11: "~~Inflammation caused by~~ these processes result~~s~~ in inflammation within the synovial fluid of the joint, known as synovitis, which disrupts production of hyaluronan and plasminogen activator production, causing thickening of synovial fluid."

Might just cross out the line above to avoid redundancy.

- *Page*
- Lin e

Page 13: "Current evidence suggests that platelet-rich plasma is able to lubricate the joint more effectively than similar treatments while also suppressing several inflammatory mechanisms and increasing cartilage production within the knee."

Without a citation, it might be a stretch to say that PRP increases cartilage production within the knee.

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REPORT OBJECTIVES & KEY QUESTIONS Comments (Pages 2, 44)

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue? **YES**
- Key questions clearly defined and adequate for achieving aims? **YES**

- *Page*
- Line

On page ES-2 (and Page 44), the Key questions are outlined 1 A-D and 2 A-D. Then in Results KQs are listed as KQ1 (ES-7), KQ2 (ES-15), KQ1 and 2 (ES-16). But then on page ES-17

suddenly there is “KQ 4. Cost effectiveness” which does not fit the prior outline, and additionally, there was never a KQ 4 listed in the ES.. Instead of KQ-4 this should be called KQ 1D and 2D.

KQ3 is only addressed on pages 58, 92 and 144. Seems like it should be called KQ 1C and 2C.

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METHODS Comments (Pages 44-51)

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate? **YES**
- Criteria for the inclusion and exclusion of studies is appropriate? **YES**
- Method for risk of bias (ROB) assessment, study quality rating is appropriate and clearly explained? **YES**
- Data abstraction and analysis/review are adequate? **YES**

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RESULTS Comments (Pages 52-59, to 214)

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate? **The number of figures is kind of overwhelming. We have 11 figures (Fig 16-27) just on PRP vs Placebos. Maybe we asked too many questions.**

- Key questions are answered? **YES** (on efficacy and adverse events/safety)
- Figures, tables and appendices clear and easy to read? **YES**
- Are the major findings clearly stated? **YES**
- Have gaps in the literature been dealt with adequately? **Not sure how to answer this**

- *Page*
- Line

Efficacy / Effectiveness:

Knees; I appreciate the summary results findings on pages ES-7 to ES-13 which list the major findings. As expected, PRP with no differences for short term results, but better for intermediate-long term vs HA; better at all times vs Saline; slightly better vs steroid (**surprised PRP did not do better vs steroid; want to look at these 9 studies more**). Inconclusive data PRP vs Exercise, vs PT, vs Prolo, for Lower vs Higher # of injections, and for LR vs LP. .

Hips: Insufficient evidence for HA vs Saline, HA vs PRP, HA vs Steroid

- *Page*
- Lin e

Adverse Events / Safety:

Knees: ES 15 to 16. On ES 16 they list mild fever as an AE, but the maximum temp was not beyond 99.5. I would not consider this a fever; rather its within realm of normal temp.

- *Page*
- Lin e

Cost effectiveness: Unable to answer for PRP. For HA, cost effective at a willingness to pay of 50K/QALY

- *Page*
- Lin e

I love Table 9 comparing this re-review to prior report.

Summary Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the general conclusions described in the summary points, strength of evidence tables, and Executive Summary valid? (Please note AAI does not suggest implications for policy)

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Some studies in the past have made the claim that saline is not necessarily a placebo. Do we want to change the term placebo to “saline” ? I am indifferent.

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OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized? **YES**.
- Are the main points clearly presented? **YES**
- Is it relevant to clinical medicine? **YES**
- Is it important for public policy or public health? **YES**

- *Page*
- Line

ES-16: The ES should at least include KQ 3(1d and 2d). It seems odd to not answer one of our Key questions within the ES.

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QUALITY OF REPORT

- *Quality Of the Report*

(Click in the gray box to make your selection)

☐ **Superior x**
☐ **Good** ☐
☐ **Fair** ☐
☐ **Poor** ☐

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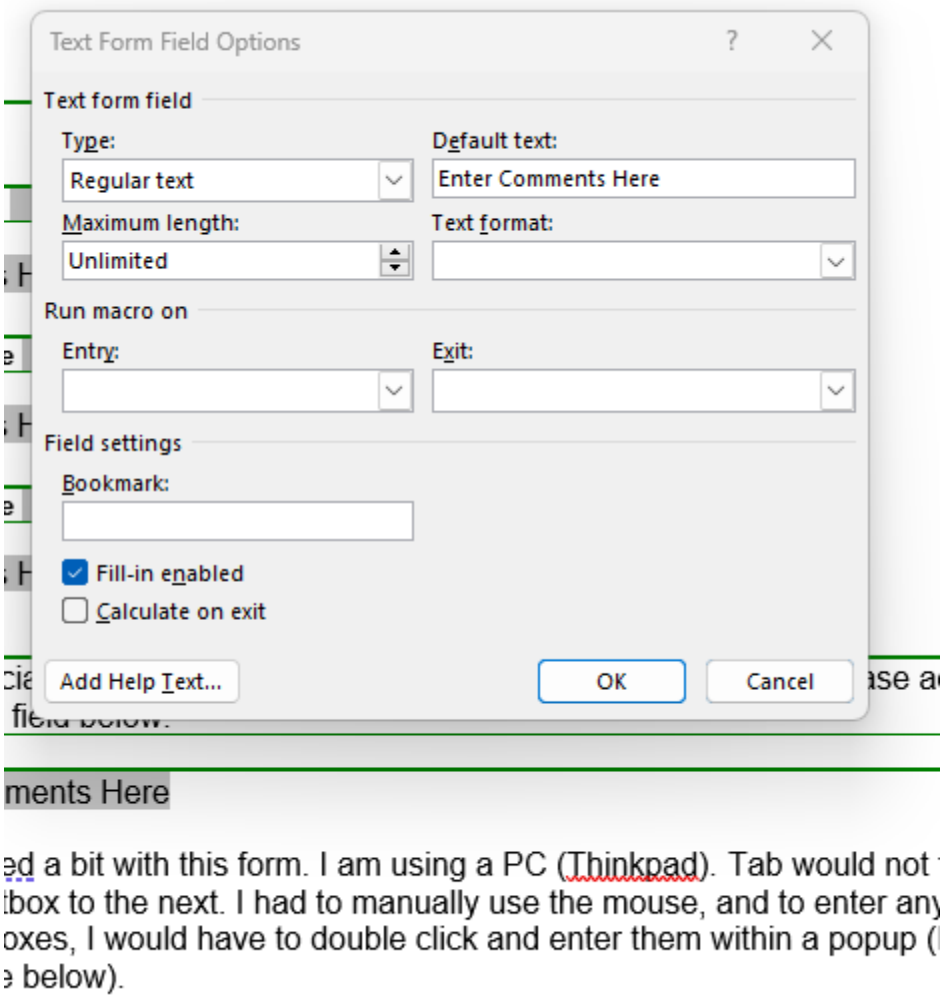
We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

I actually struggled a bit with this form. I am using a PC (Thinkpad). Tab would not take me from one textbox to the next. I had to manually use the mouse, and to enter any text within the grey boxes, I would have to double click and enter them within a popup (I've pasted the image below). Rather than do that, I just deleted the boxes and highlighted my text with a grey background.


Text Form Field Options
Text form field
Type:
Regular text
Default text:
Enter Comments Here
Maximum length:
Unlimited
Text format:
Run macro on
Entry:
Exit:
Field settings
Bookmark:
Fill-in enabled
Calculate on exit
Add Help Text...
OK
Cancel
ments Here
ed a bit with this form. I am using a PC (Thinkpad). Tab would not
box to the next. I had to manually use the mouse, and to enter any
oxes, I would have to double click and enter them within a popup (
below).

Peer Reviewer #2

Reviewer Identification Information

Reviewer Name	**Andre Abadin**
Address	[redacted]
City	[redacted]
State	[redacted]
Zip Code	[redacted]
Phone	[redacted]
Fax	
E-mail	[redacted]

- *INTRODUCTION Comments*

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

Page *ES-1*	Line 2nd to last paragraph

PRP has less adverse events compared to corticosteroid and viscosupplementation injections. Would recommend rewording

Page	Line

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BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?

Page *14*	Line

Would recommend highlighting American medical society of sports medicine (AMSSM) in the overview of guidelines from different organizations as it is the biggest organization of non-surgical orthopedics (primary care sports medicine physicians) with many of the leaders having years of experience with HA and PRP injections. Overall, literature review and background of OA is thoroughly covered including recommendations of medical organizations.

• *Page 1*	• Line

Overview of topic should include that once patient do not respond to corticosteroid injections, there are limited non-surgical options for the patients therefore HA and PRP can be alternative to repeat steroid injections and/or knee replacement

• *Page*	• Line

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REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?

• *Page 44*	• Line

Aims and objectives are clearly stated

• *Page 44*	• Line

Key questions should include what is effectiveness and harm of HA and PRP in the intermediate term as well.

• *Page*	• Line

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METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
- Criteria for the inclusion and exclusion of studies is appropriate?
- Method for risk of bias (ROB) assessment, study quality rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

- *Page* *ES-5*
- Line

Unclear if the two independent reviewers that screened all records are the same reviewers that critical appraised primary outcomes of studies and evaluating the methodological quality, study limitations and potential for bias

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RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Are the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?

- *Page* *66*
- Line 1st line under 5.1.1.2

Don't know if it is a typo, unclear if studies are comparing HA vs PRP or HA with PRP vs other treatments. Please clarify as it is written many times in the section, HA with PRP

- *Page*
- Line

Figures under the HA vs PRP section should have lines between studies are more space in between studies as the HA and PRP category columns are cramped making it difficult to read

• *Page* *80*	• Lin e

Figure 12 is difficulty read as HA category is too close together

• *Page* *61 and multiple pages*	• Lin e

Function ”success” is an unusual category. I would eliminate this section as most studies did not report this and success is subjective based on authors of the studies.

Pain and functions scores, which were included, are more objective.

Summary Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the general conclusions described in the summary points, strength of evidence tables, and Executive Summary valid? (Please note AAI does not suggest implications for policy)

• *Page* *ES-14*	• Line

Overall, general conclusions described were accurate. A table for PRP vs PRP: greater vs fewer number of injections would have been helpful. Tables were clear on concise.

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OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

- *Page* 52
- Line

The review is well structured and organized. I like how the executive summary is the first section. I am unclear why there is a section on "number of studies retained and comparison with prior reports." If anything this section should be at the end of the executive summary and not at the beginning of the result section.

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QUALITY OF REPORT

- *Quality Of the Report*

(Click in the gray box to make your selection)

☐ **Superior x**
☐ **Good** ☐
☐ **Fair** ☐
☐ **Poor** ☐

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We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

Unable to tab through the editable gray boxes, otherwise it was easy to use.

Hamann, Valerie (HCA)
From:Bob Lang bob@olympianeuro.com
Sent:Sunday, October 23, 2022 11:52 AM
To:HCA ST Health Tech Assessment ProgCc:Young, Morgan (LNI)
Subject:DRAFT Key Questions and Background: Hyaluronic acid/viscosupplementation, platelet-rich plasma injections for knee or hip osteoarthritisExternal
Email:
Dear Sir/Madam;

I have recently changed my prescribing habits to favor Curcumin capsules as opposed to standard NSAIDS which I have prescribed at therapeutic doses for over 42 years. I am including two articles https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3327-2 quoted in Harvard Health: https://www.health.harvard.edu/blog/curcumin-for-arthritis-does-it-really-work-2019111218290, that piqued my interest to initially use Curcumin for those patients who "hate taking pills' as an alternative to NSAIDS. I am also including a consumer report https://www.consumerreports.org/turmeric-supplement/turmeric-inflammation-a1205144105/ that describes some potential pitfalls of using over the counter supplements that are less regulated than pharmaceuticals.

Perhaps you would consider including curcumin in this study or in a separate study as a potentially safer and less expensive alternative to NSAIDS and injections, if it is indeed as effective as some claim. At least it has staying power – over 3000 years.

Respectfully;

Robert GR Lang MD, FACS, FRCS(C)

To: shtap@hca.wa.gov

From: Ken Long, Vice President Market Access, Orthogenrx

Subject: Comments Hyaluronic Acid/Viscosupplementation for the Treatment of OA knee pain

Date: October 27, 2022

Dear Sir/Madam:

I am the vice president of market access at Orthogenrx, an AVANOS company, Doylestown, PA and have worked closely with and supported researchers and clinical experts in treatment options for OA knee pain, including hyaluronic acid injections, since 2005. Orthogenrx manufactures TriVisc® and GenVisc850® hyaluronic acid. Thank you for permitting public comments regarding the use hyaluronic acid for the treatment of osteoarthritis knee pain. I hope you will find this information helpful.

As per the draft key questions and background, the focus of this re-review will be on symptomatic adults with knee or hip OA who may be treated with HA (or PRP) as a primary form of treatment in conjunction with conservative therapies, given that additional evidence has been published since the prior HA report in 2013. I will focus on the clinical evidence published since 2013 that continues to support HA injections as an integral component in the standard of care for the management of OA knee pain.

Intra-articular injections of HA have been widely used in the US for almost three decades for the treatment of OA knee pain[i] with overwhelming support for this practice from the majority of professional medical societies.[ii]

While the current HTCC Coverage Determination and corresponding Reimbursement Determination considers hyaluronic acid/viscosupplementation to be a covered benefit for the treatment of pain associated with osteoarthritis of the knee, when conditions are met, it only includes individuals who have a documented contraindication to **ALL** forms of non-surgical care. Given numerous supporting peer-reviewed evidence published over the past nine years, it would be prudent to ***include patients who are also refractory in addition to those contraindicated for other forms of non-surgical treatment as well as patients who are not candidates for surgical intervention due to obesity, medical co-morbidities, depression, or other prognostic indicators suggestive of non-response to TKA.***[iii]

1. In adults with symptoms related to knee or hip osteoarthritis considered for treatment **with hyaluronic acid/viscosupplementation (HA)**

1. **What is the effectiveness of HA compared with placebo/sham, common conservative treatments, PRP, or no treatment in the short and longer-term?**

Hyaluronic acid injections offer more durable pain relief and functional improvement over other commonly used conservative treatments and injections for a period of 4-26 weeks

A systematic review by ***Altman et al (2018)*** of 7 RCTs and 10 cohort studies looked at the efficacy and safety of repeated courses of hyaluronic acid injections for knee OA. All studies reported pain reduction from baseline in the HA treatment group throughout the initial treatment cycle which was sustained or further reduced with additional injections. Common adverse events were transitory joint swelling and arthralgia with no serious adverse events and additional injections well tolerated. The authors conclude that repeated courses of HA are a safe and effective treatment for knee OA and demonstrate maintenance or further improvement in pain reduction with no increased safety risk. [iv]

Vaishya et al (2017) found that HA seems to be better for pain relief and improved function in the short and mid-term period. This prospective study found that when comparing HA to intraarticular injection of triamcinolone hexacetonide, that up to 12 weeks there were no statistically significant between group difference in Knee Society Score (KSS) and VAS but that after 12 weeks, KSS and VAS in the steroid group deteriorated rapidly. At six months HA was significantly better than steroid.[v]

***Miller and Block (2013*)** conducted a systematic review and meta-analysis of randomized saline-controlled trials to determine the safety and efficacy of US-approved intra-articular HA injections for symptomatic knee OA including 29 studies of 4,866 unique subjects. HA injections resulted in very large treatment effects between 4 and 26 weeks for knee pain and function compared to pre-injection values.[vi]

Bannuru et al (2015) performed a meta-analysis on 137 studies to assess the relative efficacy of available treatments for knee OA. For pain, all interventions significantly outperformed oral placebo, with effect sizes from 0.63 (95% credible interval [CrI], 0.39 to 0.88) for the most efficacious treatment (hyaluronic acid) to 0.18 (CrI, 0.04 to 0.33) for the least efficacious treatment (acetaminophen). For function, all interventions except IA corticosteroids were significantly superior to oral placebo. For stiffness, most of the treatments did not significantly differ from one another.[vii].

2. **What is the evidence regarding short- and long-term harms and complications of HA compared with placebo/sham, common conservative treatments, PRP, or no treatment?**

Hyaluronic acid injections present no significant safety or adverse harms compared to saline injection

A systematic review of 29 studies including 4,866 patients by ***Miller and Block (2013***) found no statistically significant differences between HA and saline controls for any safety outcomes including serious adverse events.[viii] Given the favorable safety profile of HA injections over NSAIDS, HA may be a viable alternative for older patients at greater risks for systemic adverse events.[ix]

3. **Is there evidence of differential efficacy, effectiveness, or safety of HA compared with placebo/sham, commonly used conservative treatments (e.g., NSAIDs, exercise, physical therapy), PRP, or no treatment by *factors such as age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), prior treatments or contraindications to common conservative care options*?**

Hyaluronic acid injections are more effective for improving pain, function, and stiffness than intra-articular steroid injection, NSAIDs, oral analgesics and placebo. Adverse events are more common among oral treatments than intra-articular injections which may result in similar transient local reaction for all therapy types (HA or steroid). The safety profile of HA over NSAIDs suggest HA is a better therapy option for older patients at greater risk for adverse events.

A network meta-analysis by ***Bannuru et al (2015)*** examined the efficacy of treatments of primary knee OA using RCTs of adults with knee OA comparing two or more treatments: acetaminophen, diclofenac, ibuprofen, naproxen, celecoxib, intra-articular corticosteroids, IA hyaluronic acid, oral placebo, and IA placebo. 137 studies comprising 33,243 subjects were identified.

- Pain: All interventions were statistically significantly better than oral placebo (Table 1), with effect sizes ranging from 0.18 (CrI, 0.04 to 0.33) for the least efficacious treatment (acetaminophen) to 0.63 (CrI, 0.39 to 0.88) for the most efficacious treatment (IA hyaluronic acid).

- Function: All interventions except IA corticosteroids were statistically significantly superior to oral placebo (Supplement Table 5), with effect sizes ranging from 0.15 to 0.45. Naproxen, ibuprofen, diclofenac, and celecoxib were statistically significantly better than acetaminophen. Intra-articular hyaluronic acid was statistically significantly better than IA placebo and IA corticosteroids. Intra-articular placebo was not significantly better than oral placebo (effect size, 0.15 [CrI, _0.22 to 0.53]).
- Stiffness: Naproxen, ibuprofen, diclofenac, and celecoxib were statistically significantly better than oral placebo and acetaminophen. Intraarticular hyaluronic acid was statistically significantly better than IA placebo. Intra-articular placebo was not significantly better than oral placebo (effect size, 0.10 [CrI, _0.26 to 0.46]).

- Safety: Adverse events were more common among oral treatments (acetaminophen, non-selective NSAIDs, and celecoxib) than intra articular therapies. Commonly reported IA events

include transient local reactions and are similar between different IA therapies (HA and steroid). The safety profile of HA injections over NSAIDS, suggests HA may be a better alternative for older patients at greater risks for systemic adverse events.[x]

4. What is the evidence of cost-effectiveness of HA compared with placebo/sham, PRP, common conservative treatments, or no treatment?

Hyaluronic acid is more cost effective than PRP for the treatment of knee OA. HA injection in patients with knee OA is associated with an increase in time-to-TKA and significant cost savings to the health system.

Outcome data regarding the use of PRP or hyaluronic acid injections for the treatment of symptomatic knee osteoarthritis were determined from the available literature published to 2015. Costs were determined by examining typical charges for patients undergoing a series of either PRP or HA injections with the health utility values and costs used to create an expected-value decision analysis model. The results of the model revealed that the cost per quality-adjusted life-year (QALY) of a series of PRP injections was $8,635.23/QALY and that of a series of HA injections was $5,331.75/QALY.[xi]

A large retrospective analysis of 744,734 patients was conducted to examine the relationship between intra-articular hyaluronic acid treatment and delaying TKA in patients with knee OA compared with patients who did not receive HA. A delay to TKA was observed after IA-HA treatment for patients treated with IA-HA compared to those who did not receive IA-HA. At 1 year, the TKA-free survival was 85.8% (95% CI: 85.6%-86.0%) for patients who received IA-HA and 74.1% (95% CI: 74.0%-74.3%) for those who did not receive IA-HA. At 2 years, the TKA free survival was 70.8% (70.5%-71.1%) and 63.7% (63.5%-63.9%) in the 2 groups, respectively.[xii]

In patients that eventually had TKA, the median knee OA-related costs were lower among those who received IA-HA before their TKA ($860.24, 95% CI: 446.65-1722.20), compared to those who did not receive IA-HA ($2659.49, 95% CI: 891.04-7480.38). For patients who did not have TKA, the median and interquartile range (IQR) knee OA-related costs per year were similar for patients who received IA-HA compared with those who did not.[xiii]

Similarly, a French retrospective study of 14,782 patients treated for knee osteoarthritis found that of the 1,662 patients that had TKA, at each time point (1, 3, 5 and 7.5 years), restricted mean survival time without TKA was significantly higher for the patients who received HA, delaying TKA from +51 to +217

days at 1 and 7.5 years respectively. In addition, the study reported that ambulatory care costs were similar in both groups, i.e., €744 for the HA group and €805 for the non-HA group the year before TKR (p-value = 0.104).[xiv]

A study by ***Ong et al*** sought to evaluate the treatment costs following knee OA diagnosis to determine differences between patients using HA and/or TKA based commercial claims data between 2011-2015. Non-arthroplasty therapies accounted for about one third of the costs of treating knee OA and despite the consideration of limiting the use of HA to reduce costs, HA only amounted to 3% of overall costs. Among patients who underwent TKA, those treated with HA experienced elevated costs from the surgery later than those without HA, which reflects their longer time to undergoing TKA. The ability to delay or avoid TKA altogether can have a substantial impact on the cost to the healthcare system.[xv]

The published evidence continues to support hyaluronic acid injections as a safe, efficacious, and cost-effective therapy for the treatment of OA knee pain. It should continue to be a covered benefit for Washington State Healthcare Authority members however ther restrictions severely limiting patient access to this important treatment should be reconsidered in light of the continually growing body of evidence that hyaluronic acid injections are both safe and effective for the treatment of OA knee pain.

Hamann, Valerie (HCA)
From:Ken Long klong@orthogenRx.com
Sent:Friday, July 29, 2022 9:20 AM
To:HCA ST Health Tech Assessment ProgCc:carolyn.graziano@avanos.com
Subject:Washington State Comment_Aug 2022
Attachments:Washington State Comment_Aug 2022.pdf

External Email

Dear Ms. Birch and the HTCC Committee:

As per your 7/6/22 notification, hyaluronic acid (HA) has been selected as a topic for re-review "when there is new information that could change a previous determination." Since the last review in 2013, many studies and reviews both supporting and negating the use of hyaluronic acid have been published.

In 2013, the discussion was opened by a 2012 meta-analysis of 89 RCTs evaluating HA injections vs placebo which concluded that while 71 trials showed a moderate reduction in pain (effect size -0.37), 18 trials had an effect size of -0.11 which is considered not clinically relevant.[i]It has been noted that the trials included in this study were generally of very low quality, lacking adequate blinding and randomization process.[ii] A subsequent 2015 meta-analysis of 8 high quality studies found lower pain estimates with an effect size of 0.21—a discrepancy that could be due to the inclusion of the low quality trials in the earlier meta-analysis.[iii]

Based on the 2013 review, the current HTCC Coverage Determination and corresponding Reimbursement Determination consider hyaluronic acid/viscosupplementation to be a covered benefit for the treatment of pain associated with osteoarthritis of the knee, when conditions are met. While this therapy is currently restricted to patients who have a documented medical contraindication to other forms of non-surgical care including ALL of the following: NSAIDS, corticosteroid injections, and physical therapy/exercise, it is our expectation that given the numerous supporting peer-reviewed evidence published over the past nine years that these conditions will be adjusted to include patients who are refractory to or contraindicated for other forms of non-surgical treatment or not candidates for surgical intervention.

Hyaluronic Acid: The Standard of Care

Intra-articular injections of hyaluronic acid have been widely used in the US for almost three decades for the treatment of knee OA[iv]pain and have become an integral component of the standard of care. Most professional medical society clinical practice guidelines (CPGs) for the care of knee OA begin with conservative care including NSAIDs, weight loss, bracing or taping, and exercise. There are conflicting guidelines for the use of intraarticular injections of either intra-articular corticosteroids (ICS) or viscosupplementation with hyaluronic acid (HA) with the overwhelming majority of societies recommending HA injections.[v]

Despite any recommendations against the use of HA, in actual practice, physician and patient choice demonstrate an overwhelming precedent supporting hyaluronic acid to treat OA knee pain, particularly with patients refractory to other conservative therapies, to reduce pain which allows patients to delay total knee replacement (TKA) or manage pain in cases where surgical intervention is contraindicated.

Updated Evidence

A recent systematic review of clinical practice guidelines by Phillips et al found that intra-articular hyaluronic acid was recommended by most professional society CPGs. In fact even the new AAOS CPG now suggests a specific subset of patients might benefit from IA-HA use, a much different position than their statement in their previous (2013) CPG.

A systematic review conducted by Chavda et al of 39 studies included 5,025 patients from 2015-2020. All studies concluded that intra-articular injections of HA resulted in clinical improvement over baseline pain, stiffness, and function for up to three to six months.[vi]

Another recently published systematic review by Pereira et al looked at 25 large placebo-controlled trials from 1983-2021. Unfortunately, only 8 of the trials included were from 2014-2021 and included 4 unpublished (non-peer reviewed) trials. This poses significant limitations to their study and severely weakens their conclusion that “strong evidence indicates that among patients with knee osteoarthritis, viscosupplementation is associated with clinically irrelevant reduction in pain intensity.”[vii]

Altman et al(2018) reviewed the efficacy and safety of repeated courses of hyaluronic acid injection for knee OA. This systematic review of 7 RCTs and 10 cohort studies reported that all studies reduced pain from baseline in HA treatment groups throughout the initial treatment cycle and either sustained or further reduced pain with repeated courses of treatment with no increased safety risk. [viii]

A prospective randomized study, Vaishya et al, of 82 patients demonstrated statistically improved durability of HA over ICS as measured by function (KSS) and pain (VAS) beginning at 12 weeks post injection through 6 months.[ix]

Suppan et al.[x]compared single dose vs. repeated doses of HA injections concluding no significant difference between groups for pain scores up to 12 months. Results of this study correlate with a 2019 meta-analysis of 28 studies, which also concluded that single HA injections produced results comparable to those of multiple injections.[xi]

Cost Effectiveness of Hyaluronic Acid Injection

An analysis of 4 years of insurance claims data (2012-2017, Blue Cross Blue Shield), found when comparing the number of prescriptions per patient per year that those receiving HA were consistently and significantly lower than ICS. Usage rates were significantly lower for the HA cohort compared to TKA in year 1. The total adjusted 4-year costs per patient per month were lowest in the HA cohort ($733) compared to ICS ($1,230) which was 54.4% higher.[xii]

A study by Ong et alsought to evaluate the treatment costs following knee OA diagnosis to determine differences between patients using HA and/or TKA based commercial claims data between 2011-2015.

Non-arthroplasty therapies accounted for about one third of the costs of treating knee OA and despite the consideration of limiting the use of HA to reduce costs, HA only amounted to 3% of overall costs. Among patients who underwent TKA, those treated with HA experienced elevated costs from the surgery later than those without HA, which reflects their longer time to undergoing TKA. The ability to delay or avoid TKA altogether can have a substantial impact on the cost to the healthcare system.[xiii]

Role of Hyaluronic Acid Injection in Delaying TKA

A large retrospective analysis of 744,734 patients was conducted to examine the relationship between intra-articular hyaluronic acid treatment and delaying TKA in patients with knee OA compared with patients who did not receive HA. A delay to TKA was observed after IA-HA treatment for patients treated with IA-HA compared to those who did not receive IA-HA. At 1 year, the TKA-free survival was 85.8% (95% CI: 85.6%-86.0%) for patients who received IA-HA and 74.1% (95% CI: 74.0%-74.3%) for those who did not receive IA-HA. At 2 years, the TKA free survival was 70.8% (70.5%-71.1%) and 63.7% (63.5%-63.9%) in the 2 groups, respectively.[xiv]

In patients that eventually had TKA, the median knee OA-related costs were lower among those who received IA-HA before their TKA ($860.24, 95% CI: 446.65-1722.20), compared to those who did not receive IA-HA ($2659.49, 95% CI: 891.04-7480.38). For patients who did not have TKA, the median and interquartile range (IQR) knee OA-related costs per year were similar for patients who received IA-HA compared with those who did not.[xv]

Similarly, a French retrospective study of 14,782 patients treated for knee osteoarthritis found that of the 1, 662 patients that had TKA, at each time point (1, 3, 5 and 7.5 years), restricted mean survival time without TKA was significantly higher for the patients who received HA, delaying TKA from +51 to +217 days at 1 and 7.5 years respectively. In addition, the study reported that ambulatory care costs were similar in both groups, i.e., €744 for the HA group and €805 for the non-HA group the year before TKR (p-value = 0.104).[xvi]

Hyaluronic Acid Injection Coverage Determination

Based on the wide range of studies and publications demonstrating the safety and effectiveness of HA, the cost effectiveness role it has in the treatment of OA, as well as the overwhelming majority of CPGs supporting the use of HA, we request that Washington Health Care Authority continue to offer this benefit to members and strongly consider expanding the indications to include those who are refractory to or contraindicated for other non-surgical therapy or are otherwise avoiding or contraindicated for surgical intervention.

Thank you for the opportunity to provide input. We ask that you seriously consider these comments within the framework of making this valuable treatment option easily accessible to Washington State residents. If you have any questions, or if I can be of further help, please feel free to contact me.

Best regards,

Ken Long