Research Review Disposition of Comments Report

Research Review Title: *Systematic Review for the Effectiveness of Hyaluronic Acid in the Treatment of Sever Degenerative Joint Disease (DJD) of the Knee*

Project ID: *DJDT0913*

Draft review available for peer and public comment from December 9, 2014 to December 30, 2014.

Research Review Citation: Newberry, SJ, FitzGerald, J., Maglione, M.A., O'Hanlon, C.E., Booth, M., Motala, A., Timmer, M., Shanman, R., Shekelle, P.G., Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee. (Prepared by the Southern California Evidence-based Practice Center under Contract No. HHSA290201200006I.) Rockville, MD: Agency for Healthcare Research and Quality.

Comments to Research Review

The Agency for Healthcare Research and Quality Technology Assessment (TA) Program encourages the public to participate in the development of its research projects. Each research review is posted to the TA Program Web site in draft form for public comment for a 2-week period. Comments can be submitted via the AHRQ Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

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

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

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Quality of Report	Good	No response needed.
Peer Reviewer #2	Quality of Report	Good	No response needed.
Peer Reviewer #3	Quality of Report	Fair	No response needed.
Peer Reviewer #1	General Comments	This is a clinically meaningful investigation owing to the large number of individuals suffering from OA of the knee and the increasing numbers of individuals undergoing surgery. The research of interest concerns studies involving a mean age of 65. The key questions are straightforward.	Thank you. No further response needed.
Peer Reviewer #2	General Comments	The conclusions of this report are consistent with other guidelines in the literature but in the opinion of this reviewer, suffer from the concept that performing a literature review on studies with average age >=65 (but which by definition include patients under 65 as well) but excluding studies with average age <65 (but which by definition include patients over 65 as well) adequately represents the findings of the literature. This is important as the broader review (ref 14) does demonstrate both statistical significance and a MCID around pain and function which may change the policy implications of this review.	Yes, we acknowledged that trying to limit the review to studies involving an older population limited the number of studies we could include; however it was defined by the scope of work and the intended use for the review.
Peer Reviewer #3	General Comments	The report is clinically meaningful. The target population and audience are explicitly defined. The key questions are explicitly stated. I question whether the key questions are appropriate. And the key questions to not exactly match the scope of the report provided. This manuscript is in response to the AHRQ's Office of Technology Assessment and its partner, Centers for Medicare and Medicaid Services	The key questions were provided by the partner that commissioned the review. We had limited ability to modify them. But we did modify the scope a bit to include the outcomes of pain (at least a review of reviews) and safety.

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		(CMS), request for a review of evidence that intra-articular injections of hyaluronic acid (HA) in people with knee OA, improves function and quality of life and that they delay or prevent the need for knee replacement, specifically for those over 65 years of age or older. The authors of this manuscript have made a diligent effort to address these specific requests in a systematic fashion.	
Peer Reviewer #3	General Comments	From a big picture perspective, I would caution the use of knee replacement as an outcome to assess efficacy of any treatment for osteoarthritis. The literature shows that prediction of whether or not people obtain a joint replacement is difficult to predict accounting for many other variables that do not focus on severity of their osteoarthritis. This literature is reviewed by a special interest group within OMERACT who suggest as an alternative to consider 2 alternative outcomes, “time to physician’s decision to recommend surgery” and “time to fulfilling criterial for total joint replacement”. (Maillefert JF, Hawker GA, Gossec L, et al. Concomitant therapy: an outcome variable for musculoskeletal disorders? Part 2: total joint replacement in osteoarthritis trials. J Rheumatol. Dec 2005;32(12):2449-2451.) Having said this, if the specific question is whether or not IA HA can delay joint replacement, an appropriate study design would be to identify a group of people who have already been deemed “appropriate for surgery” and then within this group of people, offer IA HA v. an intra-articular placebo – where all the participants and the providers should all be blinded to the treatment assignment. Comparison of the time to total knee replacement could then be appropriately compared. No study included in this review uses	We have incorporated the reviewer's suggestion into the section on research gaps in the Discussion. In fact, one small pilot study by Blanco and colleagues did employ the design suggested by the reviewer; this study observed a (non-significant) increase in the time to TKR in the HA-treated group

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		this study design. This would be an appropriate recommendation to make based on this review.	
Peer Reviewer #3	General Comments	Minor comments The use of the abbreviation KR is not standard -- TKR is the usual abbreviation, denoting total knee replacement. There are some forms of partial knee replacements, such as unicompartmental replacements. Use of the term KR could also include those surgical procedures.	We have changed the term throughout.
Peer Reviewer #3	General Comments	It is preferable to use the term OA instead of DJD to refer to this disease.	We have changed the term throughout, with the exception of the title, which we are required to leave as is.
Peer Reviewer #3	General Comments	When the authors are referring to a particular study included in their review, they rarely cite the study by first author last name – use of this strategy would allow for easier reading of this very large manuscript (to reduce the need for frequent referral to the reference list).	We have added individual study names where we refer to a specific study. In the main text
Peer Reviewer #3	General Comments	The numbering of the tables and figures is not sequential through the document.	We're unsure what the reviewer means by the numbering being non-sequential. Following AHRQ publication guidelines, we assigned letters to tables in the Executive Summary and numbers to tables (and figures) in the main text. The tables and figures appear in the order listed in the TOC.
Peer Reviewer #3	General Comments	Misuse of the HA abbreviation (page 53, second to last paragraph) – for hyalgan v. for hyaluronic acid	Thank you. We have fixed it.
Anonymous Public Reviewer #1	General	The injections delay the patient's need for a Total knee prosthesis. The plus is if the patient has other co-morbidities, it postpone the surgery and in most cases give the patient pain relief until the patient's other health issues stabalize. Also, if the patient is not a surgery candidate, it can eleviate	We believe no response is needed.

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		or reduce the joint pain. The minus is, it only delays the need for surgery. If the patient is in need of a joint replacement, they are going to need it anyway. In some situations, the arthritis is so severe, the only solution is the joint replacement.	
Anonymous Public Reviewer #2	General	I am a white female 78 y/o. I have had DJD since age age 65 with TKR of my right knee in 2008. My left knee has deteriorated resulting in a pain level of 7-9 after 2-3 hours of standing or walking. This has diminished my balance and endurance affecting all ADLs. In November 2014 I had a Cortisone inj.in my L. knee with no effective results. After this injection I attended PT for 30 days 2x's/wk with some improvement. 12-4-14 I had Synvisc injected [one injection] in my left knee. As of 12-19-14 I see no change in the level of pain. Supposedly effectiveness should be apparent within 4-6 weeks. I am attempting to delay knee replacement as long as possible.	We have shared this comment with CMS but unfortunately, we can't address individuals' situations.
Anonymous Public Reviewer #3	General	As a 68 year old female; What else is available? Synvice-one only last 3 months.	We have shared this comment with CMS but unfortunately, we can't address individuals' situations.
Mandie DeVincentis, MSN, RN, ANP-BC	General	Interesting topic. With increasingly-older (& active elderly) patients, DJD/Arthritic changes are being seen more frequently by the primary care practitioners. It is therefore a relevant topic for the PCP as we must recognize and refer these patients for treatment.	We have shared the comment with CMS and believe no further response is needed.
Anonymous Public Reviewer #4	General	I use supartz regularly for my HA injections, giving 3 injections. It works very well for a high percentage of my OA patients, probably keeping at least 50-100 patients per year from moving on to total knee surgery which I perform as an orthopedic surgeon.	We have shared the comment with CMS and believe no further response is needed.

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		The insurance re-approval time after 6 months is adequate. Pt. improvement lasts 6-15 months.	
Michael S. Rosen, MD	General	I strongly believe that viscoelastic supplementation for DJD of the knee show be continued to be convered. I have numerous patients who have responded, and when the have a recurrence of knee pain, respond again to another series of injections. If these are disconintued, many of may patients will be knee replacements soon, since in many of them, this is the only conservative treatment which works.	We have shared the comment with CMS and believe no further response is needed.
Charles Pritchard MD FACR Drexel, private practice	General	As a rheumatologist taking care of knee degenerative arthritis I find viscosupplements relieve pain in perhaps 30% of the patients who receive this which is approximately the same as using NSAIDs but with no risk of significant organ dysfunction. I would like to continue to use this group of medications in my patients with knee osteoarthritis.	We have shared the comment with CMS and believe no further response is needed.
Aaron Broadwell Rheumatologist		Treatment with hyaluronic acid derivatives is not only safe, but effective for many patients who deal with osteoarthritis of the knee and can be a valuable option to avoid knee replacement.	We have shared the comment with CMS and believe no further response is needed.
Anonymous Public Reviewer #5	General	I have been using viscosupplementation for Osteoarthritis of the knees since 2008. I am a Rheumatologist, in private practice, for last 7years. I do viscosupplementation injections using Ultrasound guidance, in my office. The most important change I have experienced is that, most patients require to take less NSAID's and pain medications after the injections, which I think is remarkable and significant long term. Most patients have increased range of motion due to less pain, which helps with losing weight and decreasing progression of Osteoarthritis. I think indirectly it works like a Disease modifying treatment. I get lot of referrals for just injections	We have shared the comment with CMS and believe no further response is needed.

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		recommended by my patients ,since the treatment is effective and safe, and also the need to take less pain medications. Viscosupplementation is effective in reducing pain, increasing range of motion of the knees and thus in turn helps with losing weight and decreasing load on the knees. It also decreases the use of long term NSAID's and analgesics for pain control.	
Dr. Natalia Veselova, Board Certified Rheumatologist	General	As a Rheumatology Office Manager I get to see the results of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee Pain. These treatments are primarily offered to patients that do not want to undergo surgery or due to other health factors are unable to proceed with surgery. These patients have very few options for pain relief. We can use narcotics, other systemic medications that can affect other systems or with minimal risk and side effects Physicians can inject the specific area that causes the pain with FDA approved medications, that have been proven to relieve the pain associated with DJD. Our patients continue to experience relief of their symptoms. If they didn't they would not want to continue with them every 6 months. The injections allow people to continue with daily activities. In my opinion and that of my patients, they work! Please continue to allow physicians to provide these injections to their patients.	We have shared the comment with CMS and believe no further response is needed. HA has been approved by the FDA for pain relief.
J. E. Huffstutter Arthritis Associates, PLLC	General	In my capacity as the CAC representative for TN, I learned about the viscous supplementation data from my state when we developed our LCD. At the time, TN was number 1 for use of viscous supplements. We were also 50th for total knee replacements. These observations cannot be coincidental. The FDA demands evidence before a treatment will be approved, so that these treatments must be effective. Recently published	HA has been approved by the FDA for pain relief. We have shared the comment with CMS and believe no further response is needed.

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		data from the orthopedic literature suggesting a lack of efficacy may be related to patient selection and observer bias. Maybe if orthopedic doctors cannot demonstrate efficacy, the use of these agents should be restricted to rheumatologists.	
Olga Kromo ARCC, AARA	General	Effectiveness of hyaluronic Acid in the treatment of severe degenerative Joint Disease of the Knee - I personally perform viscosupplement administration almost every single day of my practice as a rheumatologist, in both moderate and severe knee DJD pts - it is my clear experience that about 90-95% of pts experience a significant improvement in their symptoms when utilized in the appropriate setting and when any inflammatory arthritis symptoms have been addressed. That being said, the efficacy of my administration has improved dramatically with the utilization of Ultrasound imaging during the procedure to ensure appropriate placement of the product. Majority of the patients receiving the product experience an improvement in pain, improvement in mobility and are typically able to decrease their reliance on analgesic medications. I feel there is a significant benefit from viscosupplement even in the patient who ultimately undergoes knee joint replacement within 6 mths of viscosupplement as it allows them to be a more active participant in a pre-surgery reconditioning program of their lower extremity in preparation for an active post-op recovery - leads to improved surgical outcomes and rehabilitation.	We have shared the comment with CMS and believe no further response is needed.
Allan H. Morton, D.O., FACR, FACOI Private Practice/Clinical	General	I'm a rheumatologist in private practice for 36 years in suburban Michigan. I'm actively involved in educating medical students, residents, and practicing physicians. The community in which I practice has an older population therefore many	We have cited a recent systematic review that compares the effect of IA HA with that of oral NSAIDs, and we specifically mention the adverse events associated with

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Professor of Internal Medicine College of Osteopathic Medicine		people with osteoarthritis. I have decades of experience caring for people with OA. I would like to review the challenges in treating people with OA. There are 3 goals--decrease pain, maintain or improve function, and retard disease progression. Unfortunately there is no FDA or generally accepted treatment to retard disease progression, but there are treatments for the other 2 goals. But these options are not limitless. I tell patients there are 3 treatment options for OA. 1. surgery, 2. medications, 3. non drug/non surgery. As a rheumatologist I orchestrate an individual treatment program for each patient. There are concerns using NSAIDs and strong analgesics in geriatric patients. Physical therapy can only do so much. Assistive devices have a place such as knee supports and canes and walkers but don't significantly reduce pain. I prescribe topicals with variable benefit. And the use of intra articular steroids have limited short term benefits with potential significant side effects.	NSAIDs, as analyzed in the review. HA has been approved by the FDA for pain relief. We have shared these comments with CMS.
Allan H. Morton, D.O., FACR, FACOI Private Practice/Clinical Professor of Internal Medicine College of Osteopathic Medicine	General	I treated my first 6 patients with intra articular HA injections in 1997 when the products were available, and continue to inject patients as needed. It is one tool in our bag of treatment options. Having injected hundreds of patients over 17 years there is no doubt that they are valuable to many, but obviously not all. I'm convinced that they do delay total joint replacement surgery, and in some patients give enough relief to negate the need for surgery. And keep in mind there are many patients who are not surgical candidates for medical reasons, and many of them can be maintained on HA injections. The Neudstat publication showed significant pain relief even in patients with KL stage 4 OA of the knee.	We have shared the comment with CMS and believe no further response is needed.

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		I have reviewed and even presented some of the studies showing good treatment efficacy, and some not showing a significant difference from placebo. And I've reviewed the AAOS recommendations not supporting the use of HA for OA of the knee. But at the same time they support the continued use of arthroscopy in spite of 2 NEJM articles not demonstrating clinical efficacy. Not to support the continued use of HA patients for symptomatic OA of the knee would be a travesty. It would be another example of throwing seniors under the bus. On behalf of my patients please do not limit this much needed treatment. Thank you for your consideration, Dr. Morton	
Fumihiro Saeki, MSc Seikagaku Corporation	General	Seikagaku Corporation is a research-based manufacturer of pharmaceuticals and medical devices for human well-being with its focus on glycoscience. We have been developing and manufacturing joint function improving agents based on hyaluronic acid (HA) since 1987, with Seikagaku?s ARTZ (currently marketed as SUPARTZ in the US) being the world?s first joint function improving agent with HA as its main ingredient. As a leading manufacturer of HA-based viscosupplementation products in the world, we are committed to providing scientific information on HA and viscosupplementation. Some of the key questions that AHRQ has been trying to address with the systematic review for effectiveness of HA in the treatment of knee osteoarthritis (OA) deal with the potential of HA to postpone or eliminate the need for knee replacement surgery. Before we get to those questions, we would like to remind AHRQ that all intra-articular HA injection products in the U.S. are indicated only for the treatment of pain associated	Thank you. We have added the important point regarding the FDA approval and indication for HA to our introduction.

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		with knee OA in patients who failed to respond adequately to non-pharmacologic therapy and simple analgesics. Reimbursement coverage of intra-articular HA injection products among payers is, and should be, in line with the indication in the official labeling approved by the US FDA, namely for treatment of pain associated with knee OA, and not for non-indicated secondary outcomes such as delay of total knee replacement (TKR). Having said that, we agree that, unlike other conventional non-operative treatments for knee OA pain such as oral or topical analgesics, intra-articular HA injection has the potential to promote positive clinical outcomes such as delay of TKR thanks to its long-lasting treatment effects.	
Fumihiro Saeki, MSc Seikagaku Corporation	General	In our public comments, we would like to call AHRQ?s attention to some of the latest findings into those very questions that were not included in the present draft. In addition, we wish to provide scientific information and clarification needed to arrive at proper understanding and interpretation of the evidence for HA?s effectiveness. Combined with the superb safety profile of HA that sets it apart from common treatment options such as corticosteroids and NSAIDs, intra-articular HA injection needs to be viewed as an indispensable treatment option in the population of knee OA patients 65 years of age and over. In the following sections, please find our specific comments on the present draft.	We did include only peer-reviewed, published efficacy findings in our analysis; however we requested and obtained the latest information from all manufacturers.
Doug White, MD American College of Rheumatology	General	Rheumatologists provide face-to-face care serving patients with serious conditions that can be difficult to diagnose and treat, including arthritis and other debilitating and disabling diseases. Early and appropriate treatment by rheumatologists can improve outcomes and prevent costly procedures. The ACR believes that	Thank you. The reviewer comments have been shared with CMS regarding the use of IA HA for OA of the knee.

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		hyaluronic acid injections are a viable treatment option and patients should have access to this treatment. We have developed a position paper on this topic that we wanted to share with you. The text of the position statement is included below. POSITIONS 1. The American College of Rheumatology recommends the use of intra-1 articular hyaluronic acid injection for the treatment of osteoarthritis of the knee in adults, in accordance with the ACR 2012 OA guidelines. 2. Hyaluronic acid injection is clinically indicated for management of osteoarthritis in patients who are not good candidates or who do not respond to other treatment options. 3. The American College of Rheumatology supports patient access to appropriate therapies including hyaluronic acid injection.	
Doug White, MD American College of Rheumatology	General	BACKGROUND The injection of hyaluronic acid (often termed viscosupplementation or HA injection) was introduced in Europe in the 1980?s as a therapeutic option for patients with knee pain due to osteoarthritis. In 1997, the U.S. Food and Drug Administration approved the use of intra-articular hyaluronic acid products ?for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g. acetaminophen.?	We believe no response is needed.
Doug White, MD American College of Rheumatology	General	When he American College of Rheumatology (ACR) developed its 2012 guidelines for management of knee, hand, and hip OA, it included HA injection in the list of evaluated therapies. In that paper, the ACR ?conditionally recommended? the use of intra-articular HA injection in patients with knee OA who have not	We have shared the comment with CMS and believe no further response is needed.

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		had an adequate response to non-pharmacologic modalities and full-dose acetaminophen (1). HA injection offers several advantages over other treatment options. As a locally administered therapy, these products minimize the risk of systemic side effects and may even delay the need for total knee arthoplasty (2,3). In addition, many patients who are candidates for HA injection are older and have common age-associated co-morbidities including heart disease, chronic kidney disease and/or hypertension which limit the utility of other options such as NSAIDSs. Furthermore, older patients are more susceptible to adverse reactions due to a number of analgesics (4). Even acetaminophen, the mainstay of treatment for pain in older adults, is commonly used in combination with other analgesics and can cause toxicity related to accidental overdose (5). None of these concerns is invoked with HA injection therapy. The ACR strongly advocates for autonomy in clinical decision making about each individual patient?s therapeutic needs, taking into consideration that patient?s values and preferences.	
Doug White, MD American College of Rheumatology	General	**References** (for above General comments) 1. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012; 64(4):465-74. 2. Neustadt DH. Intra-articular injections for osteoarthritis of the knee. Cleveland Clinic Journal of Medicine 2006; 73(10):897-911. 3. Migliore A, Bella A, Bisignani M, Calderaro M, De Amicis D, Logroscino G, et al. Total hip replacement rate in a cohort of patients affected	Thank you for providing these references. We believe we have incorporated those that met our inclusion criteria.

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		by symptomatic hip osteoarthritis following intra-articular sodium hyaluronate (MW 1,500-2,000 kDa) ORTOBRIX study. Clin Rheumatol. 2012 Aug;31(8):1187-96. 4. The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. AGS updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012; DOI: 10.1111/j.1532-5415.2012. 03923.x. 5. Bolesta S, Haber SL. Hepatotoxicity associated with chronic acetaminophen administration in patients without risk factors. Ann Pharmacother. 2002; 36(2):331-3.	
Linda McKee Rheumatic Disease Assocs. Ltd	General	It is most important to continue to offer Hyaluronic Acid Injections in the treatment of Severe Degenerative joint disease of the knee. Even if patients are over the age of 65.	We have shared the comment with CMS and believe no further response is needed.
Thomas Pontinen, MD Midwest Anesthesia and Pain Specialists	General	I am a fellowship trained interventional pain medicine specialist and perform about 20-40 intra-articular HA knee injections per week. These injections provide tremendous pain relief for my patients and almost universally improve both their pain and their quality of life. Many of the studies listed here agree with this. I feel these injections are perfect for patients who are either: 1. Not surgical candidates for medical reasons 2. Young and wanting to postpone surgery 3. Very old and not interested in knee replacement 4. Only have mild arthritis and are not yet bad enough for surgery, but are looking for pain relief in a less invasive manner. If these injections are not covered it would be a huge disservice to the American population. When I mentioned to some of my patients the other day (who have been getting HA injections for years) that the coverage was being reviewed, every single patient responded with a great deal	We believe no response is needed.

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		of concern, saying thing like "How will I control my pain", "I've been getting these for years and have been staying off medications because of them", or "Now will I need to get a knee replacement? My orthopaedic surgeon told me it would be risky for me because of my health and that he doesn't want to do the replacement on me. These injections work wonders for me, why would they stop reimbursing them?" Please, for the sake of thousands of Americans suffering from knee arthritis, continue to reimburse HA intra-articular knee injections and continue to provide these patient with the relief they have been getting from them for years. Thank you.	
Peter Heeckt, MD, PhD; Samir Bhattacharyya, PhD; Yvonne Bokelman, MBA, FACHE; Anke Fierlinger, MD Bioventus LLC; Mitek Sports Medicine; Zimmer Inc.; Ferring Pharmaceuticals Inc.	General	By way of introduction we represent a consortium of marketers of HA/Viscosupplement products in the United States* and appreciate the opportunity to offer comments on the draft report, ?Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee?. We acknowledge and thank the report authors for conducting an in-depth review. Further, we support the pursuit of evidence-based evaluations of effectiveness and are committed to advancing the research on hyaluronic acid (HA) treatment for pain associated with knee osteoarthritis (OA). Our commitment is backed up by significant funding for additional studies to further the medical knowledge of intra-articular hyaluronan treatment for knee osteoarthritis. We found it concerning that the AHRQ assessment heavily focused on key questions regarding the effect of HA injections on the delay or even elimination of knee replacement surgery in patients over the age of 65, and the effectiveness of halting degeneration. It is	The key questions that were the focus of this report were supplied by the partner agency, who expressed the need for answers to these specific questions. We did in fact add the statement regarding the indication for IA HA to the introduction. We also augmented our suggestions for further research, even including suggestions for a large-scale trial and appropriate outcome questions posed by OMERACT-OARSI.

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		important to note that all HA products in the US are only indicated for the treatment of pain associated with knee OA in patients who failed to respond adequately to non-pharmacologic therapy and simple analgesics. This is typically based on FDA-mandated clinical superiority studies comparing to saline control or non-inferiority trials comparing to an already approved product. Moreover, these studies have typically focused on patients with mild to moderate osteoarthritis who are not yet candidates for arthroplasty.	
Peter Heeckt, MD, PhD; Samir Bhattacharyya, PhD; Yvonne Bokelman, MBA, FACHE; Anke Fierlinger, MD Bioventus LLC; Mitek Sports Medicine; Zimmer Inc.; Ferring Pharmaceuticals Inc.	General	Regarding the attempt to specifically evaluate the effects of HA on patients over 65 we found your analysis to be confounded by the exclusion of studies with individuals whose average age was less than 65 years. Although the purpose criteria was to generate data that would be applicable to the CMS population, it is critical to note that no studies excluded patients younger than 65. A significant portion of the population selected for this analysis however, were under the age of 65 while a large number of randomized placebo-controlled trials and head-to-head studies that were excluded actually had a large number of patients that met the desired age. It is not possible to draw any conclusions from the analysis for the desired 65 and over population when the data is not exclusive to that subset. Further confounding the analysis is the perception of IA-Saline as a sham or placebo intervention. Over the years there have been many published randomized clinical trials of HA/Viscosupplement treatment. In most cases injected saline has been utilized as a control largely because the FDA required this vs. a true sham intervention like a needle prick. It has been noted however that the mere act of inserting a	This comment touches on several issues, notably the age issue and the placebo/comparator issue. We realize the decision to include only studies of average age 65 and over included a number of participants younger than 65. Had there been studies limited to individuals 65 and over, we would have focused on those studies. We also realize we excluded a number of studies that might have strengthened the effect size. That is why we cite the results of several recent comprehensive systematic reviews that did not consider age as an exclusion criterion. Regarding the issue of the choice of comparator, the sham saline injection is the most appropriate choice for placebo precisely because it completely mimics the experience of the IA HA injection and because it exerts a significant placebo effect. Thus any effect of the active intervention

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		needle into the knee and drawing off effusion (containing high concentrations of inflammatory mediators), and then injecting saline, which dilutes the remaining inflammatory agents, has a beneficial therapeutic effect that goes far beyond a ?placebo? effect. This is further evident when comparing IA-HA interventions to NSAIDs. A meta-analysis comparing the relative efficacy of IA-HA with NSAIDs for knee OA demonstrated an effect size favoring neither treatment (1), while in a very recent systematic review, funded by AHRQ and published in Annals of Internal Medicine, found that none of the oral NSAIDs were significantly superior to IA placebo. The authors concluded, ?One striking aspect of our results is that IA therapies were the most effective treatments for knee OA pain. This result is especially salient for hyaluronic acid?? (2).	can truly be attributed to properties of the intervention itself. We cited both of the MAs mentioned by the comments' author, and we feel certain the authors of the network MA was not asserting that IA placebo be regarded as a treatment comparable to that of HA.
Bioventus LLC; Mitek Sports Medicine; Zimmer Inc.; Ferring Pharmaceuticals Inc.	General	It is unrealistic, therefore, to label an intervention as a sham or placebo when it has been demonstrated consistently to have a significant therapeutic effect. In spite of this, US approved HA products have demonstrated statistically significant improvement in pain and function vs. saline. Unfortunately the literature frequently and incorrectly refers to saline injections as ?placebo?. Consistent with FDA approved indications, commercial insurers in the US and Medicare cover HA products for pain associated with knee OA, and not for secondary outcomes such as delay of total knee replacement. As such, delay or prevention of knee replacement surgery has largely not been studied in a prospective fashion. Interestingly, other non-operative treatments for knee OA pain such as analgesics or steroids are not being investigated by AHRQ in regard to their	In the Discussion chapter, we now cite the results of two additional analyses of large databases, one of which finds a sizable effect of HA on delaying or preventing TKR and the other which does not. Still, questions remain as to what the comparison should be (what is considered "not a delay"?) and how is the decision to undergo TKR or not undergo it affected by individual factors, such as pain tolerance, QoL, and personal interests. We provide suggestions in the Discussion chapter for study designs that would more definitively answer the questions posed by the funder, as well as a set of appropriate outcomes

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		potential effect on time to knee replacement surgery. We disagree with the assertion that only large prospective clinical studies can ultimately answer the question as to whether HA injections delay knee replacement surgery. Real world data analyses using large commercial payer or Medicare databases can also provide data of near-equivalent quality at a fraction of the cost and time needed to conduct a prospective long-term study.	recommended by OMERACT-OARSI.
Bioventus LLC; Mitek Sports Medicine; Zimmer Inc.; Ferring Pharmaceuticals Inc.	General	For example, in a recent follow-up publication to an earlier paper by Waddell et al., it was reported that knee replacement was delayed more than 7 years in 75% of HA-treated patients with Grade IV OA after a total of 1,978 courses of HA in 1,187 knees of patients with Grade IV OA (3). This is consistent with evidence (also referenced in your report) from the Truven MarketScan commercial payer database that repeated courses of HA injections delay TKR in a dose-dependent fashion by a median of 2.6 years, in a population of 16,589 patients (4). Claims analysis in the Blue Cross-Blue Shield database for New Jersey showed that mean time to total knee replacement after starting HA was approximately 2.5 years (5). Further, a study utilizing IMS Health?s PharMetrics Plus Health Plan Claims Database demonstrated a delay in time to total knee replacement of up to 3 years (6). Despite the fact that HA products are only indicated and approved for knee OA pain, we fully agree with the interpretation that the long-lasting treatment effects of HA cannot only be explained with pain relief through better shock absorption and lubrication within the joint. Synovial fluid in the joint space is a lubricant and shock absorber (7),	We identified the Waddell follow-up paper in our update search and now cite it, along with the database analyses you mention. The potential mechanism or mechanisms by which IA HA exerts its effect(s) were beyond the scope of this review.

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		and early research suggested that injected HA restores the rheological properties of synovial fluid (8). However, there is also evidence that HA suppresses the production and activity of pro-inflammatory molecules and alters immune cell function (8-10). Histological evidence demonstrates that HA can prevent cartilage degradation and may even promote cartilage regeneration (10). Consequently improved shock absorption and lubrication may not fully explain the durable improvement in pain associated with HA injection.	
Peter Heeckt, MD, PhD; Samir Bhattacharyya, PhD; Yvonne Bokelman, MBA, FACHE; Anke Fierlinger, MD Bioventus LLC; Mitek Sports Medicine; Zimmer Inc.; Ferring Pharmaceuticals Inc.	General	Additionally, improvement can be dependent upon biologic effects on the cartilage and joint space, and perhaps even on pain perception (11). Studies have also demonstrated that injected HA may stimulate endogenous HA production and normalize the rheology of synovial fluid in the OA knee (12). The physiological effects of injected HA are thus associated with a multifactorial mechanism for OA-related symptom improvement. As an industry we have already supported several claims database studies to examine the time to total knee replacement, which have been presented in poster format, and are now awaiting peer reviewed publication. Further, we are exploring study designs to identify likely responders to HA treatment so that good candidates for treatment are recognized prior to the treatment decision. In summary, the HA class of products has been approved by the FDA as effective and has been proven successful in millions of patients. This assessment, as well as some others published previously, illustrate misconceptions about the HA class indications. We support the pursuit of	We identified the Waddell follow-up paper in our update search and now cite it, along with the database analyses you mention. The potential mechanism or mechanisms by which IA HA exerts its effect(s) were beyond the scope of this review. We also note that HA has been approved by the FDA for pain relief.

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		evidence-based evaluations to demonstrate effectiveness, but only if the evaluations are consistent with the indication. We caution assessments outside of HA?s indicated use as it may lead to limiting patients? access to care. Again thank you for the opportunity to comment.	
Peter Heeckt, MD, PhD; Samir Bhattacharyya, PhD; Yvonne Bokelman, MBA, FACHE; Anke Fierlinger, MD Bioventus LLC; Mitek Sports Medicine; Zimmer Inc.; Ferring Pharmaceuticals Inc.	General	**References:** (for above General comments) 1. Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE . Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum. 2014 Apr;43(5):593-9. 2. Bannuru RR, et. al. Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis. Ann Intern Med. 2015 Jan 6;162(1):46?55 3. Waddell DD, Joseph B. Delayed Total Knee Replacement with Hylan G-F 20. J Knee Surg 2014(Oct 28. [Epub ahead of print]). 4. Abbott T, Altman RD, Dimeff R, et al. Do hyaluronic acid injections delay total knee replacement surgery? American College of Rheumatology, San Diego, CA, Program Book (October):2013 (Suppl):308 5. Khan T, Nanchanatt G, Farber K, et al. Analysis of the Effectiveness of Hyaluronic Acid in Prevention of Total Knee Replacement in Osteoarthritis Patients. Poster presented April, 2014 at AMCP Nexus 6. Dasa V, DeKoven M, Lim S et al. Effectiveness of Repeated Courses of Hyaluronic Acid Injections on the Time to Total Knee Replacement Surgery: Evidence from a Large U.S. Health Plan Claims Database. Poster presented October, 2014 at AMCP Nexus, Boston, MA	We appreciate the commenter's providing us with references.

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		7. Fam H, Bryant JT, Kontopoulou M. Rheological properties of synovial fluids. Biorheology 2007;44(2):59-74. 8. Ghosh P, Guidolin D. Potential mechanism of action of intra-articular hyaluronan therapy in osteoarthritis: are the effects molecular weight dependent? Semin Arthritis Rheum 2002;32(1):10-37. 9. Cianflocco AJ. Viscosupplementation in patients with osteoarthritis of the knee. Postgrad Med 2013;125(1):97-105. 10. Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. Arthritis research & therapy 2003;5(2):54-67. 11. Das A, Neher JO, Safranek S. Clinical inquiries. Do hyaluronic acid injections relieve OA knee pain? J Fam Pract 2009;58(5):281c-e. 12. Bagga H, D. B, Sambrook P, et al. Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. J Rheumatol 2006;33(5):946-50.	
Howard Blumstein New York State Rheumatology Society	General	The mission of the New York State Rheumatology Society is to advocate for our patients with rheumatologic illness and to promote excellence in rheumatology care. We personally treat patients with degenerative joint disease (DJD) of the knee, see their suffering, devise appropriate care regimens, and follow their progress for many years. With limited resources in the armamentarium for the treatment of patients with DJD, we are gravely concerned about the potential loss of access to care with hyaluronic acid (HA), which effectively controls DJD-associated pain for a significant number of our patients and, in some cases, affords the option of postponing or avoiding knee replacement (KR)	We believe no response is needed.

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		surgery. Many patients with DJD of the knee are aged 65 years or older. Comorbidities and polypharmacy frequently encountered with older age may contraindicate the long-term prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to address the daily pain and loss of function experienced by these patients. Many patients also are not eligible or deny KR surgery.	
Howard Blumstein New York State Rheumatology Society	General	Intra-articular hyaluronic acid injections are frequently the only feasible treatment option for patients aged 65 years or older. Hyaluronic acid agents have been FDA-approved for 17 years and they have a proven and excellent safety profile. Denying patients access to this well-tested treatment based on solid evidence would be difficult to accept; doing so based on erroneous or incomplete information would be tragic. We hope that our review comments will clarify some inconsistencies in the methods applied in the Technology Assessment (TA) and point to additional relevant facts and research from the perspective of practicing rheumatologists caring for the nearly 4 million patients with arthritis in New York. (1) **Reference:** (1) Centers for Disease Control and Prevention (CDC). State Statistics for 2011 & 2013. Last updated 14 October 2014. Available at http://www.cdc.gov/arthritis/data_statistics/state-data-list-current.htm#new_york. Accessed 9 January 2015.	Thank you. HA has been approved by the FDA for pain relief. We believe no further response is needed.
John Evangelista, MD, MPH Fidia Pharma USA	General	We have summarized our comments on the draft Technology Assessment in this ?General? section. These comments focus primarily on the draft Assessment?s review of HA for pain relief. The draft Technology Assessment?s discussion of	In describing the scope of the review at the beginning of the report, we clarified that pain was not part of the CMS request but that because it was the only

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		the effect of hyaluronic acid (HA) on pain presents several concerns that limit the utility of the review. The authors state that pain was outside the scope of this review, but nevertheless included conclusions related to pain. These results were based on a literature review that was not conducted in the same manner as the literature review on outcomes within the scope of the review. Accordingly, we are concerned that the review and analysis of literature on HA?s effect on pain was not conducted in the same systematic, rigorous manner as for other outcomes, and that, therefore, the conclusions do not fairly reflect the long-recognized value of this therapeutic option. The Assessment?s conclusions regarding pain in this report, therefore, could unfairly limit the acceptance of this therapeutic option to patients with knee osteoarthritis who cannot obtain relief with oral NSAIDs and who are not eligible for, or do not desire to undergo, knee replacement. Provided below is a summary of our more significant comments:	indication for which IA HA was approved by FDA and because nearly all studies of the efficacy of IA HA for knee OA include pain as the primary outcome, we would summarize a recent comprehensive meta-analysis on this outcome. We have now augmented that part of the report with the more recent 2015 network meta-analysis by Bannuru and colleagues, which we identified only after submitting the draft report for peer review (at which time we are required to conduct an update review; we do not continuously do update searches throughout the review process). We also made the decision to cite the other major systematic reviews of IA HA and pain in our Discussion of how the results of our review fit into the existing evidence base. Those reviews included the Miller and Block review, additional reviews by Bannuru and colleagues and the Cochrane review. We also cited these reviews to support several points we noted regarding the state of the science. And we modified our conclusion and strength of evidence determination about pain. Under the circumstances (in which pain was not part of the original scope), we believe we have fulfilled our

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			obligation.
Fidia Pharma USA	General	? In order to provide an appropriate context for the Technology Assessment, it should explain at the outset that HA is approved by the U.S. Food and Drug Administration (FDA) for treatment of pain in knee osteoarthritis patients in the U.S. and not for its role in delaying knee replacement surgery. ? For its review of the effects of HA on pain, the draft Assessment relies on a meta-analysis by Rutjes et al. Approximately half of the trials included in the pooled analysis enrolled populations of average age less than 65. In determining the effect of HA in delaying knee replacement, only studies with an average age of 65 or over were included. The rationale given for including the studies with the younger population when assessing the effects of HA on pain is that there is ?no evidence that would suggest age would affect the ability to experience pain relief.? This statement was not supported and, thus, we encourage the authors to reconsider relying only on the Rutjes meta-analysis, to the extent the Technology Assessment is intended to provide guidance on treatment of patients who are 65 and over. ? If the final Assessment will include the effect of HA on pain, it should not limit the review to only one of the six systematic reviews that summarize clinical trials on the effects of HA on pain. Other analyses assess different patient populations, treatments, and outcomes that are important to understanding the treatment effect. In particular, the Assessment should include the Miller and Block review, which published in September 2013, because it evaluated only U.S.-approved HA products.	In describing the scope of the review at the beginning of the report, we clarified that pain was not part of the CMS request but that because it was the only indication for which IA HA was approved by FDA and because nearly all studies of the efficacy of IA HA for knee OA include pain as the primary outcome, we would summarize a recent comprehensive meta-analysis on this outcome. We have now augmented that part of the report with the more recent 2015 network meta-analysis by Bannuru and colleagues, which we identified only after submitting the draft report for peer review (at which time we are required to conduct an update review; we do not continuously do update searches throughout the review process). We also made the decision to cite the other major systematic reviews of IA HA and pain in our Discussion of how the results of our review fit into the existing evidence base. Those reviews included the Miller and Block review, additional reviews by Bannuru and colleagues and the Cochrane review. We also cited these reviews to support several points we noted regarding the state of the science. And we

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			modified our conclusion and strength of evidence determination about pain. Under the circumstances (in which pain was not part of the original scope), we believe we have fulfilled our obligation.
Fidia Pharma USA	General	? If the final Assessment will include the effect of HA on pain, it should include studies that compare the efficacy of HA with oral non-steroidal anti-inflammatory drugs in the management of knee osteoarthritis. Specifically, the final document should include a meta-analysis by Bannuru et al. that published in 2014, entitled ?Relative efficacy of hyaluronic acid in comparison with NSAIDS for knee osteoarthritis: a systematic review and meta-analysis?, and a more recent meta-analysis by Bannuru et al. that published in early 2015, entitled ?Comparative effectiveness of pharmacologic interventions for knee osteoarthritis.? ? The final Assessment should justify the use of ?minimum clinically important difference? or ?MCID? to evaluate HA?s effect on pain relief, when the FDA has accepted that a statistically significant difference between HA and a control demonstrates efficacy for this endpoint. Additionally, the final Assessment should explain the methodology for determining the MCID and explain why it is an appropriate benchmark for assessing the effect of HA on pain in knee osteoarthritis patients. ? The final Assessment should include a large retrospective analysis by V. Dasa et al. (2014) on the effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement, given that the results became	In describing the scope of the review at the beginning of the report, we clarified that pain was not part of the CMS request but that because it was the only indication for which IA HA was approved by FDA and because nearly all studies of the efficacy of IA HA for knee OA include pain as the primary outcome, we would summarize a recent comprehensive meta-analysis on this outcome. We have now augmented that part of the report with the more recent 2015 network meta-analysis by Bannuru and colleagues, which we identified only after submitting the draft report for peer review (at which time we are required to conduct an update review; we do not continuously do update searches throughout the review process). We also made the decision to cite the other major systematic reviews of IA HA and pain in our Discussion of how the results of our review fit into the existing evidence base. Those reviews included the Miller and Block

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		available before the draft Assessment issued.	review, additional reviews by Bannuru and colleagues and the Cochrane review. We also cited these reviews to support several points we noted regarding the state of the science. And we modified our conclusion and strength of evidence determination about pain. Under the circumstances (in which pain was not part of the original scope), we believe we have fulfilled our obligation.. Regarding the pain assessment. Regarding the use of an MCID, we have now cited the MCIDs used and recommended by 3 different groups. Unlike statistical significance, the use of an MCID or MCII as a benchmark provides clinicians with the information they need to make decisions about the potential benefit of a product. The use of an MCID/MCII is not in question: what is in question is the threshold at which it should be set. We agree that the evidence on this point is limited. We used a level that had been used by others conducting a similar analysis. In revising the draft, we cited two additional thresholds, one endorsed by OMERACT-OARSI. We also now address these points in the Discussion chapter. Finally we have added summaries of the retrospective analysis by Dasa as

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			well as the analysis by Khan to our discussion of the analysis by Abbott.
Fidia Pharma USA	General	? The final Assessment should include a discussion regarding other factors (which generally cannot be controlled) that affect a patient?s decision to undergo knee replacement. These include the potential risks of surgery, the anticipated duration of the implant, costs, patient?s ability to take time off from work, and quality of life issues. ? The Technology Assessment should explain the differences in the assessment tools used to assess outcome measures (e.g., the WOMAC and Lequesne Index, and the inherent biases of each tool (e.g., relies heavily on patient feedback, or relies more on physician judgment). **References:** 1. Rutjes, A.W. et al., 2012. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann. Intern Med. 157(3):180-91. 2. Miller, L.E. and Block, J.E., 2013. U.S.-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. Clin. Med. Insights Arthritis Musculoskelet. Disord. 6:57-63 3.Bannaru, R.R., 2014. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: a systematic review and meta-analysis. Semin. Arthritis. Rheum. 43:593-99. 4. Bannuru, R.R., 2015. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis ? a systematic review and network meta-analysis. Ann. Intern. Med. 162:46-	We consider the point regarding the other factors that affect the decision to undergo TKR in our Discussion. We briefly mention the relative weaknesses of the various assessment tools that have been used to date in published studies and make suggestions for alternative outcome measures, but any discussion beyond that is beyond the scope of this report. We appreciate the commenter's providing the references for additional systematic reviews.

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		54.	
John Jenkins MD Arthritis and Osteoporosis Center, Billings MT	General	I am a physician that treats patients with OA of the knees. Hyaluronans are an effective treatment for many patients with OA of the knee. Removal of them from the CMS formulary would leave many patients untreated and require them to have a knee replacement, or leave them in much pain. Data for this, while limited in published form, is my extensive clinical experience. Without the availability of hyaluronans, then patients would either suffer, or need surgery.	We have shared the comment with CMS and believe no further response is needed.
Blair Barnhart-Hinkle on behalf of Joseph Iannotti, MD Cleveland Clinic	General	Cleveland Clinic (CC) is a not-for-profit, integrated healthcare system dedicated to patient care, teaching and research. Our health system is comprised of a main campus, nine community hospitals and 19 family health centers with over 2,700 salaried physicians and scientists. Last year, our system had more than four million patient visits, over 165,000 hospital admissions. The following are the comments of Cleveland Clinic. We have reviewed the metaanalysis study and believe the question raised here (delaying joint replacement) is a critical one as many prior studies have focused their area of inquiry on pain, function and quality of life. Most often, the goals of treatment for osteoarthritis of the knee include relief of pain and inflammation, slowing of progression, and improvement in or maintenance of mobility and function (ADLs and health-related quality of life [HRQoL]). In our practice at Cleveland Clinic, we have found that patients with similar radiographic findings may have widely varying levels of pain. Thus, we recognize that our understanding of chronic OA paint is incomplete. We know that the way each individual processes pain is not fully understood	We have shared the comment with CMS and believe no further response is needed.

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		thus contributing to the heterogeneity.	
Blair Barnhart-Hinkle on behalf of Joseph Iannotti, MD Cleveland Clinic	General	Hyaluronic acid has been studied by many for years, however, it remains a controversial topic as rheumatologists and surgeons may have differing viewpoints. In the 2012 update to their 2000 guidelines for the treatment of osteoarthritis of the knee, hip, and hand, the American College of Rheumatology conditionally recommended hyaluronic acid injections for patients who had an inadequate response to initial therapy. The 2013 American Academy of Orthopedic Surgeons guidelines for the treatment of osteoarthritis of the knee recommend against the use of hyaluronic acid to treat patients with symptomatic conditions. If additional indications for HA use, such as delaying joint replacement surgery can be answered critically, this would allow for even more meaningful use of HA therapy.	We believe no response is needed.
Blair Barnhart-Hinkle on behalf of Joseph Iannotti, MD Cleveland Clinic	General	We agree with the recent editorial by Lisa Mandl and Elena Losina in response to the recent article ?Relative Efficacy of Knee Osteoarthritis Treatments: Are All Placebos Created Equal?? that appeared in the Annals of Internal Medicine where they stated that they believe ?it will become increasingly important to create innovative research models to better understand how to optimize pain control and provide a roadmap for a rational approach to effective treatment.? The study undertaken by AHRQ is precisely the type of review they were referring to in helping to address this issue and provide the relief to patients that they so desperately need.	We now cite the 2015 network meta-analysis about which this editorial was written and we cite the editorial as well.
Blair Barnhart-Hinkle on behalf of Joseph Iannotti, MD Cleveland	General	While in past studies the efficacy estimates have been calculated over a short period of time, typically less than six(6) months, we believe that patients should be followed for longer periods of time as it is likely that the OA pain will last for	We have added a discussion of the issue regarding length of followup and cite a systematic review on response trajectory. We also include the issue in our

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Clinic		longer than six(6) months. To demonstrate Cleveland Clinic?s commitment to this issue, we have undertaken a study that uses a combination therapy of hyaluronic acid and physical therapy during the same treatment period. We expect the results to be released in approximately 12 months and this will help answer an unmet clinical need. Thank you for conducting a thoughtful process that allows us to provide input on such important issues and for your consideration of this information. Please do not hesitate to contact me if you need additional information.	recommendations for further research, both the shortest and the longest follow-up times that should be considered.
Stephanie J. Ott, MD FACP, FACR President, Ohio Association of Rheumatology	General	Please allow us to introduce ourselves and why we are writing to you. Our name is The Ohio Association of Rheumatology (OAR) and we on the Board govern, guide and represent all Ohio rheumatologists, allied health professionals and rheumatology patients. As such, we the OAR Board are reaching out to you advocate for our patients to continue access to care with receiving intra-articular injections of hyaluronic acid. In December 2014, we were informed that the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Medicare and Medicaid Services (CMS) have requested a review of evidence that intra-articular injections of hyaluronic acid in individuals with degenerative joint disease of the knee improve function and quality of life and that they delay or prevent the need for knee replacement, specifically for individuals age 65 and over.	We have shared the comment with CMS and believe no further response is needed.
Edward F. Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi	General	Thank you for the opportunity to review the draft Technology Assessment Report of the Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease of the Knee. While osteoarthritis of the knee is a chronic condition for which there is no cure,	We believe no response is needed here.

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U.S.		Sanofi US recognizes that the goal of treatment for the nearly 10 million Americans who suffer from this condition is to maintain function and mobility and alleviate pain. Therefore, we support the fact that the focus of this Technology Assessment review (?Review?) is on the evidence that intra-articular injections of hyaluronic acid in individuals with DJD of the knee improve function and quality of life. In addition, since this Review was undertaken at the request of the Centers for Medicare and Medicaid, we recognize the appropriateness of examining the evidence for delaying or preventing the need for knee replacement, specifically for individuals age 65 and over. Our comments address two key areas of the Review. First, there are several aspects of the methodology used that we believe require further consideration:	
Edward F. Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.	General	I. The benchmark for the minimum clinically important difference (MCID) standardized effect size for functional outcomes was set at -.37 without a justification for that benchmark and without an assessment of whether the pooled measurements had acceptable variability to justify the application of standardized effect size.	Please see above for our response to our use of the MCID.
Edward F. Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.	General	II. The reliance of the review on the 2012 Rutjes meta-analysis in summarizing the effect of HA treatment on pain relief.	Please see above for our response to our summarizing the Rutjes review.
Edward F. Greissing, Vice President, N.A. Corporate	General	III. Heterogeneity between the HA class in outcomes has been noted in several meta-analyses. Differences between compositions of the HAs may contribute to this heterogeneity;	Regarding differences in efficacy of HAs of different molecular size, the studies that enrolled older adults was too limited to enable us

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Affairs for Sanofi U.S. Sanofi U.S.		therefore, this may merit additional analysis of high-molecular-weight HA separately from the rest of the HA class. Second, there are at least three recently published research studies and analyses that, due to the date of publication, were not included in the Review. However, as they are clearly relevant to the Review?s inquiry, we respectfully request that the Review be revised and updated to include these studies in the final version of the Report.	to attempt to replicate this finding. Regarding the additional references, we believe we have included them in our revised report but if the commenter wishes to provide the citations, we will be glad to check.
Arthritis Foundation	General	On behalf of the more than 50 million adults and children living with arthritis in the United States, the Arthritis Foundation welcomes the opportunity to comment on the draft manuscript "Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee." Over 700,000 total knee replacements are performed annually in the United States, primarily for arthritis, and this number is increasing. Osteoarthritis, the most common form of chronic arthritis, affects 10 to 20% of persons age 60 and over. Osteoarthritis of the knee is twice as common as osteoarthritis of the hip. With the aging of the general population combined with the growing prevalence of the disease, and the enormous physical, emotional, and financial impact arthritis has on patients and their families, osteoarthritis of the knee is becoming an increasingly important condition to diagnose and treat early using all available and new diagnostic and treatment options. In a very recent systematic review and network meta-analysis on the effectiveness of various pharmacologic interventions for knee osteoarthritis, which was based on 137 studies comprising 33,243 participants, investigators	We have shared the comment with CMS and believe no further response is needed.

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		concluded that intra-articular treatments including hyaluronic acid showed clinically significant improvement from baseline pain.	
Arthritis Foundation	General	This study corroborates the recommendation of the American College of Rheumatology (ACR), which represent over 9,400 rheumatologists and health professionals. In their Position Statement, ACR recommends the use of intra-articular hyaluronic acid injection for the treatment of osteoarthritis of the knee in adults, and states that hyaluronic acid injection is clinically indicated for management of osteoarthritis in patients who are not good candidates for surgery or who do not respond to other treatment options. ACR supports patient access to appropriate therapies including hyaluronic acid injection. As an organization, the Arthritis Foundation is committed to ground-breaking research and welcomes new studies related to arthritis and treatment options. We appreciate the efforts by AHRQ to study the effectiveness of hyaluronic acid and summarize the findings in the current draft ?Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee?. The review included only a limited number of studies with varying quality and many of them with small numbers of patients; therefore, drawing any significant conclusion is limited until more robust data with more uniform methodologies and studies are available.	We agree with the commenter's point regarding the small number of studies. We don't think further comment is needed.
Arthritis Foundation	General	Pain is a major driver for knee replacement. The Arthritis Foundation is aware of the differing guidelines and conclusions of other major professional organizations regarding the benefits of intra-articular hyaluronic acid injection for the treatment of osteoarthritis of the knee, and is	We have shared the comment with CMS and believe no further response is needed.

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		concerned about the influence this publication by AHRQ would potentially have on the availability of this treatment. Until new evidence emerges from further studies for pain management options across all ages, the Arthritis Foundation cautiously advises against making decisions and policy changes based on inconclusive findings that may restrict people from accessing various treatment options that may ultimately be beneficial, including intra-articular hyaluronic acid injection for the treatment of osteoarthritis of the knee in adults. As the largest and most trusted nonprofit organization dedicated to addressing the needs and challenges of those living with arthritis, the Arthritis Foundation considers the patients? experience to be of primary importance when it comes to decision-making in treatments. We support the need to provide patient-centered and individualized care that leaves decisions on treatment options and assessments of effectiveness between the doctor and patient.	
Emily Graham The Coalition of State Rheumatology Organizations (CSRO)	General	The Coalition of State Rheumatology Organizations, or CSRO, is a group of state or regional professional rheumatology societies formed in order to advocate for excellence in rheumatologic disease care and to ensure access to the highest quality care for the management of rheumatologic and musculoskeletal diseases. Our coalition serves the practicing rheumatologist, whose focus is access to high-quality care rheumatology care for their patients, including those who use hyaluronic acid (HA) injection therapy in the management of osteoarthritis (OA), a complex and chronic health condition. CSRO leadership reviewed the draft Technology Assessment (TA) and are concerned that the conclusions do not fairly reflect the long-	We agree with the commenter regarding the safety profile, which is why we did an extensive re-analysis of the safety findings of the Rutjes MA.

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		recognized value of HA as a therapeutic option to a significant subset of patients. As a result, the draft TA could unfairly limit the acceptance of this therapeutic option to patients with knee OA who cannot obtain relief with oral NSAIDs or where NSAIDS are contraindicated (e.g., kidney disease, cardiovascular disease, and anticoagulation) and who are not eligible for, or do not desire to undergo, knee replacement (KR) surgery. While anecdotal, CSRO members repeatedly hear from their OA patients that they have enjoyed significant benefits from intra-articular HA injections. In fact, some patient's report that they have deferred (and continue to defer) recommended KR surgery for 5+ years and continue to be active in sports, including tennis. It is important to note that there is no adverse safety profile for HA products and patients do not experience harmful side effects when undergoing HA treatment. This is an important benefit over NSAID therapy for OA, as it is well established that long-term NSAID therapy is associated serious potential adverse events, including cardiovascular and gastrointestinal (GI) symptoms and disease, and nephrotoxicity, or interaction with other medications.	
Emily Graham The Coalition of State Rheumatology Organizations (CSRO)	General	These comments also reflect the sentiments of the following groups: California Rheumatology Alliance Florida Society of Rheumatology Rheumatology Alliance of Louisiana Kentuckiana Rheumatology Alliance Mass, Maine and New Hampshire Rheumatology Association Maryland Society for Rheumatic Diseases Michigan Rheumatism Society MidWest Rheumatology Association	We believe no response is needed.

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		Wisconsin Rheumatology Association Rheumatology Association of Iowa Mississippi Arthritis and Rheumatism Society New York Rheumatology Society Ohio Association of Rheumatology	
Public comment #6	General	I am a 68-year -old female with severe degenerative joint disease, caused by osteoarthritis in my right knee. Due to increased reliance upon my left knee for support, my left knee is well into the degenerative process, and I have a diagnosis of acute bursitus in my right hip, due to displacement of the right knee joint. Dr. [redacted] administered three injections of Hyaluronic Acid to the right and left sides of the joint during March 2014. I experienced some relief from the pain, however walking remained quite difficult. By November 2014, I was seeking additional physical therapy. At this point, I am experiencing a great deal of knee pain and anticipate I will be seeking knee surgery in the near future.	We have shared this comment with CMS but cannot respond further.
Peer Reviewer #1	Introduction	Background and aims are reasonably exposited. The study is driven by pre-specified CMS questions. The ultimate question is whether or not these agents alter disease progression. Other questions of importance not addressed here include: what is the safety and efficacy of repeated dosing?, do these agents reduce the need for long-term opioid agents?, does molecular weight matter?	These are all good questions that we actually would have addressed, had we identified studies that sought to answer them. We have added them to suggestions for future research.
Peer Reviewer #2	Introduction	(See comments above under General Comments)	No response needed.
Peer Reviewer #3	Introduction	Title: The current title of the document, “Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee” is	The title of the report was, in fact, assigned by the sponsor. Similarly, DJD was part of that title. We did not limit study inclusion by the

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		problematic for a number of reasons. Based on my perspective, this is not primarily a review of the "Effectiveness" of HA. To do so, comparative effectiveness trials would have needed to been the focus in this review, which were not. Instead, this is a review of the influence of IAHA on function, quality of life, ADLs, occurrence and delay of knee replacements, mostly in the setting of traditional randomized controlled trials though observational studies were also included, usually using a narrative approach. Also, this review is not only limited to studies of "severe" osteoarthritis. And finally, the term "DJD" while still frequently used colloquially, is not the preferred terminology used to describe osteoarthritis, so it would be preferable that it would not be used in most of the text, and especially not in the title of this document. In short, the title could use some revision.	severity of arthritis. We included both comparative effectiveness trials and placebo-controlled trials. It is true that nearly all included trials used the same severity criteria for inclusion (K-L stage II-III or IV) or did not specify severity criteria and simply enrolled patients with varying severity, although the observational studies that assessed TKR as an outcome of interest often limited enrollment to stage IV patients deemed eligible for TKR.
Peer Reviewer #3	Executive Summary	Background: Please provide a reference for the statement that the prevalence of symptomatic knee osteoarthritis may reach 50% by the age of 75.	We revised the age to 85 and provided the reference.
Peer Reviewer #3	Executive Summary	Condition and Therapeutic Strategies-Diagnosis: I would argue that the diagnosis of knee OA in the clinical setting is not usually based on pain alone. It is based on the clinical presentation: insidious onset of weight-bearing knee pain that is exacerbated by use of the joint, relieved by rest, and that tends to be worst at the end of the day. In epidemiologic studies, the radiographic presence OA is frequently how the diagnosis is made. For the purposes of this document, I don't know how important it is to go into this paragraph, particularly since radiographs and MRIs are not the focus of the key questions, but the statements related to the symptom-structure disconnect are	We have revised the statements as suggested.

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		not that straight-forward. There are studies that identify a strong relationship between radiographs and symptoms.	
Peer Reviewer #3	Executive Summary	Condition and Therapeutic Strategies-Treatments: Please consider including a reference to the HA meta-analysis published in JAMA when citing reviews of prior systematic reviews of HA. (Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. Jama. Dec 17 2003;290(23):3115-3121.) To correctly cite Rutjes et al, they did not report no effect of HA. They reported "a small, clinically irrelevant benefit and an increased risk for serious adverse event."	We have added the reference by Lo to the Introduction and Discussion and have revised our description of the findings of the Rutjes review.(p2/28)
Peer Reviewer #3	Executive Summary	Assessment of Outcomes of Treatment: WOMAC stands for Western Ontario McMaster Universities Arthritis Index.	We have revised the name.
Peer Reviewer #3	Executive Summary	Aims of the Current Report: For reference #24, the URL does not function properly. I could not see the situations that CMS covers IA HA. Please correct the URL.	We have provided the link that is posted online.
Peer Reviewer #3	Executive Summary	Scope and Key Questions: Although I do think that an analytic framework is helpful in understanding how the key questions are relevant to one another, I question the validity of the framework outlined in Figure A. Also, figure A is confusing. Use of prose to provide greater explanation of the framework would be helpful. The question is not whether placebo impacts any of these outcomes, it's just IAHA, correct? Further, it is not clear that occurrence of adverse events will necessarily reduce a participant's quality of life. What happens if someone has increase in pain, but reduction in ADLs? I don't know that there is any literature that supports that impact in quality of life is a primary driver of whether or not someone decides to have	We have modified the AF, so that QoL no longer seems to mediate the effects of pain etc on TKR.

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		arthroplasty. And as mentioned in the my initial comments, there are many more variables that go into the decision of whether someone should proceed to arthroplasty besides knee OA severity.	
Peer Reviewer #3	Executive Summary	Methods-Data Synthesis: It seems that the MCID used in by Rutjes et al (ref 14) was for WOMAC pain. I don't believe this should be extrapolated to WOMAC function. There are separate calculations of MCID for WOMAC function. And I don't think these can be extrapolated to the Lequense Index. Biostatistical input on this point would be helpful.	The Rutjes review did apply the same MCID for pain as they did for function and they included studies with many different outcome assessment scales, as results were reported as mean standardized differences.
Peer Reviewer #3	Executive Summary	Discussion-IAHA and Function: Since Rutjes et al already performed a comprehensive meta-analysis evaluating the effect of HA on function, it is unclear why this effort was repeated in this study.	We were asked as part of the scope of work to conduct a systematic review on the effect of HA on function in studies that included individuals of average age 65 or older.
Peer Reviewer #3	Executive Summary	Discussion-IAHA and Pain: The authors reviewed the meta-analysis by Rutjes et al. They comment that "although we regard sham controls and blinded outcome assessment vital for assessing the effect of HA on function, we believe that limiting the pooled analysis to larger studies is not methodologically justified, given the small proportion of studies that fit the criteria and the fact that study size is not typically a criterion in assessing study quality / risk of bias." In fact Rutjes et al did cite that there was significant heterogeneity when all studies were included. Once they restricted the sample to those studies of large sample sizes, the heterogeneity was then low. In my view, this is reasonable methodologic justification for restricting the analytic pool.	We have revised that statement in light of the new network MA by Bannuru, who found a similar effect for the largest studies.
Peer Reviewer #3	Executive Summary	Discussion-IAHA and Pain: An important message from Rutjes et al's manuscript is that there was strong evidence for publication bias including that	We have now addressed this issue in describing the reviews of Rutjes and of Bannuru as well as in the

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		the funnel plot was asymmetric with a positive Egger test and importantly that 5 of the unpublished studies that they were able to obtain as part of this study all showed a null result.	Discussion.
Peer Reviewer #3	Executive Summary	Discussion-IAHA and Pain: Limitations of the Comparative Effectiveness Review Process I think this is an incorrect title to for this paragraph. Comparative effectiveness studies were not the target for this review.	We follow AHRQ publication guidelines regarding the subheadings; they were not our choice.
Peer Reviewer #3	Executive Summary	Research Gaps: I think it would be difficult to perform a case-control study to address the issue regarding whether IA HA can delay TKR. There is a strong placebo effect to an intra-articular injection that would be difficult to control for in this type of study design. For the appropriate RCT study design, it would be helpful to provide specific design issues that need to be addressed in such a study which I delineated in my initial comments.	We have actually added summaries of two additional studies using administrative data. We have revised our suggestion of conducting a case-control study based on the reviewer's suggestions.
Peer Reviewer #3	Executive Summary	Conclusions: While it is true that the number of reported serious adverse events is low, the report by Rutjes et al identify that there was an increased risk in the IA HA arm compared to the IA placebo arm which is concerning particularly given the fact that this report identifies that very few of the RCTs systematically actively reported adverse events.	We aimed to convey the point that many of the serious AEs that were reported were in the placebo groups or could not have been plausibly related to the active treatment. Although we can't assess whether the lack of systematic assessment and reporting led to significant numbers of serious AEs not being reported, if that were the case, it would affect the placebo group as well as the active treatment group.
Mandie DeVincentis, MSN, RN, ANP-BC	Executive Summary	Good synopsis of the issue at hand.	Thank you. We believe no further response is needed.
Aaron Broadwell	Executive	Only effective non-surgical treatment for many	We have shared the comment with

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Rheumatologist	Summary	patients.	CMS and believe no further response is needed.
J. E. Huffstutter Arthritis Associates, PLLC	Executive Summary	Keep currently available viscous supplements on the market since they have been shown to work. Consider restricting their use to rheumatologists, since they are the providers with the most experience and success with their use.	HA is currently approved by the FDA for pain relief. We have shared the comment with CMS and believe no further response is needed.
Linda McKee Rheumatic Disease Assocs. Ltd	Executive Summary	Patients do benefit from these injections and they provide them pain relief and the ability to be productive and put off surgery for up to 3-5 years. this can mean the difference of the need for an additional TKR in their lifetime.	We have shared the comment with CMS and believe no further response is needed.
Fidia Pharma USA	Executive Summary	Background-Assessment of Outcomes of Treatment (p. ES-2) The Technology Assessment should explain that, although the various assessment tools used to assess outcome measures, including the WOMAC and Lequesne Index, are validated, each has inherent biases. FDA?s draft guidance on clinical development programs for products intended for treatment of osteoarthritis, states that WOMAC relies ?heavily on patient feedback,? whereas the Lequesne Index relies more on physician judgment. According to this same draft guidance, patient global assessments, such as the VAS scale are overall measurements of what the patient deems most important. Thus, it is important to understand these inherent biases in reviewing meta-analysis results that rely primarily on WOMAC versus Lequesne for a particular outcome (e.g., function versus pain).	Please see our comment above regarding discussing the relative weaknesses of the various assessment tools.
Fidia Pharma USA	Executive Summary	Background -- Scope and Key Questions (p. ES-3) The first two key questions provided by the CMS Coverage Analysis Group focus on the effect of HA products on the need for knee replacement surgery. In the U.S., HA products are approved	We believe no response is needed.

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		by the Food and Drug Administration (FDA) for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics. These products are not approved for their role in delaying knee replacement surgery. Because HA products are only approved for treatment of pain in the U.S., these comments will be limited primarily to that outcome measure. We also have included comments on the analysis of the effect of HA on function, and have identified studies on function or delay in knee replacement surgery that were excluded from the AHRQ report.	
Fidia Pharma USA	Executive Summary	Background -- Scope and Key Questions ? Criteria for Inclusion/Exclusion of Studies in the Review (pp. ES-3-4) The scope of the report as it relates to pain as an outcome, is not clear or consistent. This section of the report states that pain ?was outside the original scope? of the assessment. However, the report also states that, in addition to assessing the evidence for a role of HA in delaying or preventing the need for knee replacement, the report also assessed the evidence to date on the efficacy of intra-articular injections of HA with respect to the outcome of pain, function, and other parameters. Also, it appears that a different methodology was followed for the literature review on HA for treatment of pain than for the literature review on the effect of HA in delaying knee replacement surgery. Although several large recent, comprehensive systematic meta-analyses on the outcome of pain were identified, the authors selected and described only one meta-analysis, on the basis that they considered it to be the most recent and comprehensive. Specifically, a meta-	In describing the scope of the review at the beginning of the report, we clarified that pain was not part of the CMS request but that because it was the only indication for which IA HA was approved by FDA and because nearly all studies of the efficacy of IA HA for knee OA include pain as the primary outcome, we would summarize a recent comprehensive meta-analysis on this outcome. We have now augmented that part of the report with the more recent 2015 network meta-analysis by Bannuru and colleagues, which we identified only after submitting the draft report for peer review (at which time we are required to conduct an update review; we do not continuously do update searches throughout the review process).

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		analysis conducted by Rutjes et al., 2012 was included and described, but the authors chose not to describe five other articles summarizing results of meta-analyses, which were published in 2012 and 2013. It is significant that one of the excluded systematic reviews?by Miller and Block?directly contradicts the finding of Rutjes et al. and determined that U.S.-approved HA products are not associated with increased safety risks.	We also made the decision to cite the other major systematic reviews of IA HA and pain in our Discussion of how the results of our review fit into the existing evidence base. Those reviews included the Miller and Block review, additional reviews by Bannuru and colleagues and the Cochrane review. We also cited these reviews to support several points we noted regarding the state of the science. And we modified our conclusion and strength of evidence determination about pain. Under the circumstances (in which pain was not part of the original scope), we believe we have fulfilled our obligation.
Fidia Pharma USA	Executive Summary	Methods -Literature Search Strategy (pp. ES-4-5) In screening literature, the authors excluded those articles that enrolled a population whose mean age was less than 65 years (unless the study outcomes were reported by age group and outcomes for older individuals could be abstracted). This approach appears to have been driven by the task order from CMS, which is concerned about Medicare costs associated with knee replacement. However, a restriction to a mean age of 65 years by definition includes individuals younger than 65 years, and accordingly creates a meaningless metric for analysis. The age ranges in most reported studies include individuals in their 50s, because symptoms of osteoarthritis frequently occur more than a decade earlier than 65 years of age. It is	This comment touches on several issues, notably the age issue and the placebo/comparator issue. We realize the decision to include only studies of average age 65 and over included a number of participants younger than 65. Had there been studies limited to individuals 65 and over, we would have focused on those studies. We also realize we excluded a number of studies that might have strengthened the effect size. That is why we cite the results of several recent comprehensive systematic reviews that did not consider age as an exclusion

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		also likely to be clinically significant for outcome measures on when and for how long, therapeutic interventions are administered. Importantly, this restrictive approach was not taken for the review of studies on HA?s effect on pain. Unlike the draft AHRQ Technology Assessment, the Rutjes meta-analysis was not restricted to studies with patients with an average age of 65 or older. We recommend, therefore, that the final AHRQ Technology Assessment clarify that there were important differences in the methodology employed for the literature review on pain versus other outcome measures, so that this is fully transparent to the reader.	criterion. Regarding the issue of the choice of comparator, the sham saline injection is the most appropriate choice for placebo precisely because it completely mimics the experience of the IA HA injection and because it exerts a significant placebo effect. Thus any effect of the active intervention can truly be attributed to properties of the intervention itself. We cited both of the MAs mentioned by the comments' author, and we feel certain the authors of the network MA was not asserting that IA placebo be regarded as a treatment comparable to that of HA.
Fidia Pharma USA	Executive Summary	Methods -Data Synthesis (pp. ES-5-6) The draft Technology Assessment relies on the criterion of ?minimum clinically important difference,? to assess the effect of HA on pain, rather than the statistically significant difference used as part of the study design. To obtain an estimate of the clinical importance of the effect size?the minimum clinically important difference (MCID)?the authors of the draft Assessment multiplied the pooled effect size by the standard deviation obtained from a large trial with a similar intervention for which functional outcome was assessed using the WOMAC. The draft Technology Assessment provides no information on the ?large trial? from which the standard deviation was obtained, nor does it provide any reason for using an intervention for which functional outcome was assessed using the WOMAC, as a multiplier. Without any such	Regarding the use of an MCID, we have now cited the MCIDs used and recommended by 3 different groups. Unlike statistical significance, the use of an MCID or MCII as a benchmark provides clinicians with the information they need to make decisions about the potential benefit of a product. The use of an MCID/MCII is not in question: what is in question is the threshold at which it should be set. We agree that the evidence on this point is limited. We used a level that had been used by others conducting a similar analysis. In revising the draft, we cited two additional thresholds, one endorsed by OMERACT-OARSI.

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		explanation, the methodology for obtaining an estimate of MCID and any estimates obtained appear to be arbitrary. Some clinicians have criticized the use of MCID and MCII (minimum clinically important improvement) in guidelines and meta-analyses, because they are context specific and may not be applicable across treatments or patient populations. In other words, the MCID values differ for improvement versus deterioration, and are impacted by the baseline symptom severity. For that reason, many clinicians recommend that MCID not be a ?cornerstone of clinical decision-making? in treatment guidelines. Finally, we note that the FDA approved several HA devices based on their effectiveness and safety with a finding of statistical significance, not on whether there is an MCID. The draft Technology Assessment should justify why use of MCID is necessary or appropriate to evaluate HA?s effect on pain relief, when the FDA has accepted a statistically significant difference between HA and a control.	We also now address these points in the Discussion chapter. Finally we have added summaries of the retrospective analysis by Dasa as well as the analysis by Khan to our discussion of the analysis by Abbott.
Fidia Pharma USA	Executive Summary	Results -Delay or avoidance of total knee replacement surgery (p. ES-10) It is important to note that the draft AHRQ Technology Assessment does not include a large retrospective analysis, the results of which became available before the draft Assessment issued, on the effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement. This review evaluated patients who were continuously enrolled in a large U.S. health plan from 12-months pre-index to 36 months post-index date. The authors found that successive courses of Supartz or Hyalgan led to a greater proportion of patients without total knee	We have now included the analysis in question, which we only identified in the update literature search conducted after submitting the draft report. Please see above for further response to these comments.

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		replacement surgery 3 years after initiation of treatment. This study should properly be considered part of the evidence for HA?s role in delaying or avoiding knee replacement surgery. Additionally, the final Assessment should include a discussion regarding other factors (which generally cannot be controlled) that affect a patient?s decision to undergo knee replacement. An individual patient?s decision-making can be affected by a number of factors unrelated to the efficacy of a particular therapy, including the potential risks of surgery, the anticipated duration of the implant, costs, the patient?s ability to take time off from work, and quality of life issues.	
Fidia Pharma USA	Executive Summary	Results -Intra-articular injection of hyaluronic acid and measures of function (p. ES-10) The draft Assessment states that, in a meta-analysis of 10 studies that compared the effect of an HA to that of a sham placebo control, there was a statistically significant improvement in WOMAC-assessed function following HA treatment compared to placebo. The draft Assessment further states, however, that this effect did not achieve the ?minimum clinically important difference? of -0.37 at follow-up. MCID is an analytical technique that has been used to evaluate cohorts of knee and hip osteoarthritis patients undergoing different interventions. Some clinicians have criticized the use of MCID and MCII (minimum clinically important improvement) in guidelines and meta-analyses, because they are context specific and may not be applicable across treatments or patient populations. In other words, the MCID values differ for improvement versus deterioration, and are impacted by the baseline symptom severity. For that reason, these clinicians	Regarding the use of an MCID, we have now cited the MCIDs used and recommended by 3 different groups. Unlike statistical significance, the use of an MCID or MCII as a benchmark provides clinicians with the information they need to make decisions about the potential benefit of a product. The use of an MCID/MCII is not in question: what is in question is the threshold at which it should be set. We agree that the evidence on this point is limited. We used a level that had been used by others conducting a similar analysis. In revising the draft, we cited two additional thresholds, one endorsed by OMERACT-OARSI. We also now address these points in the Discussion chapter. Finally we have added summaries of the retrospective analysis by Dasa as

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		recommend that MCID not be a ?cornerstone of clinical decision-making? in treatment guidelines, to avoid losing therapeutic options that may benefit a subset of patients with few options available. Significantly, elsewhere in the draft Assessment (p. ES-12), the authors note that approximately 11 percent of patients included in the above-described analysis of ten placebo-controlled studies would have exceeded the MCID in improvement. When the MCID is used across the patient population, however, this effect on a significant subset of patients is not seen. We therefore recommend that use of a specific MCID in a national retrospective review of clinical studies that could impact the availability of treatment options, be justified and explained in the Technology Assessment.	well as the analysis by Khan to our discussion of the analysis by Abbott.
Fidia Pharma USA	Executive Summary	Intra-articular injection of hyaluronic acid and pain ? Key Points (p. ES-11) In its discussion on HA and pain, the AHRQ report states that it chose to describe only one of six systematic reviews that summarize clinical trials on the effects of HA on pain ? the Rutjes meta-analysis. The Rutjes meta-analysis is a comprehensive systematic review of randomized trials published in 2012 that compares the effects of HA with those of any control. However, we believe that, by excluding meta-analyses conducted subsequent to the Rutjes analysis, the AHRQ findings on intra-articular HA and pain are incomplete. One of the systematic reviews excluded by AHRQ?s report is a review by Miller and Block, which published in September 2013. Differences between the Miller and Block review and the Rutjes review relied on in the AHRQ Technology	We now include a summary of the Miller and Block review in the Discussion. We would not have included this review in our Results because of the comparatively poor reporting quality, among other factors.

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		Assessment include that: (1) the Miller and Block review was limited to studies of U.S.-approved HA products, whereas Rutjes et al., included nine (9) additional unapproved products; and (2) the Miller and Block review only included randomized, saline-controlled trials. Given that the AHRQ Technology Assessment is intended to inform the treatment of patients with osteoarthritis of the knee in the U.S., we believe that a meta-analysis that evaluates only U.S.-approved HA products should be included and described. We therefore recommend that the Miller and Block review be described in the AHRQ Technology Assessment. The Miller and Block review evaluated use of FDA-approved HA products in 29 randomized, saline-controlled trials with 4,866 subjects (IAHA: 2,673, saline: 2,193). For patients given HA injections, there was a standardized mean difference in pre-to-post treatment pain of 1.37 for 4 to 13 weeks and 1.14 for 14 to 26 weeks, both of which were statistically significant ($p < 0.001$). The standardized mean difference in pain outcome for HA patients versus saline patients was .43 at 4 to 13 weeks and .36 at 14 to 26 weeks ($p < 0.001$). Assuming a standardized effect size of .37, the U.S.-approved viscosupplements, by comparison, had a very large and clinically meaningful improvement in knee pain.	
Fidia Pharma USA	Executive Summary	Additionally, a few articles discussing the role of hyaluronic acid in the treatment of pain associated with osteoarthritis have published since the AHRQ draft was completed. In 2014, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) published an algorithm recommendation for the management of knee osteoarthritis. The authors	We now include a brief summary of the meta-analysis comparing IA HA to the use of oral NSAIDs, partly to make the point regarding the comparative safety profile. We also include a summary of the meta-analysis comparing IA HA with corticosteroids to discuss the

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		state that ?hyaluronic acid induces longer-lasting pain control compared with intra-articular corticosteroids? (citing Bannuru, R.R. et al., 2009). Specifically, this review article states that evidence suggests that corticosteroids are more effective than hyaluronic acid in the short term (up to 4 weeks), whereas hyaluronic acid is more effective in the long term (4-26 weeks). Moreover, the authors of the ESCEO algorithm recommendation for the management of knee osteoarthritis state that ?recent findings suggest that there are no significant differences in symptom efficacy compared with oral NSAIDs (citing Bannuru, R.R. et al., 2014). This latter publication by Bannuru, R.R. et al. also is not included in the AHRQ Technology Assessment. Bannuru, R.R. et al., 2014 reports on a meta-analysis conducted of articles comparing the efficacy of intra-articular hyaluronic acid with oral non-steroidal anti-inflammatory drugs in the management of knee osteoarthritis. From a universe of over 677 studies, the meta-analysis was based on five randomized, active-controlled clinical trials. The authors noted that ?[i]t has been well established that oral NSAIDs have a positive, though modest effect on pain in patients with knee osteoarthritis.? The study found that there was no statistically significant difference in efficacy for symptomatic knee osteoarthritis between intra-articular hyaluronic acid injections and continuous oral NSAIDs at 4 weeks, 12 weeks, and end of the trial. Both treatments displayed moderate improvement from baseline.	apparent trajectory of the effect of HA. Unfortunately none of the studies that report on functional outcomes reported the data that would have enable us to estimate the trajectory of the effect of IA HA on function.
Fidia Pharma USA	Executive Summary	Bannuru et al. also published another very important meta-analysis comparing the effectiveness of pharmacologic interventions	We have now included the analysis in question, which we only identified in the update

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		(including HA) on knee osteoarthritis published in early 2015, that was not included in the draft Technology Assessment. This review analyzed randomized trials of adults with knee osteoarthritis comparing one or more of the following: acetaminophen, diclofenac, ibuprofen, naproxen, celecoxib, intra-articular corticosteroids, intra-articular HA, oral placebo, and intra-articular placebo. Results for pain outcomes showed that all treatments except acetaminophen met the pre-specified criteria for clinically significant improvement, that oral NSAIDs (except for celecoxib) and HA were statistically significantly superior to acetaminophen, and that intra-articular treatments were more effective than oral treatments. We recommend that this meta-analysis be included in the final Assessment. Finally, in considering the effect of HA on pain, it is important to understand that most of the studies in both the Rutjes and the Miller and Block meta-analyses excluded subjects with end-stage knee osteoarthritis, and, therefore, the effect of HA on pain in these patients cannot be determined. For many elderly patients with knee osteoarthritis who are not eligible for surgery and for whom NSAIDs are contraindicated, HA remains an important therapeutic option.	literature search conducted after submitting the draft report. Please see above for further response to these comments.
Fidia Pharma USA	Executive Summary	Discussion -Key Findings and Strength of Evidence ? Intra-articular HA and Pain (p. ES-13) The Technology Assessment relies on the criterion of MCID, and states that, although the Rutjes review reported that HA injections significantly reduced pain (statistically and clinically) at three months, this effect was no longer clinically significant when only double-blind placebo-controlled trials enrolling at least 100 subjects per treatment group were analyzed.	Regarding the use of an MCID, we have now cited the MCIDs used and recommended by 3 different groups. Unlike statistical significance, the use of an MCID or MCII as a benchmark provides clinicians with the information they need to make decisions about the potential benefit of a product. The use of an MCID/MCII is not in

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		Based on the use of MCID, the Technology Assessment concludes that ?the strength of evidence is low that HA reduces pain, on average, by an amount that achieves or just approaches the minimum clinically important difference.? To obtain an estimate of MCID, the authors of the draft Assessment multiplied the pooled effect size by the standard deviation obtained from a large trial with a similar intervention for which functional outcome was assessed using the WOMAC. The draft Technology Assessment provides no information on the ?large trial? from which the standard deviation was obtained, nor does it provide any reason for using an intervention for which functional outcome was assessed using the WOMAC, as a multiplier. Without any such explanation, the methodology for obtaining an estimate of MCID and any estimates obtained appear to be arbitrary.	question: what is in question is the threshold at which it should be set. We agree that the evidence on this point is limited. We used a level that had been used by others conducting a similar analysis. In revising the draft, we cited two additional thresholds, one endorsed by OMERACT-OARSI. We also now address these points in the Discussion chapter. Finally we have added summaries of the retrospective analysis by Dasa as well as the analysis by Khan to our discussion of the analysis by Abbott.
Fidia Pharma USA	Executive Summary	Additionally, MCID is an analytical technique that has been used to evaluate cohorts of knee and hip osteoarthritis patients undergoing different interventions. Some clinicians have criticized the use of MCID and MCII (minimum clinically important improvement) in guidelines and meta-analyses, because they are context specific and may not be applicable across treatments or patient populations. In other words, the MCID values differ for improvement versus deterioration, and are impacted by the baseline symptom severity. For that reason, these clinicians recommend that MCID not be a ?cornerstone of clinical decision-making? in treatment guidelines, to avoid losing therapeutic options that may benefit a subset of patients with few options available. We therefore recommend that use of the MCID in a national retrospective review of	Regarding the use of an MCID, we have now cited the MCIDs used and recommended by 3 different groups. Unlike statistical significance, the use of an MCID or MCII as a benchmark provides clinicians with the information they need to make decisions about the potential benefit of a product. The use of an MCID/MCII is not in question: what is in question is the threshold at which it should be set. We agree that the evidence on this point is limited. We used a level that had been used by others conducting a similar analysis. In revising the draft, we cited two additional thresholds, one

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		clinical studies that will be relied on by physicians in treating patients with knee osteoarthritis, be justified and explained in the Technology Assessment.	endorsed by OMERACT-OARSI. We also now address these points in the Discussion chapter. Finally we have added summaries of the retrospective analysis by Dasa as well as the analysis by Khan to our discussion of the analysis by Abbott.
Fidia Pharma USA	Executive Summary	Findings in Relation to What Is Already Known (pp. ES-13-14) The draft Technology Assessment acknowledges that, in the Rutjes review, approximately half of the trials included in the pooled analysis of the effects of HA on pain enrolled populations of average age less than 65. The draft Assessment further states that there is ?no evidence that would suggest age would affect the ability to experience pain relief? and that, therefore, the Rutjes study, was more adequately powered to assess the effects of HA on pain than would be an analysis that includes a smaller number of studies limited to individuals of average age 65 and over. Given the lack of any review of studies limited to individuals of average age 65 and over, we believe that this statement is speculative and recommend that it be removed from the report.	As this statement is not part of the Conclusions and was part of our discussion of the findings, we believe the statement stands.
Fidia Pharma USA	Executive Summary	Applicability (p. ES-14) The draft Assessment states that the authors limited studies included in the current review with functional outcomes to those with an average age of 65 or older, in order to ?increase potential applicability.? It is unclear what is meant by this statement, particularly when the subsequent sentence states that no study excluded patients younger than age 65, and a focus on a mean age of 65 by definition includes individuals younger than 65 years.	We have revised the wording of this statement slightly. Because no studies were found that enrolled only patients 65 or over, and no studies assessed outcomes by age (with the exception of the observational study by Waddell), we determined that the closest proxy would be studies in which the mean age of patients was 65 or over.

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Fidia Pharma USA	Executive Summary	Research Gaps (p. ES-15) The draft Assessment states that ?in the absence of a large, high quality RCT, we advocate analyzing data from any of the large administrative databases maintained by commercial payers, to answer the question as to whether the beneficiaries who are treated with intra-articular HA proceed to KR [knee replacement] at a slower rate than do those who do not receive HA.? As noted above, such analysis has been conducted. Prior to issuance of the draft AHRQ Technology assessment, results of a new, large retrospective analysis became available on the effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement. This review evaluated patients who were continuously enrolled in a large U.S. health plan from 12-months pre-index to 36 months post-index date. The authors found that successive courses of Supartz or Hyalgan led to a greater proportion of patients without total knee replacement surgery 3 years after initiation of treatment. We recommend that this analysis be included in the final Technology Assessment.	We have now included a summary of the study in question (albeit in our Discussion section, because the results are not yet published in peer reviewed form) as well as a summary of a similar analysis that was presented at the same meeting.
Fidia Pharma USA	Executive Summary	Conclusions (p. ES-16) In the ?Structured Abstract,? the conclusion at page vi does not match the conclusion at the last page of the Executive Summary (p. ES-16). We recommend that the Executive Summary conclusion, like the abstract conclusion, exclude the statement regarding the impact of HA on pain, because: (1) this was not the primary focus of the Assessment; (2) the use of MCID has not been established as an appropriate tool in this context; and (3) the review of literature on the effect of HA on pain properly should have included the Miller	In describing the scope of the review at the beginning of the report, we clarified that pain was not part of the CMS request but that because it was the only indication for which IA HA was approved by FDA and because nearly all studies of the efficacy of IA HA for knee OA include pain as the primary outcome, we would summarize a recent comprehensive meta-analysis on

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		and Block and possibly other review articles. Additionally, any discussion of the effect of HA on pain should include studies comparing the effect of HA to oral NSAIDs. Further, the Conclusions section states that ?[t]he literature suggests a small role, of unclear importance, for HA in improving function among older individuals . . . .? (emphasis added). The reference to ?of unclear importance? unfairly diminishes the results of the studies summarized as well as the results of the meta-analysis. The meta-analysis found a statistically significant difference in function for patients treated with HA versus placebo. Because of concerns that the MCID utilized in the draft Assessment does not fairly represent the effect size and does not take into account the ?more than statistically significant effect? in certain patient subsets, we recommend that, at a minimum, the words ?of unclear importance? be deleted from the final Technology Assessment. In addition, the conclusion of ?unclear importance? is not likely based on a robust body of evidence, because of the variability inherent in the studies selected for the meta-analysis.	this outcome. We have now augmented that part of the report with the more recent 2015 network meta-analysis by Bannuru and colleagues, which we identified only after submitting the draft report for peer review (at which time we are required to conduct an update review; we do not continuously do update searches throughout the review process). We also made the decision to cite the other major systematic reviews of IA HA and pain in our Discussion of how the results of our review fit into the existing evidence base. Those reviews included the Miller and Block review, additional reviews by Bannuru and colleagues and the Cochrane review. We also cited these reviews to support several points we noted regarding the state of the science. And we modified our conclusion and strength of evidence determination about pain. Under the circumstances (in which pain was not part of the original scope), we believe we have fulfilled our obligation. Regarding the use of an MCID, we have now cited the MCIDs used and recommended by 3 different groups. Unlike statistical significance, the use of an MCID or MCII as a benchmark provides clinicians with the

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			information they need to make decisions about the potential benefit of a product. The use of an MCID/MCII is not in question: what is in question is the threshold at which it should be set. We agree that the evidence on this point is limited. We used a level that had been used by others conducting a similar analysis. In revising the draft, we cited two additional thresholds, one endorsed by OMERACT-OARSI. We also now address these points in the Discussion chapter. Finally we have added summaries of the retrospective analysis by Dasa as well as the analysis by Khan to our discussion of the analysis by Abbott. We actually strengthened the conclusion regarding pain in the conclusion within the executive summary and the report, based on the new 2015 network MA, however we have omitted it from the abstract because we did not conduct the analysis ourselves. Regarding the conclusion about function, we have modified it to "unclear clinical importance," based on the fact that our effect size exceeds two of the MCIDs used in similar studies but does not exceed the one used by Rutjes.
Fidia Pharma USA	Executive Summary	**References for above Exec Summary comments:**	Thank you for providing these references. We believe we have

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		1. FDA, Clinical Development Programs for Drug, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (OA), at 4 (Draft Guidance, July 1999). 2. Rutjes, A.W. et al., 2012. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann. Intern Med. 157(3):180-91. 3. Miller, L.E. and Block, J.E., 2013. U.S.-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. Clin. Med. Insights Arthritis Musculoskelet. Disord. 6:57-63;Bannuru, R.R., 2014. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: a systematic review and meta-analysis. Semin. Arthritis. Rheum. 43:593-99; Colen, S., et al., 2012, Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. BioDrugs 26(4):257-68; Printz, J.., et al., 2013. Conflict of interest in the assessment of hyaluronic acid injections for osteoarthritis of the knee: an updated systematic review. J. Arthroplasty 28(8 Suppl.) 30-33; Trigkilidas, D. and Anand, A., 2013. The effectiveness of hyaluronic acid intra-articular injections in managing osteoarthritic knee pain. Ann. R. Coll. Surg. Engl. 95(8):545-51. 4. Miller, L.E. and Block, J.E., 2013. U.S.-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. Clin. Med. Insights Arthritis Musculoskelet. Disord. 6:57-63.	incorporated those that met our inclusion criteria.

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		5. Bannuru, R.R. et al., 2014. Did the American Academy of Orthopaedic Surgeons Osteoarthritis Guidelines miss the mark? Arthroscopy: The Journal of Arthroscopic and Related Surgery 30:86-89. 6. ?Minimum clinically important difference? also is not a term that is used in any Medicare-related statute or regulation as a touchstone for whether a particular treatment is appropriate for Medicare beneficiaries. 7. Dasa, V. et al., 2014. Effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement surgery: evidence from a large U.S. health plan claims database. Journal of Managed Care & Specialty Pharmacy (Meeting Abstracts), Vol. 20, no. 10 (Oct. 2014) (presented at Academy of Managed Care Pharmacy, 2014 Nexus, Boston, Massachusetts, Oct. 7-10, 2014. 8.Bannuru, R.R. et al., 2014. Did the American Academy of Orthopaedic Surgeons Osteoarthritis Guidelines miss the mark? Arthroscopy: The Journal of Arthroscopic and Related Surgery 30:86-89. 9. Rutjes, A.W. et al., 2012. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann. Intern Med. 157(3):180-91. 10. Id. 11 Bruyere, O., et al., 2014. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Semin. Arthritis Rheum. 44(3): 253-63. 12.Bannuru, R.R., et al, 2009. Therapeutic trajectory of hyaluronic acid versus corticosteroids	

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		in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum. 61:1704-11. 13. Bannuru, R.R. et al., 2014. Relative efficacy of hyaluronic acid in comparison with NSAIDS for knee osteoarthritis: a systematic review and meta-analysis. Semin. Arthritis. Rheum. 43:593-99. 14. Bruyere, O., et al., 2014. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Semin. Arthritis Rheum. 44(3): 253-63. 15. Id. at 596. 16. Id. at 596-97. 17. Bannuru, R.R. et al., 2015. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis ? a systematic review and network meta-analysis. Ann. Intern. Med. 162:46-54. 18. Id. at 49. 19. Miller, L.E. and Block, J.E., 2013. U.S.-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. Clin. Med. Insights Arthritis Musculoskelet. Disord. 6:57-63. 20. Bannuru, R.R. et al., 2014. Did the American Academy of Orthopaedic Surgeons Osteoarthritis Guidelines miss the mark? Arthroscopy: The Journal of Arthroscopic and Related Surgery 30:86-89. 21. Dasa, V. et al., 2014. Effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement surgery:	

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		evidence from a large U.S. health plan claims database. Journal of Managed Care & Specialty Pharmacy (Meeting Abstracts), Vol. 20, no. 10 (Oct. 2014) (presented at Academy of Managed Care Pharmacy, 2014 Nexus, Boston, Massachusetts, Oct. 7-10, 2014.	
Peer Reviewer #3	Main body	Treatment strategies (p2) For this statement: "Progressive osteoarthritis of the knee includes loss of the cells responsible for synthesizing hyaluronic acid resulting in lower viscosity endogenous hyaluronate." Please provide a reference.	We have revised the statement and provided a reference
Peer Reviewer #3	Main body	Treatment strategies: Table 1, ordering the table by chronology that the devices were approved in the US would be more meaningful.	We have reordered Table 1.
Peer Reviewer #3	Main body	Treatment strategies: Consider providing a history of how IA HA was approved as a medical device instead of a medication. And what are the differences in the requirements to obtain approval by the FDA for a medical device v. medication?	We have provided the rationale for why approval for HA as a device was sought.
Peer Reviewer #3	Main body	Assessment of Outcomes of Treatment (p5) Please clarify reference #21 – It may be more appropriate to cite Pham et al.2 (Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage. May 2004;12(5):389-399.)	We have substituted the suggested reference.
Mandie DeVincentis, MSN, RN, ANP-BC	Introduction/Background	Good introduction and focus.	Thank you! We believe no further response is needed.
Aaron Broadwell Rheumatologist	Introduction/Background	I am a private practice rheumatologist who performs injections of hyaluronic acid of appropriate patients with knee osteoarthritis. I have seen patients able to never undergo knee replacement, as well as delay need for knee	We have shared the comment with CMS and believe no further response is needed.

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		replacements by years on HA products.	
J. E. Huffstutter Arthritis Associates, PLLC	Introduction/Background	Viscous supplements have been on the market a number of years and come in a variety of preparations. Numerous studies were done for each of the preparations demonstrating efficacy. Osteoarthritis of the knee can be a debilitating problem that is very difficult to treat I have had numerous patients that have received benefit from their use, and many of these patient have postponed knee replacement surgery for years, saving the health care system millions of dollars.	We have shared the comment with CMS and believe no further response is needed.
Howard Blumstein New York State Rheumatology Society	Introduction/Background	1. HA devices have been an effective and trusted treatment for nearly 20 years The description of HA injections as a ?more recent? treatment option for patients with DJD may be misleading. Intra-articular HA injections are a widely used and trusted treatment option available in the US since 1997 and globally since 1987. Each HA product available in the US has satisfied the stringent FDA requirements for efficacy and safety of a Class III medical device. During their 17 years of use in clinical practice, we know of no known death and very few serious adverse events attributable to the use of HA injections. The 2012 American College of Rheumatology (ACR) recommendations for the treatment of osteoarthritis (OA) describe HA injections as an option for patients with inadequate responses to other conservative treatments. (2) 2. HA injections have gained FDA-approval for the treatment of pain In addition to their long-term availability and excellent safety profile, the TA description of HA products should clarify that they have gained FDA-approval for the treatment of pain in patients with DJD; they have not been approved for the	We have clarified the point regarding FDA approval in the introduction.

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		delay or prevention of total KR. The potential additional value of HA products for the delay or prevention of KR adds to their profile as a valuable tool in the armamentarium for the treatment of DJD of the knee. **Reference:** (2) Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64(4):465-474.	
Howard Blumstein New York State Rheumatology Society	Introduction/Background	3. Methodologic differences may have contributed to conflicting research findings Conflicting findings based on systematic literature reviews and meta-analyses have led to the current reevaluation of the utility and safety of HA injections. The TA includes a long paragraph listing potential methodologic factors that may have led to these conflicting results. Clearly, currently available meta-analyses form an imperfect basis for making final reimbursement decisions. 4. Clinical practice underscores the value of HA injections Most patients receiving HA injections are not included in the published literature; however, they are included in the patient pool we see in our practices, where we find that intra-articular HA injections help a significant number of our patients with DJD to better manage their daily lives and, in some cases, postpone or avoid KR surgery.	We now address potential reasons for disagreement among the meta-analyses and studies in the Discussion.
Fidia Pharma USA	Introduction/Background	Treatment Strategies (p. 2) The draft Technology Assessment provides some background information on commercially available hyaluronic acid products. The report fails to	We believe a lengthy discussion of the standards for FDA approval of medical devices is beyond the scope of the review and does not

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		describe, however, the standard that such products are required to meet before they may be marketed in the U.S. Specifically, the U.S. FDA must determine that there is ?reasonable assurance? that a hyaluronic acid product intended to treat pain for osteoarthritis of the knee, is safe and effective for such use, before it may be marketed in the U.S. Further, reasonable assurance of safety and effectiveness must be demonstrated by randomized, controlled clinical trials. Several HA products have met this standard and, therefore, inclusion of this information is essential to provide context for the report?s conclusions on the effect of HA on pain. Additionally, the final Technology Assessment should recognize that, under the FDA?s draft guidance on clinical development programs for products intended for the treatment of osteoarthritis, improvement in symptoms (e.g., pain) is a separate claim from delay in structural progression, with different clinical substantiation requirements. For example, use of a particular assessment tool (e.g., WOMAC) may be more appropriate for assessing the effect of HA on pain than for assessing delay in structural progression or delay in knee replacement, due to the inherent biases of different assessment tools. Finally, the final Assessment document should acknowledge that the FDA?s draft guidance states that clinical trials to demonstrate structure improvement should last at least one year.	add to the evidence base we need to consider. In any case, post-market assessment of efficacy and safety is standard. The question of whether IA HA affects structural progression or improvement was not within the scope of this review, and we did not consider literature that addressed this concern: we merely raised the issue as part of the background.
Fidia Pharma USA	Introduction/Background	Scope and Key Questions (pp. 5-6) The first two key questions provided by the CMS Coverage Analysis Group focus on the effect of HA products on the need for knee replacement surgery. In the U.S., HA products are approved by the FDA for the treatment of pain in	We now acknowledge the indication for which FDA has approved IA HA. Nevertheless, the sponsor and their partner agency requested a review of the literature on a different set of outcomes.

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		osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics. These products are not approved for their role in delaying knee surgery. 1. Section 515(d) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. ? 360e(d). 2. FDA, Clinical Development Programs for Drug, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (OA) (Draft Guidance, July 1999). 3. See id. at 4 (stating that the WOMAC tool relies ?heavily on patient feedback? while the Lequesne Index is ?more driven by physician judgment?). 4. Id. at 6.	
Stephanie J. Ott, MD FACP, FACR President, Ohio Association of Rheumatology	Introduction/Background	See comments under General.	We believe no response is needed.
Emily Graham The Coalition of State Rheumatology Organizations (CSRO)	Introduction/Background	CMS' key questions focus on the use of HA to delay KR surgery, which contrast with the FDA approval of HA products, which hinge on a reasonable assurance that the product is safe and effective for the labeled indication. The improvement in symptoms (e.g., pain) is a separate claim from delay in structural progression, with different clinical substantiation requirements under FDA's current requirements. The final TA should include this information to provide the appropriate context, as the average reader may draw inappropriate conclusions without this understanding.	We have clarified this point in the introduction.
Peer Reviewer #1	Methods	The search strategy is clearly detailed so that it could be reproduced in other hands. The a priori emphasis on outcomes of an accepted nature	We clarified that the number was three or more.

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		such as ADL and IADL is reasonable. The rationale for restricting studies included in assessment of adverse events to those enrolling 500 or more is justified on the basis of seeking to capture rare adverse events. Line 46 page 14 states "If a sufficient number of studies was determined to be relatively homogenous..." but I don't see a definition of 'sufficient'.	
Peer Reviewer #2	Methods	Affirmative to the above questions.	No response required.
Peer Reviewer #2	Methods	p10l14: "bone-on-bone friction" is not a pathomechanistic explanation of clinically significant OA - in fact, the mechanism of pain induction in OA is poorly elucidated	We have revised the wording.
Peer Reviewer #2	Methods	p11l3-9: NSAIDS are not analgesics; their mechanism of action in OA of the knee is unknown	We have clarified that NSAIDs function by reducing inflammation.
Peer Reviewer #2	Methods	p11l14: it is not "loss of cells" but rather deaggregation of glycosaminoglycans which result in increased molarity and hence, water concentration in osteoarthritic cartilage	We have reworded the description of the mechanism by which synovial fluid loses its viscosity.
Peer Reviewer #2	Methods	p41l42: "severe OA" is not defined here	We have added two suggested criteria for severe OA, however later in the report we now note that we did not exclude studies that enrolled participants with less severe disease.
Peer Reviewer #2	Methods	p42l13: authors reference ROM as an outcome measure but never address in results	We did not identify any studies meeting our inclusion criteria that reported measuring ROM. We have now addressed this point at the end of the section where we report the functional outcomes.
Peer Reviewer #2	Methods	There is some inconsistency in # of studies reviewed: p15l46: 415 p15l53: 414	These numbers are fixed in the final description of the flow.

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		diagram p17: 415 p47l30: 275 rejected diagram p17: 274 rejected diagram p48: 274 rejected	
Peer Reviewer #3	Methods	In reviewing the PICOT, under "outcomes,", there are no function outcome measures listed. Further, it would be expected that explicit outcomes should be delineated in this portion of the paper, for instance, if function outcomes were listed, WOMAC function, the Lequesne Index, KOOS should be included. Same level of detail should be given for pain and for Quality of Life. For arthroplasty, they should clarify whether the arthroplasty had to be a total knee v. all inclusive (including partial arthroplasty). Did the arthroplasties have to be confirmed? Or was patient report accepted?	We have added the specific tests for which we included studies.
Peer Reviewer #3	Methods	Generally, the inclusion and exclusion criteria are justifiable. The search study is stated and logical. My main concern with the statistical method is with the identification of the MCID which I believe is from WOMAC pain, being extrapolated for measures of function. Biostatistical input on this point would be helpful.	We have checked several sources on deriving a MCID for function for studies of HA treatment of knee OA. We now present two different MCIDs; the one used by Rutjes and the one used in the recent network MA by Bannuru.
Mandie DeVincentis, MSN, RN, ANP-BC	Methods	Sufficient amount of information.	We believe no response is needed.
Aaron Broadwell Rheumatologist	Methods	Synvisc weekly injection x 3	We are not sure what the comment refers to.
J. E. Huffstutter Arthritis Associates, PLLC	Methods	A study done years ago by the manufacturers of Synvisc demonstrated that may doctors using their product were not successful in proper administration of Synvisc into the true knee joint. Family practioners were the least successful and rheumatologists were the most. This type of therapy is quite different than steroid injections in	The commenter raises an interesting point; however we saw no studies and no commentary in the peer reviewed literature on the potential role of administration in the efficacy or safety of IA HA.

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		that steroids can be effective even outside the joint, while viscous supplements must be administered into the joint after all possible synovial fluid has been aspirated.	
Fumihiro Saeki, MSc Seikagaku Corporation	Methods	A. Proper Understanding of the Nature of Different Placebo Treatments On page 8 of Method section, it describes placebo as ?sham treatment?. We believe that defining placebo as ?sham treatment? in the context of clinical studies involving HA injections is misleading. Most orthopedic surgeons acknowledge that injection of saline into the knee is an active treatment that can alter the local inflammatory environment of the affected knee. The use of the word ?sham? implies no active treatment, which is not the case for clinical studies with HA injections and saline injections. Therefore, we encourage AHRQ to recognize that HA injections provide pain-relief over and above that potentially provided by an active control of saline injections. Indeed, consistent with that view, the recent work by Bannuru et al. [Ref. 1] has demonstrated through Bayesian network-meta analysis that placebo effects vary dependent on the method of treatment delivery and once the differential placebo effect [Ref. 2] is accounted for, HA injection shows much greater effect than oral or topical treatments. References: 1. Bannuru RR, Schmid CH, Kent DM, Vaysbrot, EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Annals of Internal Medicine. 2015; 162(1): 46-54. 2. Mandl LA, Losina E. Relative efficacy of knee	We identified the Waddell follow-up paper in our update search and now cite it, along with the database analyses you mention. The potential mechanism or mechanisms by which IA HA exerts its effect(s) were beyond the scope of this review. We have included the suggested references in the revised report.

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		osteoarthritis treatments: are all placebos created equal? Annals of Internal Medicine. 2015; 162(1): 71-72.	
Linda McKee Rheumatic Disease Assocs. Ltd	Methods	there are several drugs available for this purpose even the Synvisc One that allows the patient to get only one injection. giving patients many choices and price options depending on their co pay or insurance providers.	We have shared the comment with CMS and believe no further response is needed.
Howard Blumstein New York State Rheumatology Society	Methods	1. Inclusion of studies with patients over the age of 65 years The Executive Summary clarifies that only studies reporting on patients with an average age of at least 65 years were to be reviewed in the TA. However, the literature search strategy is based, in part, on the search conducted by Rutjes and colleagues for their 2012 systematic review and meta-analysis of viscosupplementation for OA of the knee, which included studies with patients of younger average ages. (3) If this existing literature review is used as the basis of the TA review, then other systematic reviews with patients of all ages need to be included also. 2. Literature review for studies concerning the effect of HA products on pain Although intra-articular HA injections are indicated particularly to control OA pain, the TA review of studies pertaining to pain were, according to the Executive Summary, ?outside the original scope? of the assessment and was based predominantly on the 2012 literature review of Rutjes and colleagues (3) (including studies with patients of all ages) and from randomized, placebo-controlled trials published subsequently. Thus, the key performance criterion for HA products, pain control, was not reviewed with the thoroughness applied to treatment outcomes for which HA injections have not been approved (postponement	We have now augmented that part of the report with the more recent 2015 network meta-analysis by Bannuru and colleagues, which we identified only after submitting the draft report for peer review (at which time we are required to conduct an update review; we do not continuously do update searches throughout the review process). We also made the decision to cite the other major systematic reviews of IA HA and pain in our Discussion of how the results of our review fit into the existing evidence base. Those reviews included the Miller and Block review, additional reviews by Bannuru and colleagues and the Cochrane review. We also cited these reviews to support several points we noted regarding the state of the science. And we modified our conclusion and strength of evidence determination about pain. Under the circumstances (in which pain was not part of the original scope), we believe we have fulfilled our

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		or avoidance of KR). A literature search meeting currently accepted standards needs to be conducted for the assessment of HA injections for pain in patients with DJD.	obligation.
Howard Blumstein New York State Rheumatology Society	Methods	3. Use of a systematic literature review with important limitations as the basis for the TA The selection of the systematic literature review by Rutjes and colleagues (3) introduces important limitations into the TA review, because it ? Utilizes resources unacceptable in the context of evidence-based medicine such as content experts ? Includes HA products that have not met the stringent US standards for medical devices and are not available in this country We recommend the use of the literature review/meta-analysis by Miller and Block, (4) which does not show these limitations, as the basis for an evidence-based TA assessment with results applicable to rheumatologists practicing in the US. **References:** (3) Rutjes AW, Juni P, da Costa BR, et al. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med. 2012;157(3):180-191. (4) Miller LE, Block JE. US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. Clin Med Insights Arthritis Musculoskelet Disord. 2013;6:57-63.	We have added the most recent systematic review, the 2015 network MA by Bannuru and colleagues. In view of the completeness of that review, we stand by this decision. We do cite the review by Miller and Block in the discussion, however its reporting quality, among other factors, precludes us from including it as evidence.
Fidia Pharma USA	Methods	See comments on the Executive Summary.	We believe no response is needed.
Stephanie J. Ott, MD FACP,	Methods	Continued reimbursement for viscosupplementation for the relief of pain due to	We have shared the comment with CMS and believe no further

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FACR President, Ohio Association of Rheumatology		osteoarthritis is crucial to these patients? well-being. There are many patients with osteoarthritis if the knee that are not candidates for knee replacement due to advanced age, multiple co morbidities making surgery unsafe or many other reasons. There are studies proving the efficacy of these injections for pain relief, function and delaying the need for total or partial joint replacement. Several of these studies are listed for you below for reference. The first two speak to the efficacy of these injections for improving quality of life, function and pain improvement. These injections improve mobility and functioning for patients at a fraction of the cost of joint replacement surgery and give much needed treatment to those not candidates for those surgeries. If these are not available costs will go up as more patients will need more assistive devices, surgeries and medications for pain. We the OAR Board urge you to continue access to care for Medicare patients to these cost effective treatment. The last reference is a link to the American College of Rheumatology position paper on viscosupplementation for further information as well.	response is needed.
Edward F. Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.	Methods	There are several areas we believe require further consideration regarding the methodology of the review: I. The benchmark for the minimum clinically important difference (MCID) standardized effect size for functional outcomes was set at -.37 without a justification for that benchmark and without an assessment of whether the measurements pooled had acceptable variability to justify the application of standard effect size. The benchmark of a standardized effect size of -.37 for MCID functional difference between groups	Regarding the use of an MCID, we have now cited the MCIDs used and recommended by 3 different groups. Unlike statistical significance, the use of an MCID or MCII as a benchmark provides clinicians with the information they need to make decisions about the potential benefit of a product. The use of an MCID/MCII is not in question: what is in question is the threshold at which it should be set.

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		does not take into account potential variability in the baseline measures nor recognize that applying patient-level MCID to determine between-group differences leads to an unrealistic high bar for therapies to be considered clinically meaningful [Guyatt GH, Juniper EF, Walter SD, et al. Interpreting treatment effects in randomised trials. BMJ. 1998;316:690-693]. In addition, data was pooled from studies utilizing differing functional outcome tools (WOMAC and Lequesne). The benchmark of -.37 is referenced as having been used in the Rutjes meta-analysis and that is the only justification for its selection that is given in the review. It is not clear how this benchmark was derived, as functional patient-reported outcomes may have vastly differing degrees of change and yet meet the patient?s assessment of minimum clinically-important improvement. [Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain. 2009;146:238-244]	We agree that the evidence on this point is limited. We used a level that had been used by others conducting a similar analysis. In revising the draft, we cited two additional thresholds, one endorsed by OMERACT-OARSI. We also now address these points in the Discussion chapter. Finally we have added summaries of the retrospective analysis by Dasa as well as the analysis by Khan to our discussion of the analysis by Abbott.
Edward F. Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.	Methods	The level of subjective improvement patients consider to be clinically important typically is greater than the difference between treatment and placebo. Meaningful change for individual patients may reflect 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 by Zhang et al. [Zhang W, Robertson	Regarding the use of an MCID, we have now cited the MCIDs used and recommended by 3 different groups. Unlike statistical significance, the use of an MCID or MCII as a benchmark provides clinicians with the information they need to make decisions about the potential benefit of a product. The use of an MCID/MCII is not in question: what is in question is the threshold at which it should be set. We agree that the evidence on this point is limited. We used a level

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		J, Jones AC, et al. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis. 2008;67:1716-1723.] 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 standardized effect size to demonstrate meaningful clinical improvement, the benefit of intra-articular HA therapies for OA functional improvement has been obfuscated. Thus, we request that you apply MCID as a change within treatment groups, reflecting patient-level improvements.	that had been used by others conducting a similar analysis. In revising the draft, we cited two additional thresholds, one endorsed by OMERACT-OARSI. We also now address these points in the Discussion chapter. Finally we have added summaries of the retrospective analysis by Dasa as well as the analysis by Khan to our discussion of the analysis by Abbott.
Edward F. Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.	Methods	II. The reliance of the review on the 2012 Rutjes meta-analysis in summarizing the effect of HA treatment on pain relief Although the Technology Review was not focused on the effect of intra-articular HA on relief of pain due to osteoarthritis, the reviewers include a section summarizing the pain relief outcomes based on a meta-analysis by Rutjes et al., published in 2012 [Annals of Int Med 2012;157(3):1-13]. This meta-analysis has been criticized by osteoarthritis opinion leaders in regards to (1) the analysis of maximum pain relief at a point in time that likely correlated with waning treatment effect, (2) the inclusion of unpublished data, (3) the mixing of studies with both active and placebo controls and (4) the elimination of studies with a sample size of fewer than 100 patients. In an opinion piece, Drs. Timothy McAlindon and Raveendhara Bannuru [Nature Reviews/Rheumatology Volume 8 November 2012] of the Tufts University Center for Arthritis	We have subjected the Rutjes review to our own analysis and provided several comments regarding its weaknesses. We have also added the most recent (2015) review, by Bannuru and colleagues.

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		and Rheumatic Diseases, state:	
Edward F. Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.	Methods	?With regard to the efficacy of IAHA, Rutjes et al.4 concluded that this was not of clinically relevant magnitude. This result comes soon after our own 2011 meta-analysis that was able to detect a benefit that exceeded minimally important clinical improvement at 8 weeks post-injection.5 It is pertinent, therefore, to scrutinize why conclusions of meta-analyses, considered the highest level of evidence, can be dis?cordant. In our study, we detected the effect of IAHA by evaluating its therapeutic tra?jectory, rather than assuming a time-stable effect.5 Rutjes et al.4 used a time point for their primary outcome that would prob?ably coincide with a waning of effect. ?Similarly, most of the differences in results among meta-analyses are attribut?able to differences in the trials pooled and the data extracted. In most cases, these choices are made with the intent of improv?ing the quality of the included data, but sometimes can be counter-productive. For example, the Rutjes et al.4 analysis pooled data from studies with placebo and active comparator arms, which might have biased their results to the null. Also, the inclusion of studies that incorporated other types of interventions (arthroscopy, ultrasonography, cyclo-oxygenase 2 inhibitors, and so on) or controls (such as appropriate care, treatment of the contralateral knee) will introduce heterogeneity that can obfuscate interpretation. The inclusion of unpublished data, whilst considered to be important in reducing publication bias, also introduces complexities since these data are not peer-reviewed, and can vary between meta-analyses. All of these factors could have accounted for the inability of the Rutjes et al.4	We are aware of and now cite the review conducted by Bannuru and colleagues on the trajectory of the effect of HA. Unfortunately as we state in the report the data on function are insufficient to attempt to determine the trajectory for function and the peer reviewed studies that do assess function at multiple time points do not see the clear trajectory seen for analgesia.

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		analysis to discern a clinically relevant effect of IAHA.?	
Edward F. Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.	Methods	Other meta-analyses have arrived at different conclusions, most notably, a 2009 Cochrane review (the recognized gold standard in methodology) concluded: ?viscosupplementation is an effective treatment for OA of the knee with bene?cial effects: on pain, function and patient global assessment? [Viscosupplementation for the treatment of osteoarthritis of the knee (Review) Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA; The Cochrane Library 2009].	We have now cited the Bellamy review as well as the other major reviews, and as mentioned, have added an analysis of the 2015 Bannuru review, which is certainly the most up to date.
Edward F. Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.	Methods	III. Heterogeneity within the HA class has been noted in several meta-analyses. Differences between compositions of the HAs may contribute to this heterogeneity in functional outcome. The Review did not distinguish or take into account any variation in functional outcome that may have been attributable to the molecular weight (MW) composition of the viscosupplement. A recent publication [P.A. Band, et al., Hyaluronan molecular weight distribution is associated with the risk of knee osteoarthritis progression, Osteoarthritis and Cartilage 23 (2015) 70e76. http://www.oarsijournal.com/article/S1063-4584(14)01263-1/fulltext] has evaluated the importance of the molecular weight distribution of the HA in synovial fluid by evaluation of the HA in SF samples available from the NIH-sponsored POP (Prediction of OA Progression) study for which 3-year follow-up radiological data on knee OA progression are available, including data on interval knee joint replacement during the 3-year study period. The investigators hypothesized that the preponderance of low MW HA in SF would be associated with the risk of OA progression.	As we state in the report, the studies that have assessed differential effects on function by molecular weight are too small in number to draw any conclusion. The study described by the commenter here pertains only to endogenous HA, and therefore, may not be applicable.
Edward F.	Methods	The analysis revealed that a shift in the MW	Again the studies cited by the

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Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.		distribution of SF HA toward lower values is associated with an increased risk for rapid OA progression and that the MW of the HA was inversely correlated with pain. Because HA can be cleaved by reactive oxygen species generated during inflammation [Henderson EB, et al. A pathological role for damaged hyaluronan in synovitis. Ann Rheum Dis 1991;50:196e200. Halliwell B. Oxygen radicals, nitric oxide and human inflammatory joint disease. Ann Rheum Dis 1995;54:505e10.] this finding is consistent with the previously hypothesized relationship between inflammation and rapid OA progression [Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. Arthritis Rheum 2001;44:1237e47. Doherty M. Synovial inflammation and osteoarthritis progression: effects of nonsteroidal anti-inflammatory drugs. Osteoarthritis and Cartilage 1999;7:319e20] It is also consistent with data reporting that high MW HA down-regulates inflammatory cell activity [Darzynkiewicz Z, Balazs EA. Effect of connective tissue intercellular matrix on lymphocyte stimulation. Exp Cell Res 1971;66:113e23. Balazs EA. Viscoelastic properties of hyaluronic acid and biological lubrication. Univ Mich Med Cent J 1968:255e9. Forrester JV, Balazs EA. Inhibition of phagocytosis by high molecular weight hyaluronate. Immunology 1980;40: 435e46.] and that HA fragments stimulate innate immune system activity[Jiang D, Liang J, Noble PW. Hyaluronan in tissue injury and repair. Annu Rev Cell Dev Biol 2007;23:435e61.]	commenter refer to endogenous HA: we have no idea whether these observations would apply to IA HA.
Edward F. Greissing, Vice	Methods	The relationship of this finding regarding native synovial fluid HA molecular weight and the	As we state in the report, the studies that have assessed

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President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.		possible beneficial effect of exogenously supplied, high molecular weight HA on function is not yet known but bears consideration. Functional outcomes from a UK study comparing Hylan G-F 20 to Hyalgan [Raman R, Dutta A, Day N, et al. Efficacy of Hylan G-F 20 and Sodium Hyaluronate in the treatment of osteoarthritis of the knee -- a prospective randomized clinical trial. Knee. 2008 Aug;15(4):318-24. PMID: 18430574] and a real-world study conducted in France comparing Hylan G-F 20 to standard of care [Kahan A, Lleu PL, Salin L. Prospective randomized study comparing the medicoeconomic benefits of Hylan GF-20 vs. conventional treatment in knee osteoarthritis. Joint Bone Spine. 2003 Aug;70(4):276-81. PMID: 12951310.], both demonstrated a standardized treatment effect for functional outcome in excess of the predetermined benchmark of -.37 selected by the reviewers. In addition, recently published data from Dr. Waddell et al [Delayed Total Knee Replacement with Hylan G-F 20 Journal of Knee Surgery DOI http://dx.doi.org/10.1055/s-0034-1395281] of long-term follow up for patients treated with Hylan G-F 20 reveals a delay to the mean time to total knee replacement (TKR) or the end of the observation period of 2.8 years for the full cohort of 1,386 patients, confirming earlier reported delay of 3.1 years in the original published cohort. 75 percent of the treated knees in the full and original cohorts had not had a TKR in 7.3 years (95% confidence interval [CI], 5.8 _ 11.5) and 6.6 years (95% CI, 5.2 _ 9.7) from their first treatment. This publication was not included in the review due to the date of its publication. We request this publication be incorporated into the reviewers? findings and included in the final version of the Report.	differential effects on function by molecular weight are too small in number to draw any conclusion. The study described by the commenter here pertains only to endogenous HA, and therefore, may not be applicable. Again the studies cited by the commenter refer to endogenous HA: we have no idea whether these observations would apply to IA HA.

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Edward F. Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.	Methods	We also suggest that a separate analysis of functional outcomes for Hylan G-F 20 HA be considered for the future.	Were there sufficient data on functional outcomes in studies that met our inclusion criteria, we would have included them.
Emily Graham The Coalition of State Rheumatology Organizations (CSRO)	Methods	The draft report did not consider the results of a large retrospective analysis, Effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement surgery: evidence from a large U.S. health plan claims database, presented during the Academy of Managed Care Pharmacy 2014 Nexus, where the results were subsequently published in the October 2014 Journal of Managed Care and Specialty Pharmacy Meeting Abstracts, the results of which became available before the draft TA was issued, on the effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement. The study found that successive courses of two HA products led to a greater proportion of patients without total knee replacement surgery 3 years after initiation of treatment. This study should be considered part of the evidence for HA's role in delaying or avoiding knee replacement surgery.	The literature searches conducted for the draft report occurred in early 2014, too early to have identified the studies mentioned by this commentor; however we have updated our searches and have included all of the references mentioned.
Emily Graham The Coalition of State Rheumatology Organizations (CSRO)	Methods	In addition, a new AHRQ-funded study, Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis: A Systematic Review and Network Meta-analysis, which was published in the January 2015 Annals of Internal Medicine, examined the efficacy of treatments of primary knee OA using a network meta-analysis design, which estimates relative effects of all treatments against each other. The study considered randomized trials of adults with	The literature searches conducted for the draft report occurred in early 2014, too early to have identified the studies mentioned by this commenter; however we have updated our searches and have included all of the references mentioned.

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		knee OA comparing 2 or more of the following: acetaminophen, diclofenac, ibuprofen, naproxen, celecoxib, intra-articular (IA) corticosteroids, IA hyaluronic acid, oral placebo, and IA placebo. Following their study, the reviewers concluded the following: *"This method allowed comparison of common treatments of knee OA according to their relative efficacy. Intra-articular treatments were superior to nonsteroidal anti-inflammatory drugs, possibly because of the integrated IA placebo effect. Small but robust differences were observed between active treatments. All treatments except acetaminophen showed clinically significant improvement from baseline pain. This information, along with the safety profiles and relative costs of included treatments, will be helpful for individualized patient care decisions."*	
Peer Reviewer #1	Results	The inclusion of pain as an outcome seems to be a bit of an "afterthought" and hence somewhat awkwardly handled since it is likely an outcome that would be identified as important at the get-go (in addition to quality of life, function, and delay of surgery).	We agree that pain is an important outcome; most existing systematic reviews focused on pain and all original studies that assess the effects of intraarticular HA report pain, often to the exclusion of function. However our charge was to assess TKR and function. We decided to at least review systematic reviews of pain to put the functional outcomes data into perspective and focused on the most recent at the time, as it was also the most complete.
Peer Reviewer #2	Results	Affirmative to the above questions.	No response needed.
Peer Reviewer #2	Results	ref 107 authors: Thomas Abbott1, Roy D. Altman2, Robert Dimeff3, Michael Fredericson4, Vijay Vad5, Peter Vitanzo Jr.6, Sashi Yadalam1,	Thank you! That was an oversight!

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		Ronald Levine1, Brad Bisson7 and Samir Bhattacharyya7, 1Johnson & Johnson, New Brunswick, NJ, 2David Geffen School of Medicine, UCLA, Los Angeles, CA, 3UT Southwestern Medical Center, Dallas, TX, 4Stanford University School of Medicine, Menlo Park, CA, 5Weill Cornell Medical College, NY, NY, 6Rothman Institute, Philadelphia, PA, 7DePuy Synthes Mitek Sports Medicine, Raynham, MA	
Peer Reviewer #2	Results	Peer reviewed article not yet recorded in PubMed	We're not sure what this comment means: if the reviewer means that the abstract by Abbott et al., has not yet been published in a peer-reviewed journal, we are aware of that, so we mentioned it only in the Discussion. We did not include conference proceedings in the data analysis.
Peer Reviewer #3	Results	Delay or avoidance of knee replacement surgery (P18 – last line of para 2) “None of the studies specified the criteria for recommending patients to undergo surgery.” This is because none exist. I would remove this statement.	We inserted this statement at the explicit request of the sponsor's partner. We have revised the statement to the following: "None of the studies specified the criteria used by the treating physicians for recommending patients to undergo surgery."
Peer Reviewer #3	Results	Table 3 – recommend listing these in chronological order based on year of publication.	We have reordered the table chronologically.
Peer Reviewer #3	Results	Table 4 – recommend listing these in chronological order based on year of publication.	We have reordered the tables chronologically.
Peer Reviewer #3	Results	Table 4 – Study by Neustadt – it is listed that there are no inclusion/exclusion criteria, but directly after this, they list inclusion criteria. Please clarify.	We have clarified in the table that the authors did not specify any inclusion or exclusion criteria. We then went on to describe the participant characteristics.
Peer Reviewer #3	Results	Table 4 - 3 studies by Turajane should not be listed three times in this table. It is one cohort,	We have combined the descriptions for the 3 articles.

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		reported in 3 different ways. These findings should be pooled together. Also, the patient numbers for these studies are not consistently listed.	
Peer Reviewer #3	Results	Table 5 – Risk of Bias assessment is easier to synthesize if presented in the same way as Figure 4 on page 52.	We considered revising the format of that table, as well as the table that reports on the results of the McHarms and the AMSTAR assessment to the stoplight format of figure 4 but decided against it as we realized the ratings of Not Relevant and Not Assessed would be difficult to show and because we were trying to adhere to Cochrane standards as much as possible.
Peer Reviewer #3	Results	Intra-articular injection of hyaluronic acid and measures of function: It does not seem appropriate to lump in ADLs and IADLs with other measures of function tailored for knee OA.	The sponsor considered ADLs/IADLs as part of functional outcomes, and in fact some studies measure ADLs as an index of functioning. We identified only one study that met our inclusion criteria that assessed ADLs/IADLs, and we reported its findings narratively.
Peer Reviewer #3	Results	Although I understand why there is an interest to focus on patients age 65 and older, since none of the studies use this as an inclusion criteria, it seems like a mistake to use average age of the participants as a criteria for inclusion into this summary. By selecting studies where the mean age is 65 or older, still half of the participants are probably less than 65. Based on the meta-analysis by Rutjes et al (published in 2012), there are at least 52 studies that provide a function outcome. By applying the strategy of eliminating all those studies that do not have a patient mean	We think this idea has merit but is beyond the scope of this report.

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		age of 65 years or older, a substantial amount of important data is likely being lost. It's a missed opportunity. My suggestion is that since Rutjes et al has already provided a comprehensive review of the influence of IAHA on function, provide a summary based on their findings as they did for pain. After reviewing the details to Rutjes et al's review of function in HA, I don't see a comprehensive list of the function outcomes that were included. This review could provide that level of detail. I also suspect that ADLs and IADLs were probably not included in the Rutjes manuscript – and this outcome alone would be new information in the field.	
Peer Reviewer #3	Results	Before the prose description of the studies are presented, I would prefer to see the Forest Plot of the studies (Figure 3) – again, THIS should be ordered either chronologically by publication, or by molecular weight of the HA product evaluated. In fact, I think that table 6 could go in the appendix since the authors were able to pool the studies. Again, this table should be ordered chronologically by publication date. For this table, relevant outcomes field is missing on page 47.	We have redone the forest plot in chronological order and in order of product molecular weight. We have reordered Table 6 (but prefer to leave it in the main body of the report)
Peer Reviewer #3	Results	Intra-articular injection of hyaluronic acid and pain: There should be some mention of the publication bias seen in the Rutjes et al meta-analysis as well as their justification for presenting subgroup analysis of larger studies. I personally would like to see the forest and funnel plots in this document if the authors could obtain permission to reproduce these here.	We have now addressed this issue in describing the reviews of Rutjes and of Bannuru as well as in the Discussion. We do not want to place undue emphasis on the results of the Rutjes review or imply that they represent the most salient evidence regarding HA and pain, by reproducing their figures, and the information is publicly accessible.

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Peer Reviewer #3	Results	For table 7, the format used on P52 is more appealing. It would be nice if all these tables are consistent throughout the document.	We considered revising the format of that table, as well as the table that reports on the results of the McHarms and the AMSTAR assessment to the stoplight format of figure 4 but decided against it as we realized the ratings of Not Relevant and Not Assessed would be difficult to show and because we were trying to adhere to Cochrane standards as much as possible.
Peer Reviewer #3	Results	Intra-articular injection of hyaluronic acid and adverse events Since the authors of this manuscript have made excellent use of the well conducted meta-analysis by Rutjes et al for the purposes of pain, they should consider using their adverse events analyses as well. They are insightful and may lead the authors of this manuscript to a different conclusion.	In fact we completely re-analyzed all of the studies Rutjes included in their AE analysis for this report to examine possible reasons for the large discrepancy between their findings and ours, as we state in the Discussion section. Our conclusion is that the quality of AE reporting makes strong conclusions about safety very doubtful.
Peer Reviewer #3	Results	Generally, the amount of detail presented in the results section is appropriate. My main suggestion is that all the tables should be listed chronologically by publication date to make it easier to review and that the function table could go to the appendix.	We have reordered the tables chronologically.
Mandie DeVincentis, MSN, RN, ANP-BC	Results	Due to this new method of treatment, it will be interesting to see what, if any, are the long-term sequelae of this treatment.	We have shared the comment with CMS and believe no further response is needed.
Aaron Broadwell Rheumatologist	Results	Overall very good responses in at least 50% with improvement in stiffness, pain, and swelling, all performed in a population which had already failed steroid injection.	We have shared the comment with CMS and believe no further response is needed.

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Fumihiro Saeki, MSc Seikagaku Corporation	Results	B. Proper Use of Minimal Clinically Important Difference (MCID) On page 31 of this draft report, the use of MCID to assess function scores is mentioned. We wish to point out that such use of MCID measure for the assessment of clinical importance for group differences in change from baseline between the treatment and placebo groups is inappropriate and ignores the context in which MCID was originally conceived. The MCID measures have been derived from within-group patient data and defined with respect to baseline at the individual patient level. [Ref. 3-5] IMMPACT recommendations by Dworkin et al. [Ref. 5] state "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". **References:** 3. Ehrich EW, et al., Minimal perceptible clinical improvement with the Western Ontario and	Regarding the use of an MCID, we have now cited the MCIDs used and recommended by 3 different groups. Unlike statistical significance, the use of an MCID or MCII as a benchmark provides clinicians with the information they need to make decisions about the potential benefit of a product. The use of an MCID/MCII is not in question: what is in question is the threshold at which it should be set. We agree that the evidence on this point is limited. We used a level that had been used by others conducting a similar analysis. In revising the draft, we cited two additional thresholds, one endorsed by OMERACT-OARSI. We also now address these points in the Discussion chapter. Finally we have added summaries of the retrospective analysis by Dasa as well as the analysis by Khan to our discussion of the analysis by Abbott.

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		McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. J Rheumatol 2000; 27: 2635-41. 4. Strand V, Kelman A., Outcome measures in osteoarthritis: randomized controlled trials. Curr Rheumatol Rep 2004; 6: 20-30. 5. Dworkin RH, et al., Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005; 113: 9-19.	
Linda McKee Rheumatic Disease Assocs. Ltd	Results	As mentioned above in the Executive Summary.	We believe no response is needed.
Howard Blumstein New York State Rheumatology Society	Results	1. Clinically important difference as a selection criterion Only studies powered to see clinically important differences were included in the TA analysis. Although the minimum clinical important difference (MCID) is an important measure to help clinicians evaluate available treatments, it should not become the sole basis for making clinical or policy decisions. (5) As rheumatologists, we use evidence-based measures such as the MCID together with our expertise and individual patient characteristics to optimize treatment outcomes for our patients who may or may not benefit from any one therapy. Clinically meaningful improvements in individual patients may be assessed only when comparing before- and after-treatment evaluations. Conclusions based on MCIDs calculated with results from large patient pools are unsuitable for making policy decisions and should be removed from the TA. 2. Saline as a sham placebo When evaluating study results, it is important to understand the process of using saline in place of	Regarding the use of an MCID, we have now cited the MCIDs used and recommended by 3 different groups. Unlike statistical significance, the use of an MCID or MCII as a benchmark provides clinicians with the information they need to make decisions about the potential benefit of a product. The use of an MCID/MCII is not in question: what is in question is the threshold at which it should be set. We agree that the evidence on this point is limited. We used a level that had been used by others conducting a similar analysis. In revising the draft, we cited two additional thresholds, one endorsed by OMERACT-OARSI. We also now address these points in the Discussion chapter. Finally we have added summaries of the retrospective analysis by Dasa as

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		a placebo. Before HA or saline can be injected, patients receiving either treatment undergo the same first procedural step, the removal of effusion from the affected joint. This alone may lead to the reduction of inflammation and pain in some patients and may reduce the difference in subsequent treatment effects between HA and saline treatment groups. A network meta-analysis of treatments for OA of the knee reported an intra-articular placebo effect size of 0.29 (95% credible interval [CrI], 0.04 to 0.54). (6) Saline injections need to be recognized as an active treatment and HA treatment results interpreted accordingly. **References:** (5) Bannuru RR, Vaysbrot EE, McIntyre LF. Did the American Academy of Orthopaedic Surgeons osteoarthritis guidelines miss the mark? Arthroscopy: J Arthroscopic Related Surg. 2014;30:86-89. (6) Bannuru RR, Schmid CH, Sullivan MC, et al. Differential response of placebo treatments in osteoarthritis trials: a systematic review and network meta-analysis. Osteoarthritis Cartilage. 2014;22(Suppl):S24-S25.	well as the analysis by Khan to our discussion of the analysis by Abbott. This comment touches on several issues, notably the age issue and the placebo/comparator issue. We realize the decision to include only studies of average age 65 and over included a number of participants younger than 65. Had there been studies limited to individuals 65 and over, we would have focused on those studies. We also realize we excluded a number of studies that might have strengthened the effect size. That is why we cite the results of several recent comprehensive systematic reviews that did not consider age as an exclusion criterion. Regarding the issue of the choice of comparator, the sham saline injection is the most appropriate choice for placebo precisely because it completely mimics the experience of the IA HA injection and because it exerts a significant placebo effect. Thus any effect of the active intervention can truly be attributed to properties of the intervention itself. We cited both of the MAs mentioned by the comments' author, and we feel certain the authors of the network MA was not asserting that IA placebo be regarded as a treatment comparable to that of

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			HA.
Fidia Pharma USA	Results	Delay or avoidance of knee replacement surgery (p. 17) Since the AHRQ draft Technology Assessment was completed, a new, large retrospective analysis has been published on the effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement. This review evaluated patients who were continuously enrolled in a large U.S. health plan from 12-months pre-index to 36 months post-index date. The authors found that successive courses of Supartz or Hyalgan led to a greater proportion of patients without total knee replacement surgery 3 years after initiation of treatment. We recommend that this review be included in the final AHRQ Technology Assessment.	We have identified this review as well as another review presented at the same conference and we now discuss their findings in the context of the published findings we reviewed.
Fidia Pharma USA	Results	Intra-articular injection of hyaluronic acid and measures of function (pp. 31-32) The first bullet under ?Key Points? on page 31 seems inconsistent with the second paragraph of the ?Detailed Synthesis? on page 32, if both are describing the same pooled analysis of ten studies. The first bullet under ?Key Points? describes the meta-analysis of ten studies that compared the effect of HA to a placebo control, and states that there was a significant improvement in WOMAC-assessed function following HA treatment compared to placebo (SMD -0.23, 95% CI -0.34, -0.02), and that the effect size corresponds to 4.3 units on a 100 mm VAS scale. The ?Detailed Synthesis? states that a ?[p]ooled analysis of ten placebo-controlled trials showed a small increase in function for the HA-treated group? (SMD -0.23, 95% CI -0.41, -0.05) using the Dersimonian and Laird random effects method. In this section, it states that the	We have revised the wording of the bullets to clarify the intended meaning. We did not use the Der Simonian and Laird method, but instead used the Hartung-Knapp-Sidik-Jonkman (HKSJ) method for our random effects meta-analysis, as now recommended by Annals of Internal Medicine and AHRQ.

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		effect size was calculated as corresponding to an improvement of 8.28 units on a 0-100 VAS scale. It is unclear to the reader why there is a difference in VAS scale units in the ?Key Points? (4.3 units) versus the ?Detailed Synthesis? (8.28 units). If this is due to use of different methodologies, this should be more clearly explained in the Final Technology Assessment.	
Fidia Pharma USA	Results	Intra-articular injection of hyaluronic acid and pain ? Description of included studies and detailed synthesis (pp. 54-56) The draft Technology Assessment states that six articles (moderate to good quality) published in 2012 and 2013 were identified, and that these articles summarize trials comparing the effects of intra-articular HA with some other intervention on pain. The draft Technology Assessment, however, summarized only one of the six review articles (Rutjes et al., 2012), on the basis that it was the most recent and comprehensive. One of the systematic reviews excluded by AHRQ?s report is a review by Miller and Block, which published in September 2013. Differences between the Miller and Block review and the Rutjes review relied on in the AHRQ Technology Assessment include that: (1) the Miller and Block review was limited to studies of U.S.-approved HA products, whereas Rutjes et al., included nine (9) additional unapproved products; and (2) the Miller and Block review only included randomized, saline-controlled trials. The Miller and Block review included articles on studies of U.S. FDA-approved HA products that were randomized, had a saline-control study design, included patients with a primary diagnosis of knee osteoarthritis, had identical treatment and follow-up conditions between intra-articular HA and saline-control	We have now included summaries of the two most recent comprehensive meta-analyses in our scan of the pain literature. We cite most of the remainder of the existing systematic reviews in the Discussion. We would not have included the Miller and Block review for reasons stated above.

Commentator & Affiliation	Section	Comment	Response
		groups, and had at least one extractable efficacy or safety outcome. We are uncertain why a meta-analysis that includes unapproved products was used in a document intended for use in the U.S., and recommend that the Miller and Block review be described in the AHRQ Technology Assessment.	
Fidia Pharma USA	Results	The draft Technology Assessment also included two randomized trials that were completed after the Rutjes review was published. These trials enrolled populations of osteoarthritic patients of average age 65 or over, and assessed the effects of two different HA products head-to-head on pain. Although the draft Assessment lists 71 references that were excluded from the review because the average age of patients was less than 65 (see Appendix B), it did not assess whether these references included any placebo-controlled trials (with pain outcomes) that were not included in the review by Rutjes and colleagues. This approach seems incongruous, given that half of the studies in the Rutjes review included patients with an average age less than 65.	When we were drafting the report, we compared the list of trials identified in our searches against those of the Rutjes review and did not find any that they had not included.
Fidia Pharma USA	Results	Intra-articular injection of hyaluronic acid and pain ? Key points (p. 54) The draft Technology Assessment notes that, in the Rutjes study, when a subgroup analysis was performed that included only the 18 sham-controlled, assessor-blinded studies of sample size 100 or more per intervention group in the pooled analysis, the effect of HA was still statistically significant but no longer met the MCID. As noted previously, to obtain an estimate of MCID, the authors of the draft Assessment multiplied the pooled effect size by the standard deviation obtained from a large trial with a similar intervention for which functional outcome was	We have revised our description of our analytic method and the use of the MCID. For reasons noted above, we stand by the inclusion of MCID benchmarks.

Commentator & Affiliation	Section	Comment	Response
		assessed using the WOMAC. The draft Technology Assessment provides no information on the ?large trial? from which the standard deviation was obtained, nor does it provide any reason for using an intervention for which functional outcome was assessed using the WOMAC, as a multiplier. Without any such explanation, the methodology for obtaining an estimate of MCID and any estimates obtained appears to be arbitrary. As also previously noted, some clinicians have criticized the use of MCID and MCII (minimum clinically important improvement) in guidelines and meta-analyses, because they are context specific and may not be applicable across treatments or patient populations. In other words, the MCID values differ for improvement versus deterioration, and are impacted by the baseline symptom severity. For that reason, these clinicians recommend that MCID not be a ?cornerstone of clinical decision-making? in treatment guidelines, to avoid losing therapeutic options that may benefit a subset of patients with few options available. We therefore recommend that use of the MCID in a national retrospective review of clinical studies that will be relied on physicians treating patients, be justified and explained in the Technology Assessment.	
Fidia Pharma USA	Results	**References for above Results comments:** 1. Dasa, V. et al., 2014. Effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement surgery: evidence from a large U.S. health plan claims database. Journal of Managed Care & Specialty Pharmacy (Meeting Abstracts), Vol 20, no. 10 (Oct. 2014) (presented at Academy of Managed Care Pharmacy, 2014 Nexus, Boston, Massachusetts, Oct. 7-10, 2014.	We thank the commentor for providing references.

Commentator & Affiliation	Section	Comment	Response
		2. Rutjes, A.W. et al., 2012. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann. Intern Med. 157(3):180-91. 3. Miller, L.E. and Block, J.E., 2013. U.S.-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. Clin. Med. Insights Arthritis Musculoskelet. Disord. 6:57-63. 4.Bannuru, R.R. et al., 2014. Did the American Academy of Orthopaedic Surgeons Osteoarthritis Guidelines miss the mark? Arthroscopy: The Journal of Arthroscopic and Related Surgery 30:86-89.	
Stephanie J. Ott, MD FACP, FACR President, Ohio Association of Rheumatology	Results	See comments under Methods. We thank you for your time and consideration of our patients needs as you review this information. If we can be of any assistance please call and one of the OAR Board members will be happy to supply more information or answer any questions.	We thank the commentor; we believe no further response is needed.
Edward F. Greissing, Vice President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.	Results	Recent Relevant Research Not Included in the Review: As noted previously in our comments on Methods, recently published data from Dr. Waddell et al [Delayed Total Knee Replacement with Hylan G-F 20 Journal of Knee Surgery DOI http://dx.doi.org/10.1055/s-0034-1395281] of long-term follow up for patients treated with Hylan G-F 20 reveals a delay to the mean time to total knee replacement (TKR) or the end of the observation period of 2.8 years for the full cohort of 1, 386 patients, confirming earlier reported delay of 3.1 years in the original published cohort. 75 percent of the treated knees in the full and original cohorts had not had a TKR in 7.3 years (95% confidence	In revising the draft report, we have included all of the references the commentor mentions.

Commentator & Affiliation	Section	Comment	Response
		interval [CI], 5.8 _ 11.5) and 6.6 years (95% CI, 5.2 _ 9.7) from their first treatment. In addition to Waddell noted above [Delayed Total Knee Replacement with Hylan G-F 20 Journal of Knee Surgery DOI http://dx.doi.org/10.1055/s-0034-1395281], a very recently published meta-analysis of 137 studies by Bannuru et al. found that intra-articular treatments were superior to nonsteroidal anti-inflammatory drugs and all oral treatments with the exception of acetaminophen which showed clinically significant improvement from baseline pain. [Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis: A Systematic Review and Network Meta-analysis Raveendhara R. Bannuru, MD et al; Ann Intern Med. 2015;162(1):46-54. doi:10.7326/M14-1231 http://annals.org/article.aspx?articleid=2088548] This study was funded by the AHRQ. We request that the published Waddell and Bannuru findings also be incorporated into the reviewers? findings and included in the final version of the Report.	
Emily Graham The Coalition of State Rheumatology Organizations (CSRO)	Results	See comments under Methods.	We believe no response is needed.
Peer Reviewer #1	Discussion/Conclusion	The discussion and conclusion is appropriately guarded. I believe that it would be reasonable for the authors to extend their assessment to recommendations for future study design in greater detail rather than to request randomized controlled studies that try to account for NSAIDs as confounders or to rely upon industry databases. How long should such trials be conducted? What size study population would be	We now address a potential design for a RCT in the Discussion chapter under Research Gaps.

Commentator & Affiliation	Section	Comment	Response
		recommended? How would they account for the publication bias preferentially favoring academia-based work? etc.	
Peer Reviewer #2	Discussion/Conclusion	Affirmative to the above questions.	No response needed.
Peer Reviewer #2	Discussion/Conclusion	Given the difficulty in demonstrating a MCID in terms of pain and function as well as the highly variable presentation by patients with knee osteoarthritis in addition to a variety of factors which impact decision to seek total knee arthroplasty, it is the opinion of this reviewer that an adequately powered RCT in the patient population >=65 years is not feasible.	Although that is quite likely the case, we do now present a design for a possible RCT in the Discussion chapter in the section on Research Gaps.
Peer Reviewer #2	Discussion/Conclusion	I am not aware of a case control cohort study similar in concept to ref 107 having been performed using the MedPars database.	In fact CMS states that they cannot do such a study with their datasets.
Peer Reviewer #3	Discussion/Conclusion	In general this section does summarize and attempt to synthesize the data accumulated in this study. There are many aspects of the discussion I disagree with, but I have already mentioned them previously and will not reiterate them here.	See responses above.
Peer Reviewer #3	Discussion/Conclusion	In the discussion, they talk about Rutjes et al's adverse reactions analyses and observe that these findings are not concordant with their own. It seems odd that they did not include Rutjes et al's data on adverse events in their review though they used it similarly regarding other key questions. Description of reabstracting data from studies included in the Rutjes et al would be more appropriate in the methods and results sections.	Our re-analysis of the Rutjes AE data was not part of the CMS request. Therefore, we thought it only appropriate to include it in the Discussion chapter.
Peer Reviewer #3	Discussion/Conclusion	On the whole, the authors do a good job of synthesizing the major findings in the study. I do worry about the adverse events conclusions, however as they are not concordant with the review by Rutjes et al. To assist in allowing other researchers fill the research gaps, explicit suggestions about study design would be helpful.	We have augmented the discussion of research gaps considerably and present a list of needs for future research along with some suggestions for design.

Commentator & Affiliation	Section	Comment	Response
		I think it would be difficult to perform a case-control study to address the issue regarding whether IA HA can delay TKR. There is a strong placebo effect to an intra-articular injection that would be difficult to control for in this type of study design. For the appropriate RCT study design, it would be helpful to provide specific design issues that need to be addressed in such a study which I delineated in my initial comments.	
Peer Reviewer #3	Discussion/Conclusion	Minor comments The use of the abbreviation KR is not standard -- TKR is the usual abbreviation, denoting total knee replacement. There are some forms of partial knee replacements, such as unicompartmental replacements. Use of the term KR could also include those surgical procedures.	As we stated above, we have replaced KR with TKR.
Peer Reviewer #3	Discussion/Conclusion	It is preferable to use the term OA instead of DJD to refer to this disease.	We have replaced DJD with OA in the text but have left the report title as it was.
Peer Reviewer #3	Discussion/Conclusion	When the authors are referring to a particular study included in their review, they rarely cite the study by first author last name – use of this strategy would allow for easier reading of this very large manuscript (to reduce the need for frequent referral to the reference list).	We have inserted authors' names where we refer to individual studies.
Peer Reviewer #3	Discussion/Conclusion	The numbering of the tables and figures is not sequential through the document.	We're unsure what the reviewer means by the numbering being non-sequential. Following AHRQ publication guidelines, we assigned letters to tables in the Executive Summary and numbers to tables (and figures) in the main text. The tables and figures appear in the order listed in the TOC.
Peer Reviewer #3	Discussion/Conclusion	Misuse of the HA abbreviation (page 53, second to last paragraph) – for hyalgan v. for hyaluronic acid	We have corrected the error.

Commentator & Affiliation	Section	Comment	Response
Mandie DeVincentis, MSN, RN, ANP-BC	Discussion/Conclusion	It will also be beneficial to return periodically to the topic at hand as newer treatments may possess longer half-lives and in turn, potentially longer durations of action	We agree that the evidence should be updated, particularly as new products have recently entered and will continue to enter the market.
Aaron Broadwell Rheumatologist	Discussion/Conclusion	For patients with 1) Previous good response to HA product or 2) Failure of traditional NSAIDs and/or corticosteroid injection, hyaluronic acid derivative injections should be allowed for symptomatic relief of pain related to knee osteoarthritis.	We have shared the comment with CMS and believe no further response is needed.
Dr. Timothy Lonesky, DO Lake Cumberland Rheumatology	Discussion/Conclusion	I would hope that CMS would take into account the delay in knee replacements which occurs when viscosupplements are given. Our country already undergoes total knee replacement surgery at a much higher rate than other developed countries and eliminating viscosupplements will drive patients to knee replacement surgery quicker.	We have shared the comment with CMS and believe no further response is needed.
J. E. Huffstutter Arthritis Associates, PLLC	Discussion/Conclusion	Viscous supplementation in properly selected patients improves quality of life and is a safe, effective alternative to more aggressive surgical knee replacement. Its use should be restricted to practioners that are skilled in knee injections	We have shared the comment with CMS and believe no further response is needed.
Fumihiro Saeki, MSc Seikagaku Corporation	Discussion/Conclusion	C. Delay of Knee Replacement by HA: The Latest Evidence from the Real-World Data On page 67 of Discussion section under the heading ?Research Gaps?, AHRQ mentions that ?we (AHRQ) advocate analyzing data from any of the large administrative databases maintained by commercial payers, to answer the question as to whether beneficiaries who are treated with intra-articular HA proceed to KR at a lower rate than do those who do not receive HA?. We agree with AHRQ?s opinion and advocate the same approach, looking to the evidence presented by the real-world data. In contrast to traditional	We identified the analyses to which the commentor refers and now summarize them in the section of the Discussion where we describe the findings of our review in the context of previous research.

Commentator & Affiliation	Section	Comment	Response
		randomized controlled clinical trials, examination of large administrative databases offers the benefit of being able to probe realistic efficacy of treatments in actual clinical environments in a very large number of patients with heterogeneous backgrounds. For this purpose, we would like to bring to AHRQ?s attention the results of latest such studies sponsored by Seikagaku Corporation and conducted with administrative claims database of commercial payers. Confirming the finding from Truven MarketScan database [Ref. 6] already mentioned within page 67 of the draft report, researchers found from the analysis of total knee replacement (TKR) patients in a selection window of 6 years in the IMS Health PharMetrics Plus database [Ref. 7, 8] that the greater the number of treatment courses of HA injections, the longer the time interval from diagnosis to TKR. When no HA injection was used, the average time from diagnosis to TKR was only 0.3 year, whereas a single course of HA injection extended the average time to TKR to 1.1 year, with 5 or more courses of HA injection extending it to 3.6 years. In another similar investigation with IMS Health PharMetrics Plus database, when researchers analyzed the claims data from users of Supartz / Hyalgan in a span of 3 years [Ref. 9], they found that successive courses of Supartz / Hyalgan led to greater proportions of patients without TKR 3 years after Supartz / Hyalgan treatment initiation, and multiple courses of Supartz / Hyalgan injections significantly decreased risk of TKR (96.3% without TKR for 5+ courses vs. 72.7% without TKR for 1 course, hazard ratio 0.113, $p < 0.0001$). Both studies confirmed the dose-response relationship previously exhibited by the result of Truven	

Commentator & Affiliation	Section	Comment	Response
		MarketScan study between the numbers of treatment courses of HA injections and the increase in time to TKR. These findings indicate strong association between HA injections and longer time to TKR and suggest that HA injections can provide clinical benefits substantial enough to delay the need for TKR for a period of time far longer than have been examined by conventional randomized controlled clinical trials. References: 6. Altman RD, Dimeff RJ, Fredericson M, Vad V, Vitanzo PC, Abbott T, Yadalam S, Levine R, Bisson B, Bhattacharyya SK. Do hyaluronic acid injections delay total knee replacement surgery? American College of Rheumatology 2013 Annual Meeting. Poster presentation on Oct 29, 2013. (Abstract publicly available at https://ww2.rheumatology.org/apps/MyAnnualMeeting/Abstract/37383 accessed on Jan 9, 2015.) 7. Altman R, Lim S, Steen RG, Dasa V. Intra-articular hyaluronic acid delays total knee replacement in patients with knee osteoarthritis: evidence from a large U.S. health claims database. Poster abstract submitted to OARSI 2015 Annual Meeting (under review). 8. Altman R, Lim S, Steen RG, Dasa V. Hyaluronic acid injections delay total knee replacement surgery in patients with knee osteoarthritis: evidence from a large U.S. health claims database. (To be submitted to a medical journal in Feb 2015) 9. Dasa V, DeKoven M, Lim S, Long K, Heeckt P. Effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement surgery: evidence from a large U.S. health plan claims database. Academy of	

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		Managed Care Pharmacy Nexus Meeting 2014. Poster presentation on Oct 8-9, 2014. (Abstract publicly available at http://www.amcp.org/SupplementsForYear.aspx?year=2014&folderid=40412 accessed on Jan 9, 2015; see abstract M12 in Volume 20 Issue 10 Meeting Abstracts ? 2014 Nexus.)	
Linda McKee Rheumatic Disease Assocs. Ltd	Discussion/Conclusion	what will be next? persons over 65 are expected not to do anything with their lives? if they have a disability? Not be able to be and stay active just provides them with many other health issues.	We believe no response is needed.
Howard Blumstein New York State Rheumatology Society	Discussion/Conclusion	We recommend these new research findings for inclusion into the TA: 1. HA versus other pharmacologic treatments for OA of the knee Although the comparison of intra-articular HA therapy with other available pharmacologic treatments was excluded from the TA analysis as an ?outcome of no interest?, it is of utmost importance to rheumatologists devising treatment strategies to effectively reduce chronic pain and preserve function in their patients with OA of the knee. New analytic tools facilitate more comprehensive comparisons of various treatments. A recent network meta-analysis including 137 trials with 33 243 participants compared the efficacy of acetaminophen, NSAIDs, corticosteroids, and HA injections. (7) Intra-articular HA was identified as the most efficacious treatment for knee OA-associated pain with an effect size of 0.63 (95% CrI, 0.39 to 0.88). Hyaluronic acid injections were more efficacious than inter-articular corticosteroids for function and similarly effective as other treatments for stiffness. The analysis further highlights the excellent safety profile of HA products. 2. Effect of HA on total KR	Yes, we have included these references in the revised report.

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		A retrospective analysis of a medical claims database showed the value of HA injections for reducing the risk of total KR. (8) In the 3-year period considered, 18 217 patients had received HA injections for the treatment of OA of the knee; 13 561 (74.4%) had received a single course of treatment, 2999 (16.5%) 2 courses, 1012 (5.6%) 3 courses, 404 (2.2%) 4 courses, and 241 (1.3%) 5 or more courses. Of those receiving 5 or more courses of HA treatment, 96.3% did not undergo KR; of those receiving a single course, 72.7% did not have the surgery during the subsequent 3-year follow-up period. Thus, patients who had received 5 or more courses of HA injections had a significantly ($p<0.0001$) lower risk of total KR than those receiving 1 course of treatment.	
Howard Blumstein New York State Rheumatology Society	Discussion/Conclusion	3. Cost-effectiveness analyses Studies published in 2014 have demonstrated the cost-effectiveness of HA injections for OA of the knee. In the first analysis, 214 patients received 2 courses of 3 injections per week of bioengineered HA. (9) At 52 weeks, intra-articular HA resulted in an average utility gain of 0.163 quality-adjusted life years (QALYs; 95% confidence interval [CI], -0.162 to 0.488). With conventional care (NSAIDs and analgesics) as a baseline strategy, the incremental cost-effectiveness ratio (ICER) for HA injections was $38 741 per QALY gained. In the second study, 553 patients with OA of the knee had participated in an 8-week treatment program comprising HA injections, physical therapy, rehabilitation, and education, and had been encouraged to continue regular exercise after leaving the program. (10) Knee braces had been prescribed when indicated. When contacted after 1 and 2 years, 10% and 18% of patients, respectively, had undergone KR. Compared to	We find these results interesting but unfortunately, a cost-effectiveness analysis or cost-benefit analysis was beyond the scope of this review.

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		pre-treatment, a gain of 0.138 QALYs (95% CI, 0.128 to 0.148) was seen at 1 year and of 0.281 QALYs (95% CI, 0.254 to 0.309) at 2 years. The cost per QALY gained was $26 100 at 1 year and at $12 800 at 2 years. **References:** (7) Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis. Ann Intern Med. 2015;162:46-54. (8) Dasa V, DeKoven M, Lim S, et al. Effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement surgery: evidence from a large U.S. health plan claims database. J Managed Care Specialty Pharmacy. 2014;20(10-a):S53. (9) Hatoum HT, Fierlinger AL, Lin SJ, Altman RD. Cost-effectiveness analysis of intra-articular injections of a high molecular weight bioengineered hyaluronic acid for the treatment of osteoarthritis knee pain. J Med Econ. 2014;17(5):326-337. (10) Miller LE, Block JE. An 8-week knee osteoarthritis treatment program of hyaluronic acid injection, deliberate physical rehabilitation, and patient education is cost effective at 2 years follow-up: The Osteoarthritis Centers of America(SM) experience. Clin Med Insights: Arthritis Musculoskelet Disord. 2014;7:49-55.	
Howard Blumstein New York State Rheumatology Society	Discussion/Conclusion	Conclusions from the Perspective of the New York State Rheumatology Society: The TA presents an extensive literature review and meta-analysis concerning the efficacy and safety of intra-articular HA injections for the treatment of patients with DJD of the knee. We are pleased to provide our comments to solidify the results of this monumental effort and propose	For reasons stated above in response to each of the original points, we stand by the methods we used to conduct the review. We are unclear on what is mean by" a review that is based, in part, on expert opinion."

Commentator & Affiliation	Section	Comment	Response
		the following changes: - Clarification of the extensive experience with HA products in the US (since 1997) and their FDA-approval as treatment options for pain - Consistent application of inclusion criteria such as patient age - Consistent literature search strategies for all outcome parameters, including pain - Reconsideration of using a literature review that is based, in part, on expert opinion and research findings for HA products not approved in the US - Removal of the MCID as a key assessment criterion because it is not an appropriate basis for making policy decisions - Correct interpretation of saline injections in HA trials, as they are not equivalent to placebo sugar pills - Inclusion of research findings published after the search cut-off used for the TA	
Howard Blumstein New York State Rheumatology Society	Discussion/Conclusion	Intra-articular HA injections remain a viable and necessary treatment for patients with OA of the knee. The safety data on HAs is robust and, when compared to NSAIDs or narcotics, demonstrates superiority. While total KR is an option for patients with endstage OA, it is not appropriate for all patients, and there are many who would try to pursue a nonoperative approach as long as possible before undergoing surgery. Hyaluronic acid treatment remains the only longer-term treatment option without major long term safety risks. We are confident that revisiting the points listed above will result in a more valid assessment of HA products and help retain this safe and effective treatment option in the very limited armamentarium available for the treatment of patients with OA of the knee. Based on the	We have modified our conclusions somewhat in light of re-analysis of the data and additional publications that have been releases since we wrote the draft report.

Commentator & Affiliation	Section	Comment	Response
		published literature and clinical experience, HA injections should remain available for those patients with DJD who experience good outcomes with them.	
Fidia Pharma USA	Discussion/Conclusion	Discussion -- Key Findings and Strength of Evidence ? Intra-articular HA and Pain (p. 63) The draft Technology Assessment notes that, in the Rutjes study, when a subgroup analysis was performed that included only the 18 sham-controlled, assessor-blinded studies of sample size 100 or more per intervention group in the pooled analysis, the effect of HA was still statistically significant but no longer met the criterion of clinical importance. The authors conclude that ?the strength of evidence is low that HA reduces pain, on average, by an amount that approaches the minimum clinically important difference.? (See a fuller discussion of our concerns with use of the MCID in comments on the Executive Summary and Results sections.) We recommend that the final Technology Assessment provide a justification for use of MCID to support the strength of evidence of HA products on pain relief.	We believe we have justified using the MCID, as we state above.
Fidia Pharma USA	Discussion/Conclusion	Conclusions (p. 67) We recommend that the Conclusions section exclude the statement regarding the impact of HA on pain, because: (1) this was not the primary focus of the Assessment; (2) the use of MCID has not been established as an appropriate tool in this context; and (3) the review of literature on the effect of HA on pain properly should have included the Miller and Block review and other review articles, as well as articles comparing the efficacy of HA to oral NSAIDs.	The concluding statement for the report did not, and still does not, refer to the outcome of pain.
Edward F. Greissing, Vice	Discussion/Conclusion	The draft report identifies inherent limitations with some of the available studies or analyses included	We have greatly expanded the Discussion, including the

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President, N.A. Corporate Affairs for Sanofi U.S. Sanofi U.S.		for the Review. We agree with the comments made in the discussion section ?Findings in Relation to What is Already Known? regarding the 2012 Rutjes analysis: ?[W]e believe that limiting the pooled analysis to large studies is not methodologically justified given the small proportion of studies that fit the criteria and the fact that the study size is not typically a criterion is assessing study quality/risk of bias.? Furthermore, we believe that this limitation is equally applicable to the pain relief outcome aspect of the Rutjes analysis. We acknowledge that insufficiencies or gaps exist in the evidence available for the effectiveness of HA among individuals 65 years of age and older and the effect of HA, if any, on delay or avoidance of knee replacement surgery in that age group. However, in the absence of studies that focus specifically on this age group, we suggest that available studies that focus on primarily middle-aged adults (aged 50-65) still provide meaningful data with which to assess effectiveness in adults over age 65. Sanofi cannot understate the importance that this Review contains the most up-to-date findings and urges AHRQ to evaluate relevant new data sources, specifically the recent studies and analyses of Waddell, Bannuru and Band for inclusion in this Review and incorporation into any Final Report. Sanofi appreciates your thoughtful consideration of our comments.	Limitations section, in an attempt to clearly delineate not only the concerns that kept existing studies from having more weight but also the issues that need to be considered for future research.
Emily Graham The Coalition of State Rheumatology Organizations (CSRO)	Discussion/Conclusion	We remain concerned about the use of MCID and MCII in guidelines and meta-analyses, because they are context specific and may not be applicable across treatments or patient populations. Specifically, the MCID values differ for improvement versus deterioration, and are	For reasons we have discussed in response to a number of previous comments, we stand by the use of the MCID/MCII, while admitting that the process of setting the appropriate threshold is

Commentator & Affiliation	Section	Comment	Response
		impacted by the baseline symptom severity. For that reason, we recommend that MCID not be a "cornerstone of clinical decision-making" in treatment guidelines.	challenging.
Emily Graham The Coalition of State Rheumatology Organizations (CSRO)	Discussion/Conclusion	As you know, the FDA approved several HA products based on their effectiveness and safety with a finding of statistical significance, not on whether there is an MCID. The draft Technology Assessment should justify why use of MCID is necessary or appropriate to evaluate HA's effect on pain relief, when the FDA has accepted a statistically significant difference between HA and a placebo.	We believe we have justified using the MCID, as we state above. Further, it was the expressed wish of the sponsor that the outcomes be compared to an MCID.
Emily Graham The Coalition of State Rheumatology Organizations (CSRO)	Discussion/Conclusion	Finally, the final TA should exclude any statement regarding the impact of HA on pain, because: (1) this was not the primary focus of the Assessment; (2) the use of MCID has not been established as an appropriate tool in this context; and (3) the review of literature on the effect of HA on pain should include other review articles, as well as articles comparing HA to oral NSAIDs.	We agree and have purposely not included the outcome of pain in our concluding statement.
Mandie DeVincentis, MSN, RN, ANP-BC	Figures	Impressive.	Thank you. We believe no further response is needed.
Mandie DeVincentis, MSN, RN, ANP-BC	References	Good display.	We believe no response is needed.
Stephanie J. Ott, MD FACP, FACR President, Ohio Association of Rheumatology	References	Clin Med Insights Arthritis Musculoskeletal Disord. 6: 57-63, 2013 Cochrane Database Syst. rev April 18, 2005 Rheumatol Int. 26: 325-330, 2006 Curr Med Res Opin 24: 3307-22, 2008 Rheumatol Int. 31: 427-44, 2011 Phys Sportsmed 41: 16-24, 2013 https://www.rheumatology.org/Practice/Clinical/Po	Thank you. We have considered these references.

Commentator & Affiliation	Section	Comment	Response
		sition/Position_Statements/	
Emily Graham The Coalition of State Rheumatology Organizations (CSRO)	References	Please consider the results of and include the following study references in the final TA: Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. Ann Intern Med. 2015;162:46-54. doi:10.7326/M14-1231 Dasa, V. et al., 2014. Effectiveness of repeated courses of hyaluronic acid injections on the time to total knee replacement surgery: evidence from a large U.S. health plan claims database. Journal of Managed Care & Specialty Pharmacy (Meeting Abstracts), Vol. 20, no. 10 (Oct. 2014) (presented at Academy of Managed Care Pharmacy, 2014 Nexus, Boston, Massachusetts, Oct. 7-10, 2014.	Thank you. We have now included these references.
Peer Reviewer #1	Clarity and Usability	The conclusions are clear and may be used to inform policy. However, the conclusions are weakened by the fact that pooling is not possible since not enough studies reported ADLs or quality of life. Conclusions are further weakened by the fact that study designs across randomized and observational studies are too disparate or poorly powered to allow for inference about delay or avoidance of surgery.	No response needed.
Peer Reviewer #2	Clarity and Usability	Affirmative regarding the presentation of the report.	No response needed.
Peer Reviewer #2	Clarity and Usability	Pending further case control cohort investigations around time to TKR as well as pain and function after viscosupplementation, it is the opinion of this reviewer for reasons stated above, that the review by Rutjes etal (ref 14) should guide current CMS policy regarding coverage for hyaluronate therapy in knee osteoarthritis.	The Rutjes review finds a small but clinically significant effect for intra-articular HA (and they did not assess studies that reported the percent of patients who reported improvement, which could show a greater effect). However, we are

Commentator & Affiliation	Section	Comment	Response
			concerned about the conclusion of the Rutjes' review regarding serious AEs. As we describe in the Discussion chapter, after re-analyzing their data, we believe the data do not support a conclusion that HA is associated with a larger number of serious AEs than is placebo treatment.
Peer Reviewer #3	Clarity and Usability	This is my first time reviewing such a document, so please bear this in mind. Because of its length, it was difficult to go through. It was helpful to have a table of contents to provide a description of the organization. Much of the content is repetitive. The executive summary is long for what I would expect. I would prefer the format of using general length of the executive summary as the overall length of the document and then make an attempt to put much of the large tables in the appendix.	We appreciate this input on the organization and length of the report. We are required to conform to publication guidelines that dictate the organization of the report. However, we are aware that many readers will read only the executive summary so we have tried to make it stand on its own.
Peer Reviewer #3	Clarity and Usability	I am concerned that the ultimate review performed is not entirely aligned with the 4 key questions. It would help if greater detail is provided in the methods section with regard to the appropriate outcomes that are relevant to the questions at hand.	We have now listed the specific outcomes and revised the description of outcomes in the Methods section.
Peer Reviewer #3	Clarity and Usability	That being said, I do think that the conclusions are generally correct. More explicit direction regarding informative future directions, I think would be helpful in guiding other researchers to fill the needed gaps.	We have greatly expanded the section future research needs, addressing each of the issues we and the reviewers identified