Washington State Health Care Authority

Health Technology Assessment

Hyaluronic Acid/ Viscosupplementation (Re-Review)

Final Evidence Report

October 14, 2013

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Hyaluronic Acid/Viscosupplementation

A Health Technology Assessment

Prepared for Washington State Health Care Authority

FINAL REPORT – October 14, 2013

Acknowledgement

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Key Abbreviations

Acronyms

HA, hyaluronic acid (sometimes used to refer to all viscosupplementation products and sometimes used to mean non–cross-linked hyaluronan, as opposed to cross-linked [higher molecular weight] hyaluronan)

HTA, health technology assessment

ITT, intention-to-treat

OA, osteoarthritis

OR, odds ratio

RR, relative risk

RCT, randomized controlled (or comparator) trial

SMD, standardized mean difference (also referred to as effect size)

WMD, weighted mean difference

Shorthand References

2009 Bannuru review, meta-analysis of viscosupplementation versus corticosteroids (Bannuru et al., 2009)

2010 report, the HTA report on viscosupplementation presented to the Washington Health Care Authority in May 2010

2011 Bannuru review, meta-analysis of trajectory of effect (versus placebo) over time (Bannuru et al., 2011)

Bellamy review, 2006 Cochrane Review (Bellamy et al., 2006). Included in 2007 Samson review.

Colen review, 2012 meta-analysis (Colen et al., 2012)

Reichenbach review, meta-analysis of differential effect of hylan (Synvisc) versus HA (Reichenbach et al., 2007)

Rutjes review, 2012 meta-analysis (Rutjes et al., 2012)

Samson review, 2007 technology assessment prepared for the Agency for Healthcare Research and Quality (AHRQ) (Samson et al., 2007)

Update report, this document

EVIDENCE SUMMARY

Summary of Background and Technology Description

Osteoarthritis (OA), the most common form of chronic articular disease, is characterized by damage to articular cartilage, changes in subchondral bone and osteophyte formation. Knee OA is the most common form of OA. Estimates of the prevalence of symptomatic knee OA range from 6% in all adults older than 30 years of age to 9.5% to 12.1% in adults older than 60 years of age. One study has estimated that by age 85 years, nearly half of all adults will have developed symptomatic knee OA. Knee OA is a key cause of disability among noninstitutionalized adults and may lead to substantial productivity losses.

Nonpharmacological therapy generally includes education and support, physical therapy (including exercise), occupational therapy, and assistive devices. If pharmacological therapy is also required, good practice suggests starting with nonopioid analgesics (e.g., acetaminophen), followed by nonsteroidal anti-inflammatory drugs (NSAIDs). A 2009 Cochrane Review concluded that NSAIDs are more effective than acetaminophen for OA pain, and NSAIDs are the most commonly prescribed medications for OA. However, NSAIDs may cause serious adverse gastrointestinal and cardiovascular events.

When oral and topical medications are inadequate, intraarticular injection of corticosteroids, typically following fluid aspiration, is an option but provides relatively short-lived benefits and is more appropriate for rapid relief of a flare-up. Additionally, repeated intraarticular injections of corticosteroids have the potential to cause postinjection flare, infection, and progressive long-term cartilage damage. An alternative to corticosteroid injection is intraarticular hyaluronic acid (HA), also referred to as hyaluronan or sodium hyaluronate. The treatment is often called viscosupplementation. HA is a naturally occurring component of synovial fluid and cartilage. The viscous nature of the compound allows it to act as a joint lubricant, whereas its elasticity allows it to act as a shock absorber. In patients with osteoarthritic joints, both the molecular weight and concentration of endogenous hyaluronan are reduced, and hence, the joint is more susceptible to damage.
More than 20 HA products are marketed worldwide. Six HA products are currently marketed in the United States: Euflexxa, also known as Bio-HA (Ferring Pharmaceuticals), Gel-One (distributor Zimmer Inc.; manufacturer Seikagaku Corporation), Hyalgan (U.S. distributor Sanofi-Aventis; manufacturer Fidia Pharmaceuticals), Orthovisc (U.S. distributor DePuy Mitek Inc.; manufacturer Anika Therapeutics), Supartz (U.S. distributor Bioventus; manufacturer Seikagaku Corporation), and Synvisc and Synvisc-One (Genzyme). Different products vary according to molecular weight, which is related to chemical structure. Both Synvisc and Gel-One are derivatives of HA and consist of chemically cross-linked chains of hyaluronan, which adds to molecular weight. Synvisc is often referred to as Hylan G-F 20, or simply *hylan*. The term *hylan* does not refer to Gel-One. Gel-One is the most recently approved viscosupplementation product for marketing in the U.S.

Policy Context

Hyaluronate preparations have been approved by the Food and Drug Administration (FDA) for treatment of pain associated with OA of the knee in patients who have not had an adequate response to nonpharmacological conservative treatment and simple analgesics. The systematic reviews covered in the 2010 Washington Health Technology Assessment (HTA) Report on viscosupplementation for knee OA came to contradictory conclusions regarding the effectiveness of viscosupplementation, and national guidelines varied in their recommendations. The product has been approved as a medical device rather than a pharmaceutical because of its intended effect on the synovial fluid viscosity (Bannuru et al., 2009).

The 2010 Washington HTA report concluded that:

> There is consistent evidence demonstrating that viscosupplementation results in lower mean pain scores and improves mean function scores a few weeks after treatment. However, the magnitude of benefit of HA alone may be too small to be clinically important. (Average change in pain score typically did not meet the threshold of minimal clinical importance, as defined by the OA research community.) There is a much greater volume of evidence regarding impact on pain than on function, and many studies did not follow patients beyond 3 months. Therefore, the impact of viscosupplementation on the eventual recovery of function is uncertain. Compared with intraarticular corticosteroid injection, viscosupplementation appears to confer longer-lasting benefit, but the evidence was considered low quality. For comparisons with other treatments, there was insufficient evidence to allow any conclusion. Adverse events occur at a frequency of approximately 2% in single courses of treatment and are primarily transient local reactions; although rare, serious adverse reactions are possible. The rate of adverse events per patient has been shown to increase with repeat courses of treatment, but the only available data were for hylan (i.e., high molecular weight HA).

New systematic reviews and meta-analyses have been published since 2010, including 1 meta-analysis suggesting serious safety concerns with viscosupplementation (Rutjes et al., 2012). Additionally, new guidelines with new (more negative) recommendations have been published by the American Academy of Orthopaedic Surgeons (AAOS) and the American College of Rheumatology (ACR). These various publications and the lack of a National Coverage Determination (NCD) from the Centers for Medicare & Medicaid (CMS) led to a re-review of this topic.

Summary of Review Objectives and Methods

Review Objectives

The scope of this report is defined as:

> **Populations:** Adults with OA of the knee
>
> **Intervention:** Viscosupplementation (hyaluronic acid injection – Hyalgan, Synvisc, Supartz, Orthovisc, Euflexxa, Gel-One)

Comparators: NSAIDs, corticosteroid injection, physical therapy, oral pain medications, placebo, arthroscopic lavage and/or debridement

Outcomes: Pain, function, quality of life, adverse events

Key Questions

The following key questions will be addressed:

1. (a) What is the clinical effectiveness of viscosupplementation for treatment of OA of the knee? (b) Do different viscosupplementation products vary in effectiveness?

2. What are the adverse effects associated with viscosupplementation in patients with OA of the knee?

3. Does the effectiveness of viscosupplementation vary by subpopulation defined by these factors: age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), and prior treatments?

4. What are the cost implications and cost-effectiveness of this type of product?

Methods

See the **Methods** section of the **TECHNICAL REPORT**, **Appendix I**, and **Appendix II** for details.

Search Strategy and Selection Criteria

Systematic reviews and guidelines were identified in an initial search of key databases and websites. PubMed and Embase searches were conducted to identify randomized controlled trials and randomized comparator trials (both referred to as RCTs) that were published after the last search dates of the latest systematic review. PubMed and Embase were also searched for observational studies with safety or differential effectiveness/safety data. For the current update, literature published since December 2009 was considered. Various searches were conducted in February, May, and June of 2013, with an update search conducted on July 5, 2013.

Quality Assessment

The process used by Hayes for assessing the quality of primary studies and bodies of evidence is in alignment with the methods recommended by the GRADE Working Group. The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines.

Evidence Selection

See the **Evidence Selection** section in the **TECHNICAL REPORT** for full details.

Systematic Reviews

Six main systematic reviews with meta-analyses are included in this update report. Three reviews have been retained from the 2010 report (Reichenbach et al., 2007; Samson et al., 2007; Bannuru et al., 2009), and another 3 systematic reviews with meta-analyses have been added (Bannuru et al., 2011; Colen et al., 2012; Rutjes et al., 2012). The Samson review was actually a review of 6 previously published meta-analyses, the most comprehensive of which was a Cochrane Review (Bellamy et al., 2006). Pooled estimates reported in the Bellamy review are highlighted in this update report; pooled estimates from the other meta-analyses covered in the Samson review appear primarily in Appendix V. All systematic reviews included only RCTs or pseudo-randomized trials. See **Appendix IV** for an overview of the included reviews, **Appendix V** for results of meta-analyses of randomized (generally placebo-) controlled trials, and **Appendix VI** for results of meta-analyses of randomized comparator trials.

Three of the 6 systematic reviews covered in this update were concerned primarily with the general efficacy of viscosupplementation (Samson [represented primarily by Bellamy], Colen, and Rutjes reviews). Of the other 3 systematic reviews, 1 evaluated the relationship between efficacy and time, i.e., peak effect and duration of effect (2011 Bannuru review), 1 analyzed trials comparing hylan with non–cross-linked HA (Reichenbach review), and 1 analyzed trials comparing viscosupplementation with intraarticular corticosteroid injection (2009 Bannuru review). The Bellamy and Colen reviews also included analyses of trials comparing different forms of HA and comparing viscosupplementation with other treatments.

Randomized Controlled/Comparator Trials (RCTs)

The update literature search yielded 5 RCTs that were not included in any systematic review, but only 4 (5 publications) are included in the update report. A pilot trial comparing a single injection of Synvisc (hylan) with a single injection of Hyalgan (non–cross-linked HA), was excluded because it was not clear whether the single-injection form of Synvisc was used and, as acknowledged by the authors, Hyalgan has not been approved for single-injection use (Khanasuk et al., 2012). Three of the 4 included trials were double-blind placebo-controlled RCTs (Altman et al., 2011; Navarro-Sarabia et al., 2011; Strand et al., 2012a; Strand et al., 2012b). The fourth compared HA products of 3 different molecular weights (Petrella et al., 2011). Study details are presented in **Appendix VII**.

Supplemental Studies and Reviews

Information provided in the 2007 Samson review on 3 large case series was retained from the previous report. A large multicenter case series evaluating the effectiveness and tolerability of a non–cross-linked HA product (Hyalubrix, Fidia Farmaceutical SpA; not available in the U.S.) was selected for additional safety data (Foti et al., 2011). A review article (Goldberg and Coutts, 2004) was selected for additional data on the risk of pseudosepsis.

Cost Studies and Economic Evaluations

No new economic evaluations or cost studies were identified in the literature published since the 2010 report. The original publications of 4 economic evaluations (Torrance et al., 2002; Kahan et al., 2003; Yen at al., 2004; NICE, 2008) that were summarized in the 2010 report have been re-reviewed and the summary of their findings for Key Question #4 has been edited for better clarity. Two studies that were briefly reviewed in the 2010 report have been omitted because study weaknesses did not allow

meaningful conclusions. One omitted study was a retrospective cost analysis showing that when HA was ineffective and surgery was necessary, HA contributed only 6% of the total direct medical costs of treatment. However, there was no analysis of how often the cost of surgery could be avoided altogether by HA injection or how long it could be delayed in patients who responded to HA (Turajane et al., 2007). Another omitted study, an RCT, included a cost-effectiveness analysis to test the hypothesis that Synvisc is cost-effective compared with Artz. However, the trial was considered to be of poor quality (Chou et al., 2009).

Practice Guidelines

Searches of the core sources and relevant specialty groups identified current guidelines from 4 organizations: the American College of Rheumatology (ACR) (Hochberg et al., 2012), the American Academy of Orthopaedic Surgeons (AAOS) (AAOS, 2013), the National Institute for Health and Clinical Excellence (presently the National Institute for Health and Care Excellence) (NICE) (NICE, 2008), and the Osteoarthritis Research Society International (OARSI) (Zhang et al., 2007; Zhang et al., 2008; Zhang et al., 2010).

Findings

Key Question #1a: What is the clinical effectiveness of viscosupplementation for treatment of OA of the knee?

Efficacy of Viscosupplementation

Quantitative synthesis of the evidence for efficacy came from 4 main systematic reviews, all considered to be of good quality: an Agency for Healthcare Research and Quality (AHRQ) Technology Assessment (2007 Samson review) that was included in the 2010 report, and 3 newer systematic reviews with meta-analysis (Bannuru [2011], Colen, and Rutjes reviews. See Appendix IV (overviews) and **Appendix VI** (detailed findings. As previously noted, the Samson review was actually a review of 6 previously published meta-analyses, the most comprehensive of which was a Cochrane Review (Bellamy et al., 2006). Thus, a total of 9 meta-analyses (6 in the Samson review and 3 new) of the efficacy of viscosupplementation are included in this report, representing a total of 81 generally placebo-controlled trials and > 10,000 patients. In addition to the 9 meta-analyses, 3 recent RCTs (4 publications) evaluated the placebo-controlled efficacy of viscosupplementation.

To provide a more complete profile of trial participants than was available in the systematic reviews, baseline patient characteristics and inclusion/exclusion criteria were reviewed for 21 trials with ≥ 200 participants. These characteristics are summarized in **Table 1a** (below the Pain findings); additional detail is provided under **Findings: Effectiveness of Viscosupplementation**, *Study and Patient Characteristics* in the **TECHNICAL REPORT**. In most trials, patients had not received an intraarticular corticosteroid injection within recent months. In the few trials that report previous use of NSAIDs, a strong majority of patients had previously used NSAIDs.

Mean Group Differences in Pain, Physical Function, and Quality of Life (QOL)

The representative data summarized in **Table 1a** (following this discussion) provide **moderate**-quality evidence of benefit from viscosupplementation for improvement in pain and function, typically

considered primary outcomes in individual studies. Meta-analyses of RCTs of viscosupplementation versus control (typically, placebo in the form of sham injection) have shown statistically significant, although modest, effects on pain and physical function in patients with OA of the knee, with benefits generally peaking by 3 months. Although there is considerable inconsistency in the direction of results across studies, pooled estimates for effects at approximately 3 months were consistently positive and were statistically significant, i.e., there was no imprecision. The Rutjes review included several subset analyses according to study characteristics such as sample size and allocation concealment; each subset estimate was also statistically significant and positive. (NOTE: Although the Rutjes review used the term *subgroup* in this context, the term *subset* has been substituted to clarify that this analysis is at the study level, i.e., involves groups of studies, as opposed to patient-level analyses within individual trials, which are referred to in this report as subgroup analyses.)

Nearly all pooled estimates expressed as absolute group differences in pain were smaller than 20 mm on a 100-mm scale, which is the most widely used definition of clinically relevant improvement from baseline within individual patients or within a single treatment group. The most comprehensive analyses of a weighted mean effect (WMD) at 3 months were 11.0 (Bellamy review) and 10.20 (Colen review). However, according to guidance provided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group, clinically meaningful *between-group* differences can be expected to be smaller than clinically meaningful improvement from baseline because of the adjustment for placebo effect. The IMMPACT statement advises that placebo-controlled trial results be interpreted in light of differences in responder rates (see following discussion). The 3-month pooled estimates for pain and function reported in the most comprehensive meta-analysis, the Rutjes review, were expressed as effect sizes. The effect size for both pain and function was statistically small according to conventional guidelines. However, according to the authors' a priori criteria, the effect met but did not exceed a prespecified minimal clinically important difference (MCID) that was relevant for between-group pain differences in trials. These updated findings are consistent with the findings of the 2010 report.

In the Rutjes review, 2 methodological quality factors—blinded outcome assessment and samples involving ≥ 100 patients in each treatment arm—were associated with smaller estimates of pain effect. When analysis was restricted to trials with those characteristics, the effect size fell to a value that would be considered clinically irrelevant, although it was still statistically significant. The Rutjes review also showed funnel plot asymmetry and negligible pain effect in a small subset of unpublished studies; both of these observations are consistent with publication bias. However, the Rutjes analysis did not detect an association between individual study findings and industry sponsorship.

Regarding other outcomes, 3 of the 4 general reviews analyzed the effect on physical function; the results followed very similar patterns to analyses of pain outcomes. The available evidence suggests no effect on general QOL.

Likelihood of a Clinically Relevant Benefit (Responder Rates)

Evidence regarding responder rates, i.e., the likelihood that some patients would benefit according to a prespecified definition of clinical relevance, complements findings expressed as mean group differences in pain or function scores or as effect sizes. In placebo-controlled trial results, the differences in response rates in 9 of 11 trials implied that 7 to 16 patients, depending on the follow-up interval and definition of response, would need to be treated with HA injection **rather than a sham injection** in order to have meaningful benefit (2 trials reported results favoring placebo groups). However, of the 9 trials reporting positive results, only 4 trials reported statistically significant differences according to

intention-to-treat (ITT) or modified ITT analysis. This evidence was considered to be of **low** quality because of study weaknesses and inconsistency. Two pragmatic trials suggested that when viscosupplementation is **used as an add-on treatment** after other measures have failed, rather than as an alternative to sham injection, only 4 to 6 patients would need to be treated for 1 patient to experience clinically meaningful benefit. This evidence was considered to be of **moderate** quality. However, given the non-U.S. settings (France and Canada) and publication dates (2002 and 2003), generalizability of the pragmatic trial results to current U.S. practice is uncertain.

Repeat Injections

Three RCTs, all with high loss to follow-up between the first and second treatment courses, have suggested that a repeat course of HA injections, separated by 3 to 6 months, may be effective (**low**-quality evidence). One of the trials showed favorable but nonsignificant results from a third course.

Viscosupplementation Versus Alternative Treatments

The Bellamy review identified 4 trials comparing viscosupplementation with **NSAIDs**; the results suggested that the 2 treatments had comparable efficacy (**no quality assessment** by the systemic review authors). The literature does not suggest that viscosupplementation would necessarily be offered as a complete replacement of NSAIDs. A meta-analysis of 7 RCTs (2009 Bannuru review) suggested that viscosupplementation is inferior to **intraarticular injection of corticosteroids** for rapid relief of pain but provides more long-lasting benefit (**low**-quality evidence). Viscosupplementation versus **glucosamine or chondroitin** has not been studied in randomized trials (**no evidence**).

Table 1a. Summary of Findings, Key Question #1a (see Appendix III for detail on measurement scales)

Key: BL, baseline; BMI, body mass index; CI, confidence interval; HA, hyaluronic acid; IACS, intraarticular corticosteroid; ITT, intention-to-treat; MA, meta-analysis; MCID, minimal clinically important difference; NS, not (statistically) significant; NSAID, nonsteroidal anti-inflammatory drug; PICO, Populations, Interventions, Comparators, Outcomes; pt(s), patient(s); RCT, randomized controlled trial; RR, relative risk; SMD, standardized mean difference; SR, systematic review; VAS, visual analog scale; WMD, weighted mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Studies	Quality Assessment (see Quality Assessment Methods in TECHNICAL REPORT	Main Findings*, † (Results favored HA unless otherwise noted; 100-mm scales unless otherwise noted; 95% CI)
Pain:		
Most comprehensive SRs with unpublished studies included: Bellamy 2006: 21 placebo-controlled RCTs (2090 pts) Rutjes 2012: 68 RCTs (9617 pts). 50 RCTs published in full, ~20% of RCTs (14/68) involved nonplacebo control. ***Most comprehensive SR with unpublished studies excluded:*** Cohen 2012: 18 RCTs (2801 pts) ***SR of effect over time (unpublished studies included):*** Bannuru 2011: 54 RCTs (6545 pts) ***Published after SRs:*** 1 RCT (375 pts) (Strand 2012a)	**Moderate** Large volume of evidence. Good-quality MAs Generally fair-quality studies. Mean 3.6, median 3 on Jadad scale (1-5) according to Rutjes review. 30% of RCTs were "high" quality according to Bannuru review. RCT published after SRs was fair quality. Inconsistency in direction across individual studies; statistical heterogeneity in overall estimates but consistent direction and statistical significance in pooled estimates; heterogeneity in trial design accounted for some inconsistencies. Some evidence of publication bias (Rutjes review), but positive effect in analysis restricted to large trials.	***Mean effect (pooled estimates) on pain at ~3 mos*** Weight-bearing pain, VAS (Bellamy 2006) ***WMD –11.0*** *(CI, –17.8 to –8.2)*; I^2=82% Weight-bearing pain, WOMAC (Bellamy 2006) ***SMD –1.0*** *(CI, –1.6 to –0.5)*; I^2=88% (data available in only 7 RCTs, 639 pts) VAS preferred (Colen 2012) ***WMD –10.20*** *(CI, –15.97 to –4.42)*; I^2=92% Mean relative improvement: 30%-66% in HA arms; 30% in placebo arms WOMAC preferred (Rutjes 2012) All trials: ***SMD –0.37*** *(CI, –0.46 to –0.28)*; *P*<0.001; τ^2=0.09, *P*<0.001 for heterogeneity n=100/grp and adequate assessor blinding: ***SMD –0.11*** *(CI, –0.18 to –0.04)*; τ^2=0.01 (18 RCTs, 5094 pts) No other trial characteristics significantly associated w/ effect size. ***RCT published after SRs*** Difference in mean improvement at ~3 mos, favoring HA: 5.5 to 7.10, depending on model ***Clinical relevance*** WMDs in largest MAs (11.0 and 10.20) were smaller than generally recognized nonadjusted clinically important difference for pain improvement in individual pt (≥20). No prespecified trial-relevant MCID in Bellamy and Colen reviews. SMD 0.37 met Rutjes review definition of MCID for trial effect, which was 0.37 (equivalent to 0.9-point difference on 100-mm VAS). ***Peak Effects*** Bannuru 2011: **7-10 wks,** SMD 0.46 (CI, 0.28-0.65); I^2=75% (26 RCTs). Other SMDs were 0.31 at 3-6 wks, 0.21-0.25 at ≥10 wks. Rutjes 2012: **<3 mos**, SMD –0.54. Other SMDs were –0.23 at 3-6 mos and –0.36 at <6 mos. Bellamy 2006: **5-13 wks**, SMD –11.0. Other SMDs were –7.7 at 1-4 wks and –9.0 at 14-26 wks.
TYPICAL PATIENT (Trial Participant): Age 53-71 yrs; sex (varied widely); BMI 29-33 kg/m^2; OA duration 6-9 yrs; severity Kellgren-Lawrence grade 2-3 (0-4 scale); BL pain 42-60 on 100-mm scales or equivalent; NSAIDs had previously been tried; no IACS w/in previous 3 mos; concomitant pain medication allowed (~67% larger studies disallowed NSAIDs; washout period prior to assessment often required). Not reported: Hx of trauma; compliance w/ tx regimens prior to trial enrollment; whether IACS during study period was allowed.		

Studies	Quality Assessment (see Quality Assessment Methods in TECHNICAL REPORT	Main Findings*, † (Results favored HA unless otherwise noted; 100-mm scales unless otherwise noted; 95% CI)
Physical Function:		
3 SRs: Bellamy 2006: 7 RCTs (2090 pts) Rutjes 2012: 48 RCTs (# pts NR). Bannuru 2011: 54 RCTs (6545 pts) ***Published after SRs:*** 1 RCT (375 pts) (Strand 2012a)	**Moderate** Large volume of evidence. Good-quality M-As Generally fair-quality studies. Mean 3.6, median 3 on Jadad scale (1-5) according to Rutjes review. 30% of RCTs were "high" quality according to Bannuru review. All RCTs published after SRs were fair quality. Inconsistency in direction across individual studies; statistical heterogeneity in overall estimates but consistent direction and statistical significance in pooled estimates; heterogeneity in trial design accounted for some inconsistencies. Some evidence of publication bias (Rutjes review), but positive effect in analysis restricted to large trials.	***Mean effect (pooled estimates) on pain at ~3 mos*** Weight-bearing pain, WOMAC (Bellamy 2006) ***SMD –0.9*** *(CI, –1.3 to –0.4)*; I^2=84% WOMAC preferred (Rutjes 2012) All trials: ***SMD –0.33*** *(CI, –0.43 to –0.22)*; *P*<0.001; τ^2=0.10, *P*<0.001 for heterogeneity n=100/grp and adequate assessor blinding: ***SMD –0.09*** *(CI, –0.17 to –0.00)*; τ^2=0.01 (15 RCTs, 4296 pts) ***RCT published after SRs*** Difference in mean improvement at ~3 mos, favoring HA: 5.42 (NS) or 5.29 (*P*=0.049), depending on model ***Clinical relevance*** Small according to largest MA. Literature suggests thresholds are the same as for pain. ***Peak Effects*** No clear pattern (Bannuru 2011)
Quality of Life:		
6 RCTs (2147 pts) (Karlsson 2002, Altman 2004, Lundsgaard 2008, Altman 2009, Baltzer 2009, Jorgenson 2010)	**Moderate** Good quantity of data Fair-to-good quality of studies (indirect assessment based on size and adequate assessor blinding, as reported in Rutjes review) Slight inconsistency No analyses of publication bias available.	No effect suggested in 4 studies (no difference between HA and placebo groups). In 2 studies w/ positive conclusions, only improvement from BL in HA arms was reported (no information about placebo arms).
Effect of a Repeat Course of Injection:		
3 RCTs (Jubb 2003, Altman 2011, Strand 2012b),	**Low** Small # trials; high dropout rate between tx courses	Efficacy of 2nd course comparable to that of 1st course.

Studies	Quality Assessment (see Quality Assessment Methods in TECHNICAL REPORT	Main Findings*, † (Results favored HA unless otherwise noted; 100-mm scales unless otherwise noted; 95% CI)
Pain or Function (likelihood of clinically relevant benefit compared with placebo):		
11 double-blind RCTs (4029 pts) (Very similar to placebo-controlled trials with respect to typical pt characteristics and exclusion of pts w/ recent IACS)	**Low** Large # studies. Lack of or unclear statistical significance in some studies. Some inconsistency in direction of findings. Applicable to PICO. No analyses of publication bias available.	***Response rates in HA arms:*** 30%-81% ***Response rates in placebo arms:*** 27%-68% ***Absolute rate differences:*** 0.03-0.16 in studies favoring HA (9 RCTs); –0.02 to –0.03 in studies favoring placebo (2 RCTs) ***NNT values:*** 7-16 in studies favoring HA; –33 to –46 in studies favoring placebo; 8-16 for f/u at 2-3 mos (3 RCTs) ***Caution:*** (1) Composite measures do not allow an assessment of whether pain, function, or both improved. (2) Whether most or many pts benefit cannot be assessed because of variable response rates across trials (lower in strictly ITT analyses).
As Add-on to Usual Care Alone (likelihood of clinically relevant benefit in real-world setting):		
2 pragmatic RCTs (761 pts) (control groups received usual care, not placebo injection)	**Moderate** Small # studies. Randomized; lack of blinding consistent w/ study objectives; good completion rates. Consistent findings. Applicable to PICO. No analyses of publication bias available.	All differences statistically significant. ***Response rates in HA arms:*** Pain, 69%-88%; composite, 31%-65% ***Response rates in placebo arms:*** Pain, 40%-68%; composite, 14%-40% ***Absolute rate differences:*** 0.15-0.27 ***NNT values:*** 4-6 ***Caution:*** Publication dates 2002 and 2003; Canadian and French settings. Uncertain generalizability of results to current U.S. practice.
Versus NSAIDs:		
4 RCTs described in Bellamy review	**No quality assessment** Good-quality SR No study quality ratings in Bellamy review. Fair consistency. No studies published since 2006. Applicable to PICO. No analyses of publication bias available.	Comparable efficacy.
Versus Intraarticular Corticosteroids:		
1 SR (7 RCTs (606 pts) (Bannuru 2009)	**Low** Fair- to good-quality MA Studies were of poor quality according	***Pooled estimates for effect on pain*** Favored IACS initially. Significantly favored HA at 11-16 wks.

Studies	Quality Assessment (see Quality Assessment Methods in TECHNICAL REPORT	Main Findings*, † (Results favored HA unless otherwise noted; 100-mm scales unless otherwise noted; 95% CI)
	to Bannuru review. No serious inconsistency. Applicable to PICO. No analyses of publication bias available.	At 17-26 wks: ***SMD** –0.39 (CI, 0.18-0.59)*; I^2=0
Versus Glucosamine and/or Chondroitin: No Evidence		

*When different studies used the same outcome measures, pooled estimates were expressed in terms of WMDs, referring to the between-group difference in pain or function score at follow-up or difference in improvement, depending on the particular meta-analysis. When different studies used different outcome measures, SMDs, also referred to as effect sizes, were calculated in lieu of WMDs.

†Heterogeneity was typically assessed according to I statistic (I^2) and was interpreted as follows: 25% = low heterogeneity, 50% = moderate, and ≥ 75% = high (Colen et al., 2012). In the review by Rutjes et al. (2012), heterogeneity was measured by τ^2 and interpreted as follows: 0.04 = low; 0.09 = moderate, 0.16 = high.

Key Question #1b: Do different viscosupplementation products vary in effectiveness?

Low-quality evidence, summarized in **Table 1b** (following this discussion), suggests that **hylan (Synvisc)** may have a superior benefit compared with that of non–cross-linked HA, but the magnitude of difference is unlikely to be clinically significant. To date, **low**-quality evidence suggests no difference in benefit between **low and medium molecular weight HA**. The Reichenbach review authors concluded that because of a lack of clear superior effectiveness over that of HAs, and an increased risk of local adverse events, use of hylan should be discouraged in research and clinical practice. Likewise, the Colen review authors concluded that due to conflicting evidence, it was not possible to determine that one brand of HA is more effective than another.

Differential effectiveness according to **FDA approval** could not be assessed because of **insufficient** evidence. None of the systematic reviews analyzed findings according to whether products were FDA-approved. In the 21 RCTs with sample sizes of n ≥ 200, more than half the trials used non–FDA-approved products or did not specify brand names. Among the trials that specified brands, no pattern of difference in the results was apparent between those trials that did and did not use FDA-approved products.

Table 1b. Summary of Findings, Key Questions #1b

Key: CI, confidence interval; PICO, Populations, Interventions, Comparators, Outcomes; pt(s), patient(s); FDA, Food and Drug Administration; MCID, minimal clinically important difference; RCT, randomized controlled trial; RR, relative risk; SMD, standardized mean difference; SR, systematic review

Studies	Quality Assessment (see Quality Assessment Methods in TECHNICAL REPORT	Main Findings (Results favored HA unless otherwise noted; 100-mm scales unless otherwise noted; 95% CI)
Hylan (Synvisc) vs Non–cross-linked HA		
3 SRS: Reichenbach 2007: 13 comparator RCTs (2085 pts) Colen 2012: 12 comparator RCTs (2492 pts) Rutjes 2012: 75 noncomparator RCTs (9722 pts) (sensitivity analysis; indirect comparison)	**Low** Study quality poor according to Reichenbach review; uncertain for other reviews. Inconsistency/imprecision. Applicable to PICO. No analyses of publication bias available.	***Pooled estimates*** Pain (Reichenbach 2007) ***SMD –0.27 (CI, –0.55 to 0.01)***; I^2=88%. No effect after 2 outliers removed (MCID defined as –0.30). Pain (Colen 2012) ***SMD –0.07 (CI, –0.24 to 0.10)***; I^2=72%. Inconsistency across trials. Pain (Rutjes 2012) Subset analysis: –0.53 vs –0.29 (*P*=0.099) Adverse events (Reichenbach 2007) ***RR 1.91 (CI, 1.04-3.49)*** (6 RCTs w/ consistent findings favoring non–cross-linked HA) ***Clinical relevance*** Estimates are less than the MCID defined for the Reichenbach review (–0.30).
By Molecular Weight		
1 SR (Reichenbach 2007): 13 RCTs (2085 pts) 1 RCT (Petrella 2011) (200 pts)	**Low** Generally poor study quality Metaregression is an indirect substitute for trials designed to compare molecular weights	***Molecular weight as continuous variable*** Pain (Reichenbach 2007): Metaregression showed **no association**. Pain (Petrella 2011): Relative pain improvement w/ combination of **high and low** molecular weight **slightly greater than** for **high or low** molecular weight **alone** (*P*<0.001). **NS difference favoring low** molecular weight **in comparison of high and low** weight arms.
FDA vs Non-FDA Approval: Insufficient evidence (no analyses within RCTs or MAs; missing information on brands)		

Key Question #2: What are the adverse effects associated with viscosupplementation in patients with OA of the knee?

Key safety evidence is summarized in **Table 2** (following this discussion)**.** There is **high-quality** evidence that viscosupplementation is a safe procedure, at least in the **short term**. According to the 2007 Samson review, as well as the recently published RCTs selected for the update report, the most common adverse events after viscosupplementation include injection site pain, joint pain or swelling, and joint effusion. Large case series suggest that the absolute overall rate of short-term adverse events is approximately 2% to 3% per injection with the use of hylan (Synvisc), and that the rate is smaller—possibly < 1% per patient for a 3-injection course—with the use of a non–cross-linked HA product. The Rutjes meta-analysis of 25 RCTs resulted in a relative risk (RR) of 1 (no increased risk) with a very small confidence interval for overall occurrence of adverse events. Pooled estimates in the Rutjes review indicate that compared with a saline injection or other control, HA injections are associated with a 34% greater incidence of local adverse events such as flares (hot, painful, swollen knee within 24 to 72 hours after an injection) and effusions. Similarly, the Bellamy review found that the only adverse event for which there was a difference between HA and placebo injection was pain at the injection site. Another possible, although rare, local adverse event is pseudosepsis, which mimics true sepsis and may constitute a severe reaction. However, the literature describes local events as being generally transient.

The 2012 Rutjes review reported a pooled estimate suggesting a 40% increase in *serious* adverse events, comparing viscosupplementation with some form of control (saline injection, usual care, or other). However, many of the serious events that were counted in the Rutjes analysis were systemic and, as acknowledged by the review authors, of unknown relationship to the HA injection. The review did not comment on whether clinical history and the length of time between treatment and the occurrence of systemic events were sufficient to support a suspicion of a possible causal relationship. (Among the study articles retrieved for this report, trials followed patients 3 to 12 months.) The overall crude rate of serious events enumerated in the Rutjes review was 0.9% per patient; the absolute risk difference between viscosupplementation and the control treatment would be < 0.9 percentage points. In the 21 double-blind trials with sample sizes ≥ 200, no serious *treatment-related* adverse events were observed, no serious adverse events at all were observed, or there was no mention of the issue of serious adverse events. The Rutjes review, HA-versus-NSAIDs comparator trials, and a pragmatic trial reported a *lower* incidence of gastrointestinal events in HA arms. The 2 pragmatic trials reported conflicting results regarding the overall safety of viscosupplementation versus usual care but also did not report any serious event.

No data regarding **long-term** safety are available (**insufficient evidence**). Two fair-quality RCTs (Euflexxa in one and Gel-One in the other) suggested similar risk between a first and second course of treatment. However, 2 case series have demonstrated a much higher incidence of adverse events during a second course of treatment than during a first course, but these data pertain only to hylan (Synvisc). Most studies have not followed patients for longer than 3 to 6 months and none have followed patients for longer than a year. However, the literature does not reflect any concerns about long-term safety.

Table 2. Summary of Findings, Key Questions #2

Key: CI, confidence interval; f/u, follow-up; GI, gastrointestinal; grp(s), group(s); HA, hyaluronic acid; MAUDE, Manufacturer and User Facility Device Experience; NR, not reported; NS, not (statistically) significant; OA, osteoarthritis; pt(s), patient(s); RCT, randomized controlled trial; RR, relative risk; SR, systematic review

Studies	Main Findings (Results favored HA unless otherwise noted; 100-mm scales unless otherwise noted; 95% CI)
Any Adverse Event:	
1 SR: Rutjes 2012: 25 RCTs (5204 pts) **3 RCTs published since SR** (1114 pts) (Altman et al., 2011; Navarro-Sarabia et al., 2011; Strand et al., 2012a) **4 case series** (3 series as described in Samson review; 1 recently published [Foti 2011])	***Pooled estimates (Bellamy 2006)*** 12 adverse events: No difference Pain at injection site: RR, 1.7 (95% CI, 1.19 to 2.44; *P*=0.004) (# RCTs NR) ***Pooled estimate (Rutjes 2012)*** All trials: ***RR 1.04*** *(CI, 0.99-1.09)*; no heterogeneity n=100/grp and adequate assessor blinding: ***RR 1.01*** *(CI, 0.96-1.06)*; no heterogeneity (11 RCTs, 3214 pts) ***Recent RCTs*** Similar rates between HA and placebo. ***Case series rates (f/u ≤2 wks after last injection)*** Hylan (Synvisc) 5.3%-8.3% persons (2 series, 4589 pts, mix of first-time and repeat courses of treatment) 2.1%-2.7% injections (2 series, 5468 injections, mix of first-time and repeat courses of treatment) Non–cross-linked HA 0.8% pts (1 series, 1266 pts; f/u 2 wks after 3rd injection; some hip OA included)
Local Adverse Event:	
1 SR: Rutjes 2012: 31 RCTs (5241 pts) **1 narrative review** Goldberg 2004 **1 case report** Idrissi 2012	***Rutjes review*** Local, any: ***RR 1.34*** *(CI, 1.13-1.60)*; no heterogeneity RR 1.51 (significant) for flares and 1.34 (NS) for effusions. Neither event rates nor # events were reported. ***Goldberg review and case report*** 29 cases of pseudosepsis, all but 1 following a hylan as opposed to HA injection, and typically after ≥2 injections within a course of treatment
Serious Adverse Event: Very small increased risk (causality uncertain)	

Studies	Main Findings (Results favored HA unless otherwise noted; 100-mm scales unless otherwise noted; 95% CI)
1 SR: Rutjes 2012: 14 RCTs (3667 pts) **22 RCTs** w/ sample size ≥200 (overlap w/ the 14 RCTs analyzed in Rutjes review) **4 case series** (>10,987 injections)	***Pooled estimates (RCTs)*** All trials w/ data: ***RR 1.41*** *(CI, 1.02-1.97)*; no heterogeneity. Serious events (n=35) included 10 gastrointestinal events (2 HA, 8 control), 7 cardiovascular events (5 HA, 2 control), 6 cases of cancer (6 HA, 0 control), and 6 cases of musculoskeletal disorders (4 HA, 2 control). Crude overall rate (both arms included): 0.9% (35/3667) n=100/grp and adequate assessor blinding: RR 1.55 (CI, 1.07-2.24); no heterogeneity (11 RCTs) ***Individual RCT results*** No serious adverse events, no serious treatment-related events, or no mention. ***Case series*** 1 event (large effusion w/ synovitis) in 3 series (all involving hylan) described in Samson review. 0.08% of pts in a 2011 series (pain or swelling at injection site, other). ***Note on pseudosepsis*** Evidence from a narrative review, FDAs MAUDE database, and a recent case report document this reaction as a possibility, sometimes serious enough to require emergency treatment.
Versus Other Alternatives or Usual Care: Mixed results	
1 SR: Bellamy 2006 (6 RCTs) **2 pragmatic RCTs** (773 pts)	***Vs NSAIDs (Bellamy 2006)*** More local reactions but fewer systemic adverse events with HA. ***Vs usual care (2 pragmatic RCTs)*** Raynauld 2002: All events, 52% vs 68% (*P*=0.0116); no serious events in HA arm. Kahan 2003: All events, 44.2% vs 31.9% (significance NR); GI events, 3.5% vs 11.9%; no serious events mentioned.
Long Term: Mixed results	
2 RCTs (691 pts) **2 case series**	Incidence during 2nd round of treatment similar to incidence during 1st round; 1 RCT, non–cross-linked HA (Euflexxa; Altman 2011); 1 RCT, cross-linked HA (Gel-One; Strand 2012b). Per-person or per-injection rate much higher during a repeat course (2 series; hylan both series.
Quality, Overall Short-Term Safety **High.** Relative rates in large volume of RCTs and real-world data on absolute rates from case series are consistent; precise pooled estimates. **Quality, Long-Term Safety** **Insufficient.** Mixed results concerning safety of repeat course. No trials followed pts >1 year; most followed pts 3-6 mos. NOTE: Evidence quality does not speak to direction, magnitude of effects, or severity of effects.	

Key Question #3: Does the effectiveness of viscosupplementation vary by subpopulation defined by these factors: age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), and prior treatments?

Individual trial data regarding the influence of age and disease severity have been conflicting, but a meta-regression and subset analysis of 20 trials suggested an association of **age ≤ 65 years** and **less severe OA** with greater benefit. Evidence pertaining to age and disease severity is of **low** quality because the review did not present the results in a manner that allows an assessment of the magnitude of difference or the precision of the estimate, and the 2004 publication date means that a substantial volume of currently published trials were not represented in the analysis. Although 2 trials failed to detect an association between effect and sex or body mass index (BMI), this evidence is of very low quality due to the small number trials, a substantial, albeit nonsignificant, difference according to BMI in 1 of the trials, and the lack of quantitative estimates in the other trial. For other factors, no evidence was available, the results were conflicting between 2 trials, or the issue was evaluated in only 1 trial. Thus, evidence pertaining to differential effects according to **race/ethnicity**, **gender**, **primary versus secondary OA**, **disease duration**, **weight (body mass index)**, **and prior treatments is insufficient**.

Key Question #4: What are the cost implications and cost-effectiveness of this type of product?

An online source suggested that various HA products are comparably priced, with injection kit costs for a standard course of treatment ranging from approximately $300 to $400. According to this site, the purchase price for Synvisc One was comparable to the price for 3 doses (standard course of treatment) of the more conventional Synvisc product. No price information was available for the newest single-injection product, Gel-One.

No definitive statement can be made regarding the cost-effectiveness of viscosupplementation. Two economic evaluations were based on pragmatic trials evaluating viscosupplementation as it is used in practice, i.e., as an add-on to usual or appropriate care. Both trials evaluated hylan (Synvisc). (The 2 trials were the same as those referenced in the discussion of viscosupplementation as an add-on treatment in the findings for Key Question #1a) Both of these economic evaluations were conducted from a societal perspective (Canada and France). The **Canadian** study reported a 1-year cost-utility ratio (**CAD 10,000/QALY**, **1999 costs**; **USD 11,273/QALY**, **2013 dollars**), which was considered by the authors to be acceptable, as well as a cost-effectiveness ratio (**CAD 2505/QALY per patient improved**, **1999 costs**; **USD 2824/QALY**, **2013 dollars**). The **French** study reported **comparable costs** with and without the use of viscosupplementation, and the trial on which the French evaluation was based showed HA to be more effective than usual care alone. Thus, the authors did not compute a cost-effectiveness or cost-utility ratio.

Two economic evaluations used placebo-controlled trials as a source for effectiveness assumptions; the trials involved non–cross-linked (non-hylan) HA products not available in the U.S. A modeling study (societal perspective, **Taiwan**) compared viscosupplementation with 2 NSAIDs (celecoxib and naproxen) for patients who had not obtained adequate relief, had not yet tried NSAIDs, and had declined total knee replacement. HA was more expensive and more effective than either of the 2 NSAIDs, and celecoxib was more expensive and more effective than naproxen. The model predicted the following incremental cost-effectiveness ratios (ICERs), comparing each of the 3 products with no change in treatment as the reference: **HA versus naproxen**, **$33,148/QALY**, **2001 costs** (**$42,652 in 2013 dollars**)

(calculated with data from the study report); **celecoxib versus naproxen**, **$21,226/QALY**, **2001 costs** (**$27,312 in 2013 dollars**); **HA versus celecoxib**, **$42,000/QALY**, **2001 costs** (**$54,042 in 2013 dollars**). The authors concluded that celecoxib was a cost-effective alternative to naproxen but that HA would not be affordable in the Taiwanese setting. Sensitivity analysis showed that the results were dependent on assumptions of cost and effectiveness. An informal, non–peer-reviewed cost-effectiveness evaluation conducted in the development of **NICE guidelines** suggested that according to 1 trial, the cost-effectiveness ratio exceeded the National Health Service cost-effectiveness threshold and according to another trial, placebo was both more effective and less expensive than HA injection.

Evidence pertaining to the cost-effectiveness of viscosupplementation has numerous deficiencies:

- The number of cost analyses and cost-effectiveness studies is very small, methodological limitations have been noted for most of these studies, and the more meaningful studies are > 10 years old.
- Evaluations were not conducted in the United States. The results may not apply to the U.S. due to differences in prices, reimbursement policies, standards of care, and definitions of cost-effectiveness limits.
- The most meaningful studies used hylan (Synvisc) and the results may not be generalizable to non–cross-linked HA products.
- There were no cost data or cost-effectiveness data specific to single-injection treatments, now possible for 2 products (Synvisc One, Gel-One).
- There was no cost-effectiveness analysis of HA versus intraarticular corticosteroid injection.
- Three of the economic evaluations were performed from a societal perspective, taking productivity losses into account, and thus may not be generalizable to a payer perspective.

Practice Guidelines

See **Practice Guidelines** in the **TECHNICAL REPORT** for additional detail.

The 4 guidelines selected for this update report were considered to be of good quality. Two organizations—the American College of Rheumatology (ACR) and the American Academy of Orthopaedic Surgeons (AAOS)—have replaced the guidance described in the 2010 report with more negative recommendations regarding viscosupplementation for OA of the knee. The National Institute for Health and Care Excellence (formerly the National Institute for Health and Clinical Excellence) (NICE) previously made a negative recommendation that has not been updated. Guidance issued by the Osteoarthritis Research Society International (OARSI) now provides an update literature review unavailable at the time of the 2010 report, but OARSI has not changed the previous positive although weak endorsement of viscosupplementation for knee OA.

Table 3. Summary of Practice Guidelines

Key: AAOS, American Association of Orthopaedic Surgeons; ACR, American College of Rheumatology; HA, hyaluronic acid; NICE, National Institute for Health and Care Excellence; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; VAS, visual analog scale

Sponsor, Title	Relevant Recommendations	Quality/Comments
AAOS (2013)	Cannot recommend using HA for patients with symptomatic OA of the knee.	6 (A number of eligible RCTs seem to be missing; literature review findings are consistent with more inclusive systematic reviews. No apparent consideration of comparative safety.)
ACR (Hochberg et al., 2012)	No evidence-based recommendation regarding the use of intraarticular HA. Conditional recommendation tramadol, duloxetine, or intraarticular HA in lieu of oral NSAIDs for elderly individuals (≥75 years of age). *Not evidence based.*	5 (Literature search only through December 2010.)
NICE (2008)	Intraarticular HA injections are not recommended for the treatment of OA.	Rated as "good" in 2010; no numerical score.
OARSI (Zhang 2007, Zhang 2008, and Zhang 2010)	Injections of intraarticular hyaluronate may be useful in patients with OA of the knee (level of evidence Ia, strength of recommendation 64% on a 100-point VAS).	6 (Possible corporate influence and somewhat outdated.)

Selected Payer Policies

See **Selected Payer Policies** in the **TECHNICAL REPORT** for additional detail and links to policy documents.

Aetna considers viscosupplementation medically necessary for members with symptomatic OA of the knee, according to American College of Rheumatology (ACR) criteria, when physical therapy and pharmacological (may or may not include NSAIDs) treatment have not resulted in functional improvement after ≥ 3 months and when intraarticular steroid injection has not provided adequate relief. Aetna considers additional series of injections as medically necessary when it has been ≥ 3 months since the last series of injections and the medical record documents a reduction in analgesics or anti-inflammatory medication during the 3 months following the previous series as well as an improvement in pain and function.

The Oregon Health Evidence Review Commission (HERC) has concluded that viscosupplementation should not be covered for treatment of pain associated with OA of the knee. This conclusion is based on a review of 2 reports prepared in 2010 by Hayes, Inc. for the Medicaid Evidence-based Decisions (MED) Project and for the Washington Health Technology Assessment Program and a review of a 2007 Evidence Report prepared for the Agency for Healthcare Research and Quality (AHRQ) (Samson review).

No CMS National Coverage Determination (NCD) was identified for viscosupplementation. No coverage policy per se was identified for GroupHealth or for Regence BCBS. However, the medication policies of

both GroupHealth and Regence require prior authorization and limit coverage to 2 courses of treatment per year.

Overall Summary and Discussion

Evidence-Based Summary Statement

There is consistent evidence demonstrating that viscosupplementation results in lower mean pain scores and improves mean function scores a few weeks after treatment, with benefit peaking by 3 months. However, the magnitude of benefit of HA may be too small to be clinically important for many if not most patients. Although very comprehensive meta-analyses have reported effects at approximately 3 months that may be interpreted as meeting or slightly exceeding a minimal clinically important difference (MCID), placebo-controlled trials reporting responder rates have not established that viscosupplementation substantially increases the likelihood of clinically meaningful improvement. Two pragmatic trials have shown viscosupplementation to increase the likelihood of clinically meaningful improvement when it is added to usual care, but these trials were conducted more than 10 years ago in non-U.S. settings. There is a much greater volume of evidence regarding impact on pain than on function, and many studies did not follow patients beyond 3 months. Therefore, the impact of viscosupplementation on the eventual recovery of function is uncertain. Viscosupplementation and NSAIDs appear to provide comparable benefit. Compared with intraarticular corticosteroid injection, viscosupplementation appears to confer longer-lasting benefit, but the evidence was considered low quality. No effect on overall QOL has been conclusively demonstrated.

HA injections may produce local transient adverse effects. Although serious local effects are possible and a meta-analysis has suggested an increase in serious systemic events, both local and systemic serious adverse events following HA injection are very rare and the relationship between systemic events and HA injection is unclear. There is some evidence that gastrointestinal events are less common following HA injection when HA injection is compared with NSAIDs or with control groups (placebo or usual care).

Future RCTs should report results in terms of both mean change and responder rates (proportion of patients achieving clinically important improvement according to a standard definition). Trials should also adopt a standard definition of treatment-related adverse events. Trials powered to test for differential effect according to prior and concomitant use of medication or intraarticular corticosteroids are needed. Trials with preplanned subgroup analyses and sufficient power are also needed to determine the patient and disease characteristics that are associated with clinically important benefit. Pragmatic trials designed to measure the effectiveness of viscosupplementation in real-world practice are needed. In the absence of randomized trials designed to answer these questions, large cohort studies could make meaningful contributions to the evidence base. Lastly, more studies assessing the overall patient utility (effect on QOL) and current, U.S.-based evaluation of cost-effectiveness are needed.

Systematic Review Authors' Conclusions

The 2010 report relied primarily on the 2007 Samson review (technology assessment prepared for AHRQ). The authors of the 6 meta-analyses covered in the Samson review came to a variety of conclusions regarding the efficacy of viscosupplementation. These ranged from negative to moderately positive to strongly positive. However, the authors of the Samson review considered only 1 meta-

analysis (not the Bellamy review) to have reported data and analysis that fully supported the meta-analysis authors' conclusion. This was also the meta-analysis with a negative conclusion—that the clinical effectiveness of viscosupplementation has not been proven and that viscosupplementation may be associated with a higher risk of adverse events. The primary flaws that Samson and colleagues reported for the other, more positive meta-analyses were failure to search Embase and use of language restrictions. The conclusion of Samson and colleagues was that a clinical benefit has not been clearly demonstrated for viscosupplementation as a treatment for OA of the knee and that rigorous, multicenter RCTs are needed.

Among the 3 most comprehensive meta-analyses conducted to date, all of which were considered to be of good quality in terms of methods, the conclusions are somewhat variable. The authors of the 2006 Bellamy review (1 of the meta-analyses included in the 2007 Samson review) concluded that viscosupplementation is effective, especially at the 5- to 13-week postinjection period. The 2 most recent reviews (Colen et al., 2012; Rutjes et al., 2012), state conclusions similar to the conclusion of the 2007 Samson review. The Colen review acknowledged that a statistical effect was demonstrated but that its clinical relevance was debatable. The Rutjes review concluded that a benefit for pain and function is minimal or nonexistent and maintained that HA injection should be discouraged because of the increased risk of serious adverse events. The discrepancy between the conclusions of the Bellamy review, which is the most recent Cochrane review on the topic, and the conclusions of the more recent reviews is perhaps explained by the larger body of evidence available to the 2012 reviews. In addition, the Rutjes review made a more serious attempt to assess publication bias and difference in effect according to various aspects of study bias, and both the Colen and Rutjes reviews emphasized the lack of demonstrable clinical relevance. The Bellamy review put more emphasis on differential effectiveness by product, and their analysis of the hylan-versus-placebo trials available at the time suggested substantially larger effects than those observed for the entire class. However, subsequent meta-analyses of comparator trials have cast doubt on the superiority of hylan.

Gaps in the Evidence

- Limited quantity of data pertaining to treatment effect in real-world practice, and in terms of proportions of patients who have clinically important improvement (responder rates).
- A paucity of data regarding differential effectiveness and safety according to patient characteristics and previous treatment history.
- No studies comparing viscosupplementation with glucosamine and/or chondroitin.
- A paucity of evidence concerning efficacy and safety of different dosing regimens or repeat treatments.
- Unknown causal relationship between viscosupplementation and systemic adverse events.
- No long-term safety data.
- No recent economic evaluations and no evaluations conducted in the U.S. healthcare system.

Other Considerations

Magnitude of Benefit from Other Conservative Therapies

One of the sources cited for definitions of MCID, the IMMPACT group, suggested that among other factors, group differences in trials testing chronic pain treatments should be evaluated in light of the magnitude of benefit from alternative treatments (Dworkin et al., 2009). Research summarized in the latest practice guidelines issued by OARSI suggests that most other nonsurgical treatments for knee OA

also have uncertain or small-to-moderate mean effects (Zhang et al., 2010). The OARSI guideline authors calculated effect sizes for a range of treatments, using data from the largest and best-quality systematic review for each treatment modality, combined with data from RCTs published after the selected systematic review. They report the following effect sizes (standardized mean differences [SMDs]) for the placebo-controlled effect on pain:

> For treatment of knee OA: Strengthening, 0.32; aerobic exercise, 0.52; weight reduction, 0.20; heat/ice, 0.69 (NS); massage, 0.10 (NS); acupuncture, 0.35; intraarticular corticosteroid, 0.58; glucosamine hydrochloride, –0.02 (NS); chondroitin sulfate, 0.75
>
> For treatment of either knee or hip OA: Acetaminophen, 0.14; NSAIDs, 0.29; Cox-2 inhibitors, 0.44; glucosamine, 0.58
>
> For treatment of any OA: Opioids, 0.78

The effect sizes for function that were reported by Zhang et al. (2010) were of similar magnitude to those calculated for pain. The follow-up interval represented by these calculations was unclear. By way of comparison with effect sizes for other OA treatments, the effect sizes for viscosupplementation calculated in the largest meta-analysis to date (Rutjes review) were 0.37 for pain and 0.33 for function.

Possible Therapeutic Effect from Control Treatments

Some authors have pointed out that there is theoretically a therapeutic effect from saline injection, which is used as a "sham" treatment in most placebo-controlled trials, since the saline alters the joint environment. It is unknown whether the apparent effect of saline injection shown by some uncontrolled studies is a real effect, a placebo effect, or the result of concomitant treatments such as exercise or physical therapy. Furthermore, arthrocentesis (aspiration of synovial fluid), which may precede saline injection, can itself be considered a short-term symptomatic treatment since it involves removal of inflammatory cytokines and cartilage-degrading enzymes. To the extent that these effects create unintended differences favoring outcomes in the control groups, the magnitude of benefit demonstrated by placebo-controlled trials may be an underestimation of the true effect of HA injection (Bannuru et al., 2011; Colen et al., 2012). The results from 1 RCT (Lundsgaard et al., 2008) argue against the possibility of a therapeutic effect of saline injection: no difference in outcomes was observed between groups that received a 2-mL injection of saline, a 20-mL injection of saline, or HA injection. Subgroup analysis in the review by Rutjes et al. (2012) did show a smaller effect size in 54 trials that used sham (saline) control (SMD, –0.34) compared with 18 trials that used non-sham controls (SMD, –0.48), but the difference was nonsignificant (P=0.33) and the confidence intervals of the two estimates overlapped considerably.

Limitations of This Report

The following limitations apply to the methodology used for this report:

- As noted in the OARSI guidelines, systematic reviews and meta-analyses may not provide better evidence than RCTs, and determining which of several systematic reviews or meta-analyses provides the best evidence may also be difficult (Zhang et al., 2010). However, the authors of this update report retrieved the largest trials for key data to aid interpretation of systematic review results.
- This report does not address the comparative effectiveness of viscosupplementation versus nonconventional alternatives such as injections with blood products.

TECHNICAL REPORT

Background and Technology Description

Clinical Overview

Osteoarthritis (OA), the most common form of chronic articular disease, is characterized by damage to articular cartilage, changes in subchondral bone and osteophyte formation. Knee OA is the most common form of OA (Iannitti et al., 2011; Colen et al., 2012). Estimates of the prevalence of symptomatic knee OA range from 6% in all adults over the age of 30 to 9.5% to 12.1% in adults over the age of 60. One study has estimated that by age 85 years, nearly half of all adults will have developed symptomatic knee OA (Murphy et al., 2008). Knee OA is a key cause of disability among noninstitutionalized adults (CDC, 2011) and may lead to substantial productivity losses (Hermans et al., 2012).

To date, neither a known cure for OA nor a disease-modifying agent is available. Therefore, treatments focus on reducing pain, maintaining and/or improving joint mobility, and limiting functional impairment. Optimal management generally requires a combination of both nonpharmacological and pharmacological therapies. Nonpharmacological therapy includes education and support, physical therapy (including exercise), occupational therapy, and assistive devices. If pharmacological therapy is also required, good practice suggests starting with nonopioid analgesics (e.g., acetaminophen), followed by nonsteroidal antiinflammatory drugs (NSAIDs) (Colen et al., 2012; Hochberg et al., 2012; Rutjes et al., 2012). A 2009 Cochrane Review (Towheed et al., 2006) concluded that NSAIDs are more effective than acetaminophen for OA pain, and NSAIDs are the most commonly prescribed medications for OA. However, NSAIDs may cause serious adverse gastrointestinal and cardiovascular events. Topical analgesics may also be tried, especially for individuals at high risk of gastrointestinal side effects from NSAIDs. Opioids represent another option if NSAIDs are ineffective or contraindicated (Colen et al., 2012; Hochberg et al., 2012; Rutjes et al., 2012).

When oral and topical medications are inadequate, intraarticular injection of corticosteroids, typically following fluid aspiration according to some experts, is an option. However, intraarticular corticosteroid inject provides relatively short-lived benefits and is more appropriate for rapid relief of a flare-up. Additionally, repeated intraarticular injections of corticosteroids have the potential to cause postinjection flare, infection, and progressive, long-term cartilage damage. Another option when oral and topical medications have failed is intraarticular hyaluronic acid (HA), also referred to as hyaluronan or sodium hyaluronate. The treatment is often called viscosupplementation. HA is a naturally occurring, non-sulfated glycosaminoglycan polymer, sometimes referred to as a polysaccharide, and a normal component of synovial fluid and cartilage. It plays a major role in the maintenance of the structural and

functional characteristics of both the extracellular matrix of the cartilage and the synovial fluid. The viscous nature of the compound allows it to act as a joint lubricant, whereas its elasticity allows it to act as a shock absorber. In patients with osteoarthritic joints, the molecular weight of endogenous hyaluronan is reduced due to depolymerization and the concentration is reduced due to higher than normal clearance rates, and hence, the joint is more susceptible to damage. (Samson et al., 2007; Iannitti et al., 2011; Colen et al., 2012; Rutjes et al., 2012).
More than 20 HA products are marketed worldwide (Foti et al., 2011). Six HA products are currently marketed in the United States (CDER, 2013): Euflexxa, also known as Bio-HA (Ferring Pharmaceuticals), Gel-One (distributor Zimmer Inc.; manufacturer Seikagaku Corporation), Hyalgan (U.S. distributor Sanofi-Aventis; manufacturer Fidia Pharmaceuticals), Orthovisc (U.S. distributor DePuy Mitek Inc.; manufacturer Anika Therapeutics), Supartz, also known as Artz or Artzal (U.S. distributor Bioventus; manufacturer Seikagaku Corporation), and Synvisc and Synvisc-One (Genzyme).

Technology Description

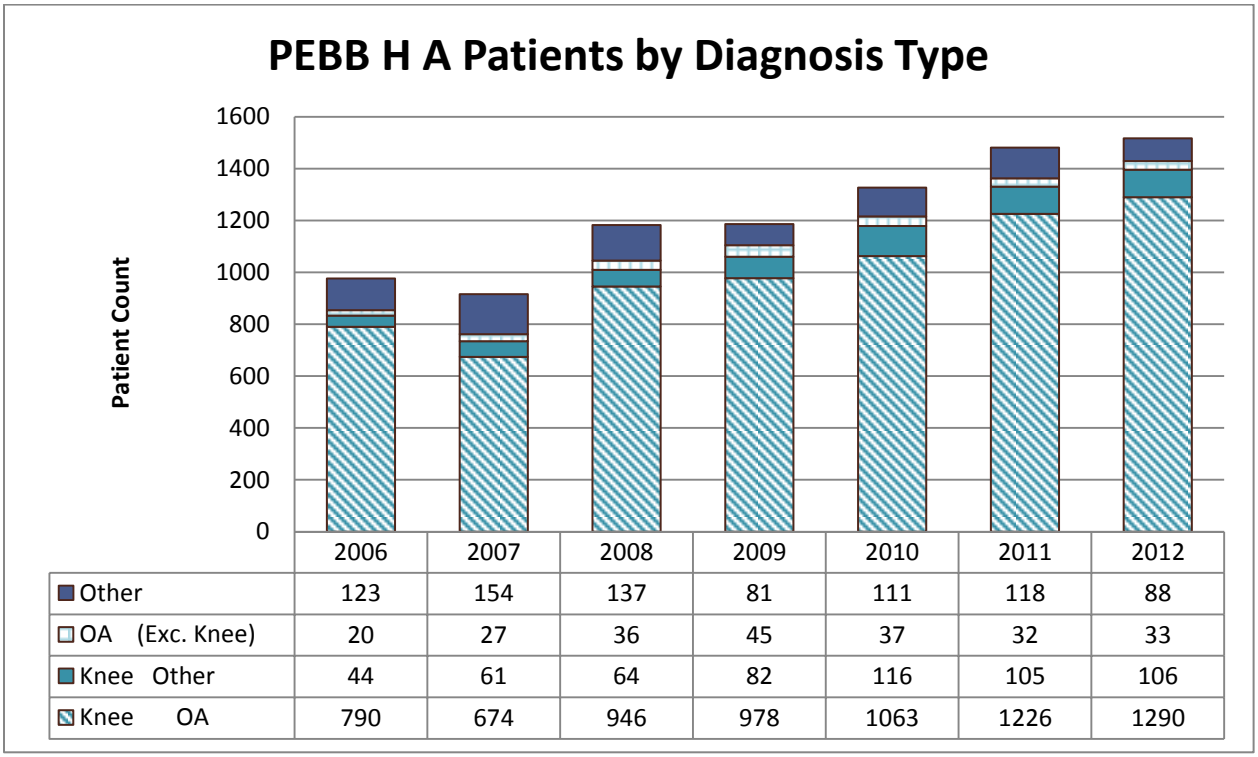
Hyaluronic products are derived from bacterial cells through a fermentation process, by extraction from rooster combs, or by cross-linking of rooster comb extractions. Hyaluronic products can be characterized by molecular weight. According to manufacturers' Prescribing Information publications, at least 4 of the FDA-approved products—Euflexxa, Hyalgan, Orthovisc, Supartz, and Synvisc/Synvisc-One—are high-molecular-weight HA products (Fidia Pharma, 2011; Genzyme, 2011; Bioventus, 2013; DePuy, 2013; Ferring, 2013). However, they represent a wide range of molecular weights and some authors characterize them as low-medium (Hyalgan, Orthovisc, Supartz), medium (Euflexxa), and high (Synvisc) (Samson et al., 2007). Lower (0.5 to 3.6 million Daltons) versus higher (6.0 million Daltons) molecular weight is associated with different protective biochemical mechanisms (Iannitti et al., 2011). Another characteristic that differentiates hyaluronic products is chemical structure. Both Synvisc and Gel-One are derivatives of HA and consist of chemically cross-linked chains of hyaluronan, which adds to molecular weight. Synvisc is often referred to as Hylan G-F 20, or simply *hylan* (Genzyme, 2011). The term *hylan* is not used to refer to Gel-One; nor was the molecular weight of Gel-One reported in any of the reviewed sources, but it is presumably at the higher end of the spectrum. Gel-One is the most recently approved viscosupplementation product for marketing in the U.S. (Strand et al., 2012a; VA, 2013).

Most viscosupplementation products require 3 to 5 injections for a single course of treatment. Synvisc One and Gel-One are designed for delivery as a single injection (Fidia Pharma, 2011; Genzyme, 2011; Bioventus, 2013; DePuy, 2013; Ferring, 2013; Zimmer, 2013). Any type of intraarticular injection carries the risk of adverse effects such as injection-related pain, post-injection flare, skin pigment changes, fat atrophy, and joint infection. Systemic events such as disruption of diabetes and hypertension control, facial flushing, inhibition of the hypothalamo-pituitary-adrenal axis, sepsis, and death and also been observed. With injection of any product into a joint, synovial fluid aspiration might be performed beforehand for faster relief of acute pain (Iannitti et al., 2011).

Washington State Utilization and Cost Data

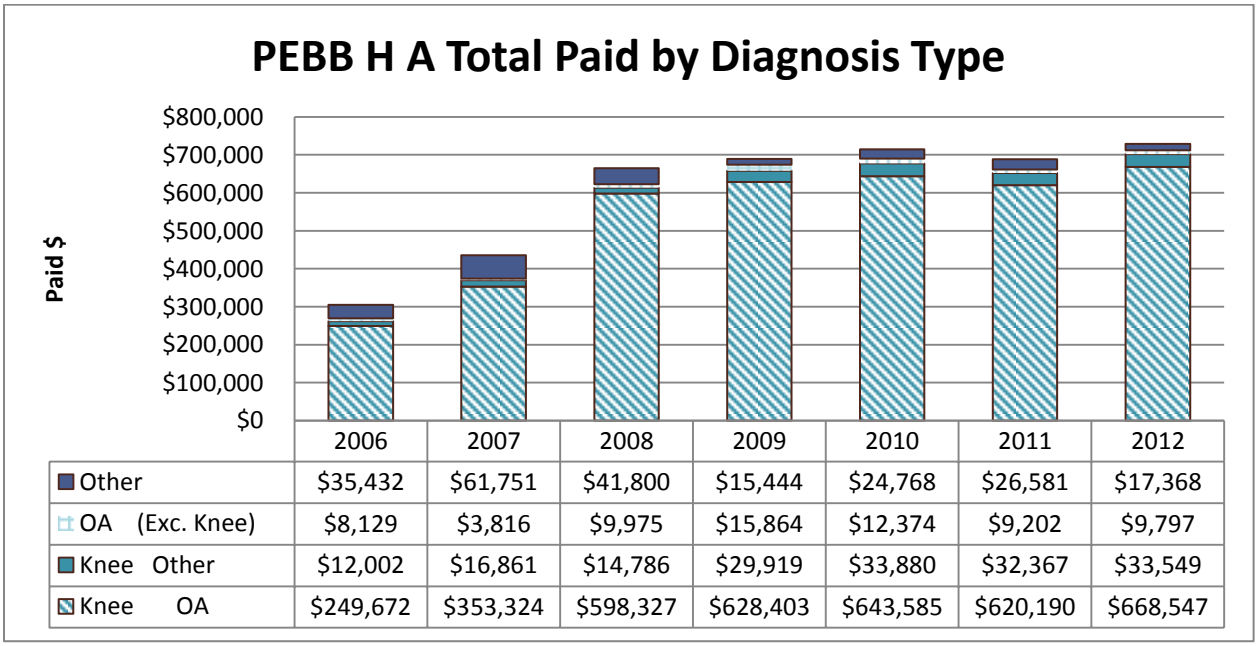
SECTION 1 – All Diagnoses

Figure 1a PEBB HA Patient Counts by Diagnosis Type, 2006-2012



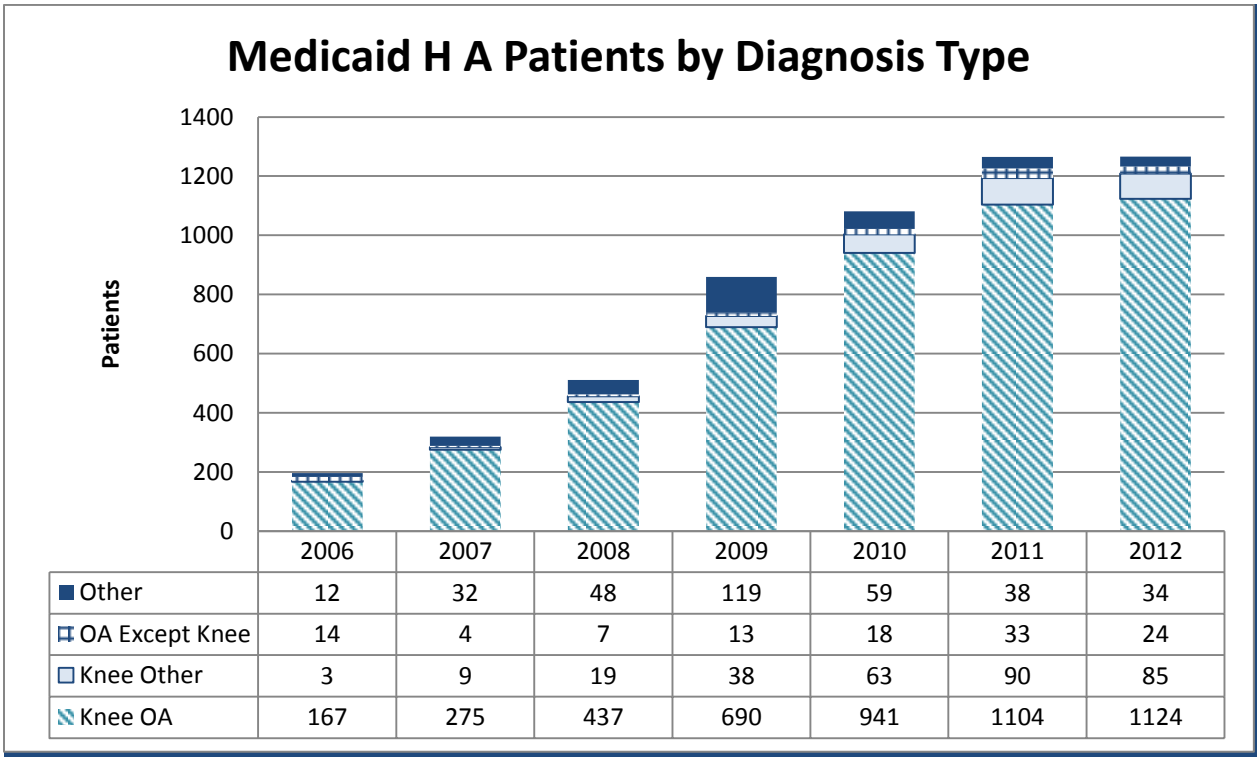
	2006	2007	2008	2009	2010	2011	2012
Other	123	154	137	81	111	118	88
OA (Exc. Knee)	20	27	36	45	37	32	33
Knee Other	44	61	64	82	116	105	106
Knee OA	790	674	946	978	1063	1226	1290

Figure 1b PEBB HA Total Paid by Diagnosis Type, 2006-2012



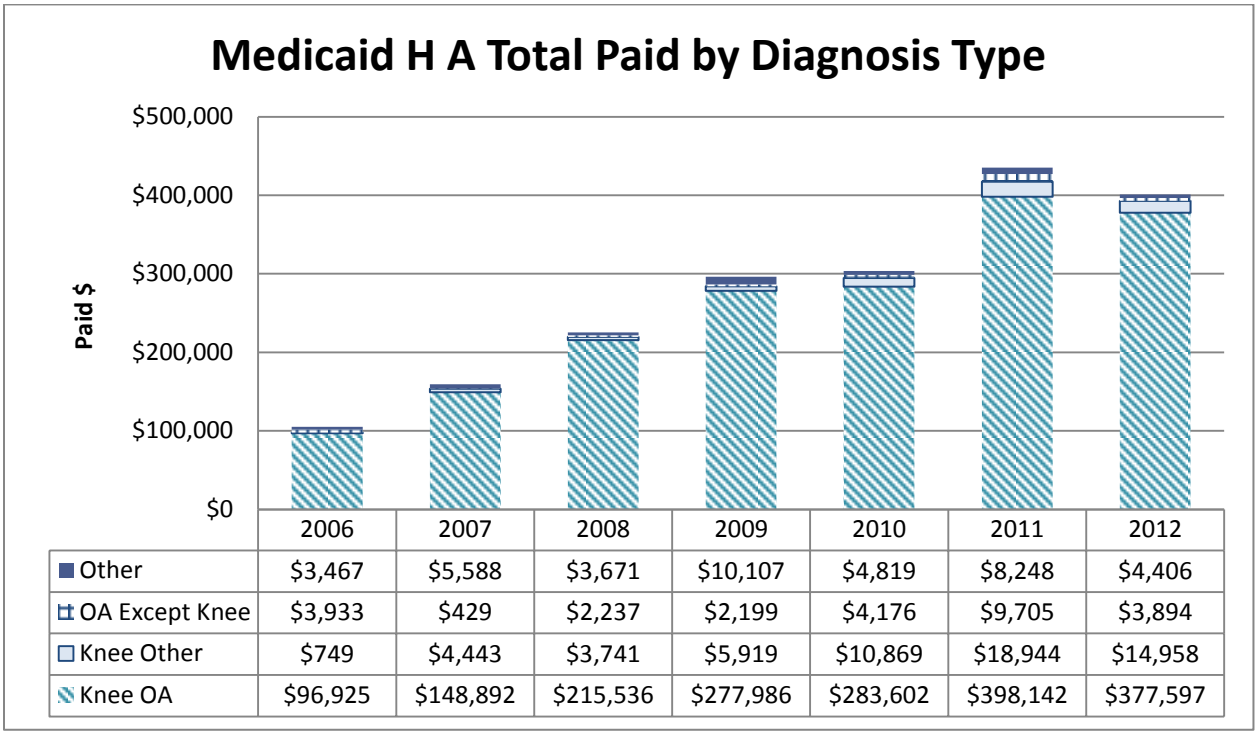
	2006	2007	2008	2009	2010	2011	2012
Other	$35,432	$61,751	$41,800	$15,444	$24,768	$26,581	$17,368
OA (Exc. Knee)	$8,129	$3,816	$9,975	$15,864	$12,374	$9,202	$9,797
Knee Other	$12,002	$16,861	$14,786	$29,919	$33,880	$32,367	$33,549
Knee OA	$249,672	$353,324	$598,327	$628,403	$643,585	$620,190	$668,547

Figure 1c Medicaid HA Patients by Diagnosis Type, 2006-2012



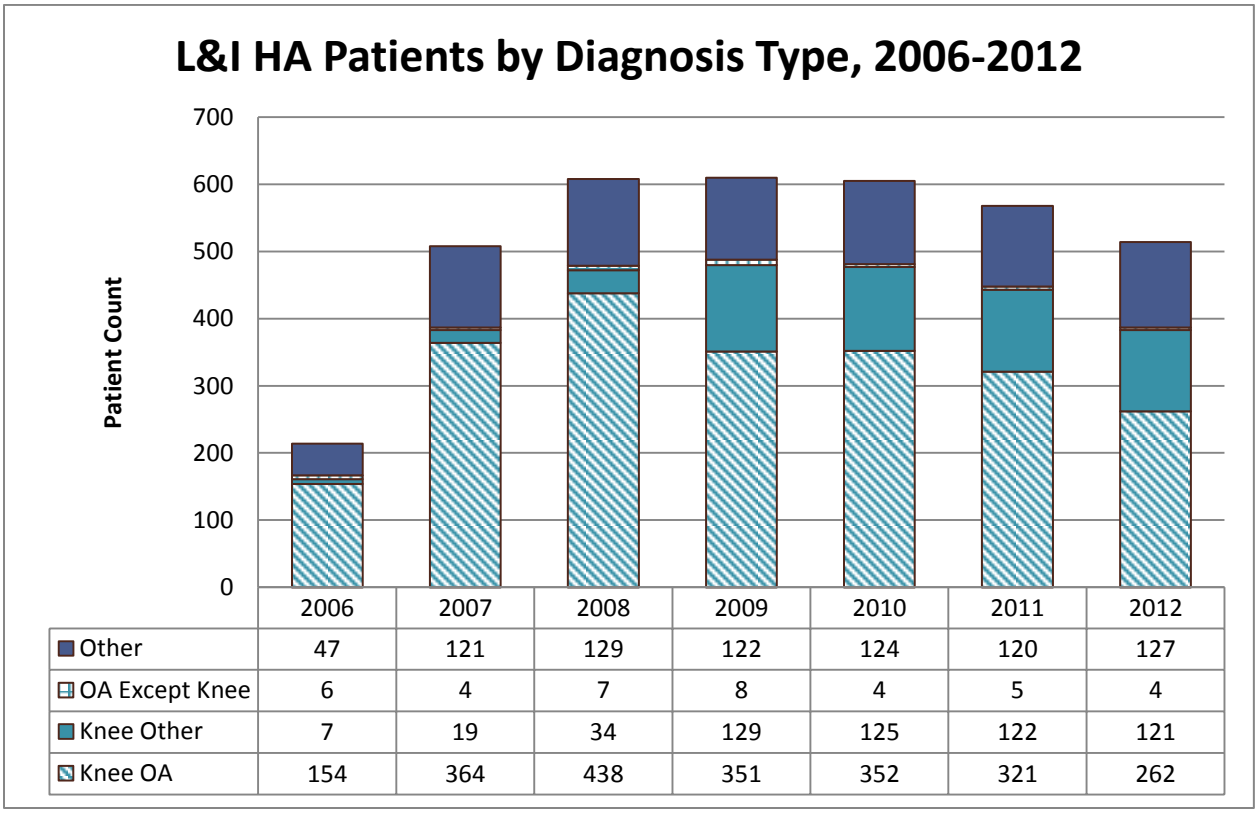
	2006	2007	2008	2009	2010	2011	2012
Other	12	32	48	119	59	38	34
OA Except Knee	14	4	7	13	18	33	24
Knee Other	3	9	19	38	63	90	85
Knee OA	167	275	437	690	941	1104	1124

Figure 1d Medicaid HA Total Paid by Diagnosis Type, 2006-2012



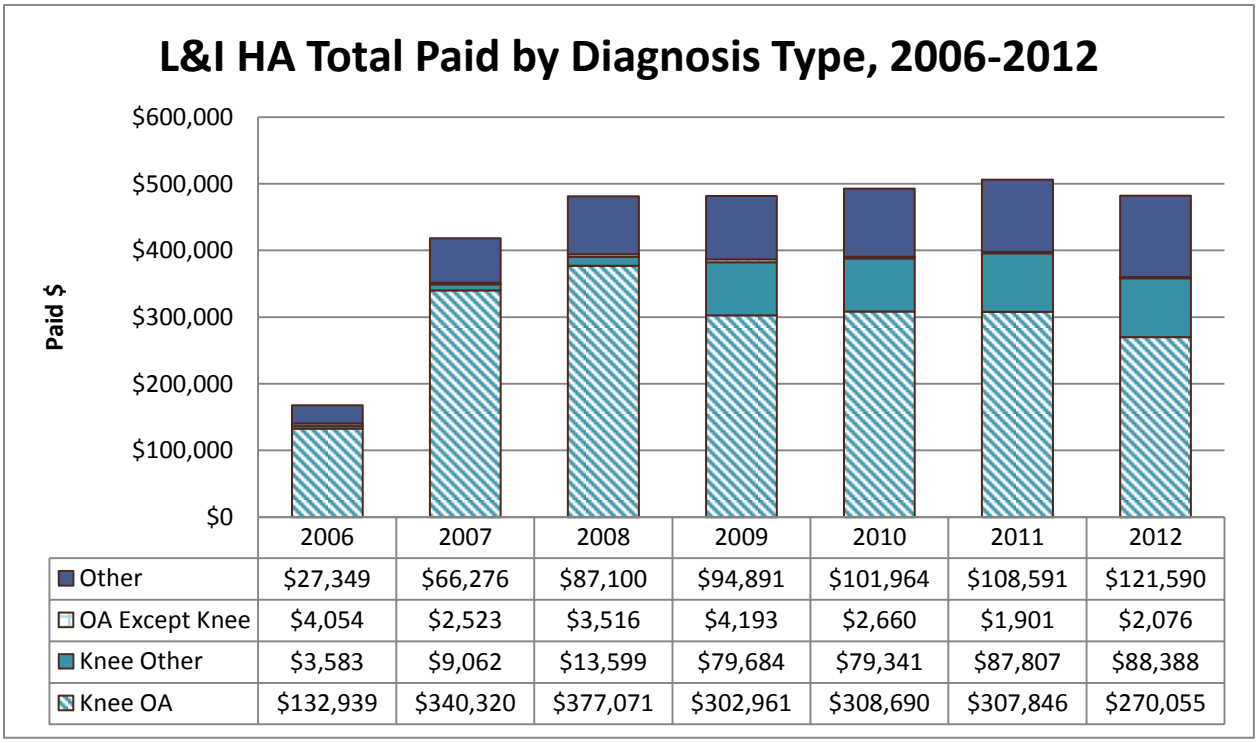
	2006	2007	2008	2009	2010	2011	2012
Other	$3,467	$5,588	$3,671	$10,107	$4,819	$8,248	$4,406
OA Except Knee	$3,933	$429	$2,237	$2,199	$4,176	$9,705	$3,894
Knee Other	$749	$4,443	$3,741	$5,919	$10,869	$18,944	$14,958
Knee OA	$96,925	$148,892	$215,536	$277,986	$283,602	$398,142	$377,597

Figure 1e L&I HA Patient Count by Diagnosis Type, 2006-2012



	2006	2007	2008	2009	2010	2011	2012
Other	47	121	129	122	124	120	127
OA Except Knee	6	4	7	8	4	5	4
Knee Other	7	19	34	129	125	122	121
Knee OA	154	364	438	351	352	321	262

Figure 1f L&I HA Total Paid by Diagnosis Type, 2006-2012



	2006	2007	2008	2009	2010	2011	2012
Other	$27,349	$66,276	$87,100	$94,891	$101,964	$108,591	$121,590
OA Except Knee	$4,054	$2,523	$3,516	$4,193	$2,660	$1,901	$2,076
Knee Other	$3,583	$9,062	$13,599	$79,684	$79,341	$87,807	$88,388
Knee OA	$132,939	$340,320	$377,071	$302,961	$308,690	$307,846	$270,055

Figure 1g PEBB HA Top Diagnoses "Other" categories, 2009-2012

PEBB Top 5 Diagnosis Codes for "Other" Categories, 2009-2012	Total Allowed*	% of Knee OA Total Allowed*
Knee-Other		
JOINT PAIN-L/LEG	$116,951	3.4%
CHONDROMALACIA PATELLAE	$16,199	0.5%
TEAR LAT MENISC KNEE-CUR	$15,156	0.4%
TEAR MED MENISC KNEE-CUR	$12,005	0.3%
ARTHROPATHY NOS-L/LEG	$7,619	0.2%
Other		
CATARACT NOS	$6,685	0.2%
RHEUMATOID ARTHRITIS	$5,995	0.2%
GOUT NOS	$4,148	0.1%
JOINT EFFUSION-L/LEG	$3,262	0.1%
INFLAMM POLYARTHROP NOS	$3,154	0.1%

*Most recent 4 years only, HA only (no professional services)

Figure 1h Medicaid HA Top Diagnoses "Other" categories, 2009-2012

Medicaid Top 5 Diagnosis Codes for "Other" Categories, 2009-2012	Total Allowed*	% of Knee OA Total Allowed*
Knee-Other		
Joint pain-l/leg	$43,802	2.1%
Arthropathy NOS-l/leg	$9,552	0.5%
Chondromalacia patellae	$9,261	0.4%
Tear med menisc knee-cur	$3,140	0.2%
Int derangement knee NOS	$2,563	0.1%
Other		
Rheumatoid arthritis	$2,982	0.1%
Chronic pain NEC	$1,683	0.1%
Rotator cuff rupture	$1,346	0.1%
Pain in limb	$1,263	0.1%
Backache NOS	$989	0.05%

*Most recent 4 years only, HA only (no professional services)

Figure 1i L&I HA Top Diagnoses "Other" categories, 2009-2012

L&I Top 5 Diagnosis Codes for "Other" Categories, 2009-2012	Total Allowed*	% of Knee OA Total Allowed*
Knee-Other		
TRAUMATIC ARTHROPATHY, LOWER LEG	$43,827	5.5%
SPRAIN&STRAIN OF UNSPECIFIED SITE OF KNE	$36,689	4.6%
TEAR MEDIAL CARTILAGE OR MENISCUS KNEE C	$35,735	4.5%
CHONDROMALACIA OF PATELLA	$22,703	2.8%
PAIN IN JOINT, LOWER LEG	$19,562	2.4%
Other		
OSTEOARTHROSIS UNSPEC WHETHER GEN/LOC	$251,529	31.5%
CHONDROMALACIA	$5,694	0.7%
UNSPECIFIED OSTEOCHONDROPATHY	$3,340	0.4%
LUMBAR SPRAIN AND STRAIN	$2,869	0.4%
OLD BUCKET HANDLE TEAR OF MEDIAL MENISCU	$2,494	0.3%

*Most recent 4 years only, HA only (no professional services)

SECTION 2. Osteoarthritis of the Knee Diagnosis: Figure 2 Hyaluronic Acid (HA) Injections for Knee OA Summary

Agency/Year	2006	2007	2008	2009	2010	2011	2012	7 Yr Total[1]	Avg % Change[2]	
PEBB Average Annual Members	**159,569**	**172,009**	**204,804**	**210,501**	**213,487**	**212,596**	**212,684**		**1.0%**	
All PEBB HA Patients	**977**	**916**	**1183**	**1186**	**1327**	**1481**	**1517**		-1.2%	
PEBB Total Paid for Knee OA HA Injections	**$249,672**	**$353,324**	**$598,327**	**$628,403**	**$643,484**	**$620,190**	**$668,547**	**$3,761,947**	**-4.5%**	*
Average Paid per Procedure [3]	$139	$131	$152	$152	$169	$161	$174	$156	3.6%	
Average Paid, PEBB Primary**				$257	$270	$275	$309	$277	6.5%	
PEBB Primary % of Injections				45.6%	49.74%	45.76%	45.58%	30.31%		
PEBB Knee OA HA Counts										
Knee OA HA Patients	790	674	946	978	1063	1226	1290		0.3%	*
Knee OA HA Injections	1797	2695	3932	4937	4594	4359	4372	26,686	-4.3%	*
Average Injections per patient	2.3	4.0	4.2	5.0	4.3	3.6	3.4		-3.8%	
Average Injection courses per patient				1.6	1.6	1.5	1.5		-2.5%	
PEBB Comparator Procedure Counts										
Knee OA Diagnosis Patients**		3929	5174	5602	5906	6179	6472		-1.9%	*
Knee Arthroplasty Patients**		543	674	772	837	834	885		-0.6%	*
Medicaid Average Annual Members		**378,915**	**392,808**	**416,871**	**424,230**	**435,187**	**477,727**		**4.7%**	
All Medicaid HA Patients	**196**	**320**	**511**	**860**	**1081**	**1265**	**1265**		9.6%	*
Medicaid Total Paid Knee OA HA Inj	**$96,925**	**$148,892**	**$215,536**	**$277,986**	**$283,602**	**$398,142**	**$377,597**	**$1,798,681**	**7.8%**	
Average Paid per Procedure [2]	$196	$173	$151	$165	$93	$104	$100	$119	-12.3%	
Average Paid non-Medicare				$188	$205	$240	$254	$214	10.8%	
Non-Medicare % of Procedures				51.0%	30.7%	32.3%	28.2%	33.2%		
Medicaid Knee OA HA Counts										
Knee OA HA Patients	167	275	437	690	941	1104	1124		13.7%	*
Knee OA HA Injections	494	860	1426	1682	3042	3843	3782	15129	30.2%	*

Agency/Year	2006	2007	2008	2009	2010	2011	2012	7 Yr Total[1]	Avg % Change[2]	
Average Injections per patient	3.0	3.1	3.3	2.4	3,2	3.5	3.4		12.3%	
Average Injection courses per patient				1.2	1.1	1.2	1.2		1.1%	
Medicaid Comparator Procedure Counts										
Knee OA Diagnosis Patients**				9,714	10,770	11,447	10,866		-0.3%	*
Knee Arthroplasty Patients**				564	616	646	529		-5.4%	*
L&I Average Annual Members	**163,226**	**155,766**	**147,445**	**125,611**	**122,712**	**121,043**	**121,660**		**-1.0%**	
All L&I HA Patients	214	509	479	504	508	488	433		3.7%	*
L&I Total Paid for Knee OA HA Injections	$132,939	$340,320	$377,071	$302,371	$307,543	$307,286	$269,638	$2,037,168	2.4%	*
Average Paid per Procedure[3]	$621	$669	$787	$600	$605	$630	$623	$130	1.3%	
L&I Knee OA HA Counts										
Knee OA HA Patients	154	364	438	351	352	321	262		7.9%	*
Knee OA HA Injections	395	1136	1303	1131	992	954	868	6779	7.5%	*
Average Injections per patient	2.6	3.1	3.0	3.2	2.8	3.0	3.3		1.5%	
Average injection courses per patient				1.1	1.1	1.1	1.3		6.9%	
L&I Comparator Procedure Counts										
Knee OA HA Diagnosis Patients	7,888	8387	8578	8,028	7,375	7,168	7,209		2.5%	*
Knee Arthroplasty Patients	242	281	328	362	355	366	314		3.3%	*

*Avg % Change adjusted for population.

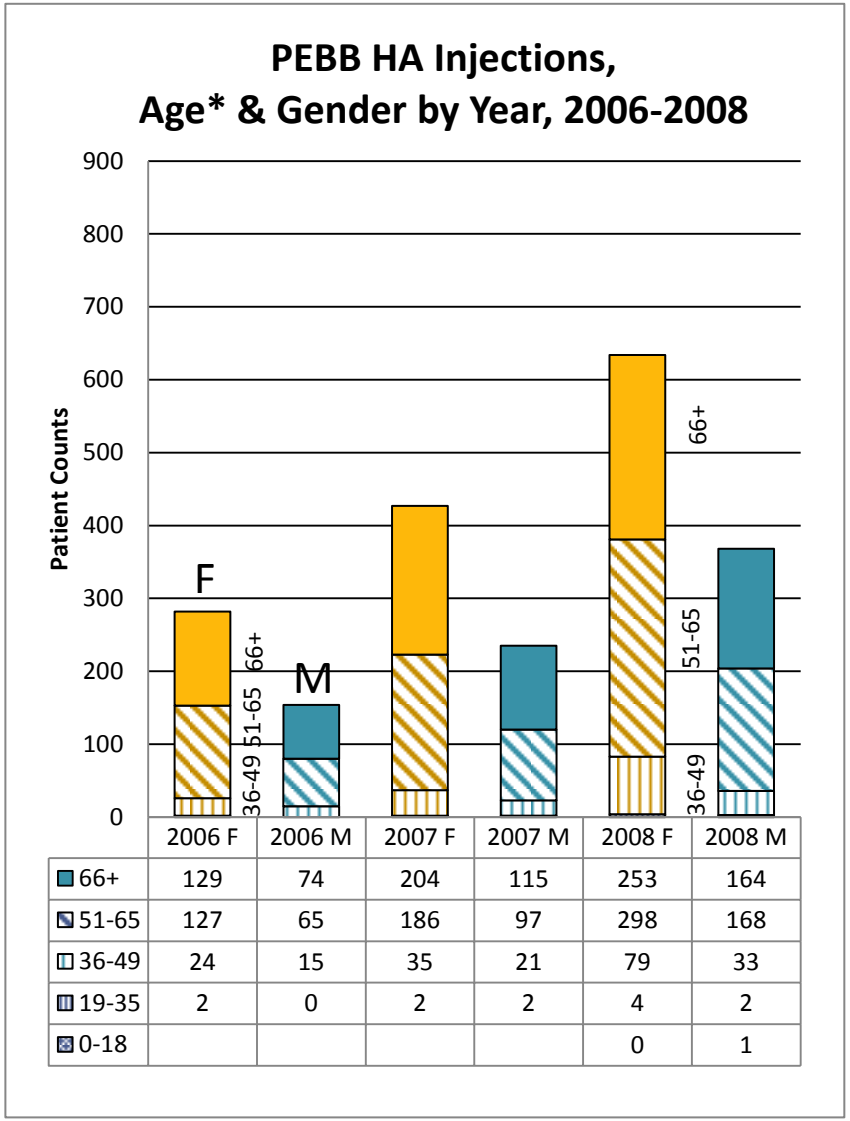
** Indicators for PEBB Primary (non-Medicare), injection courses, and comparator procedures were not available for all years prior to 2009.

[1] 7 year unique patient totals could not be reliably calculated.

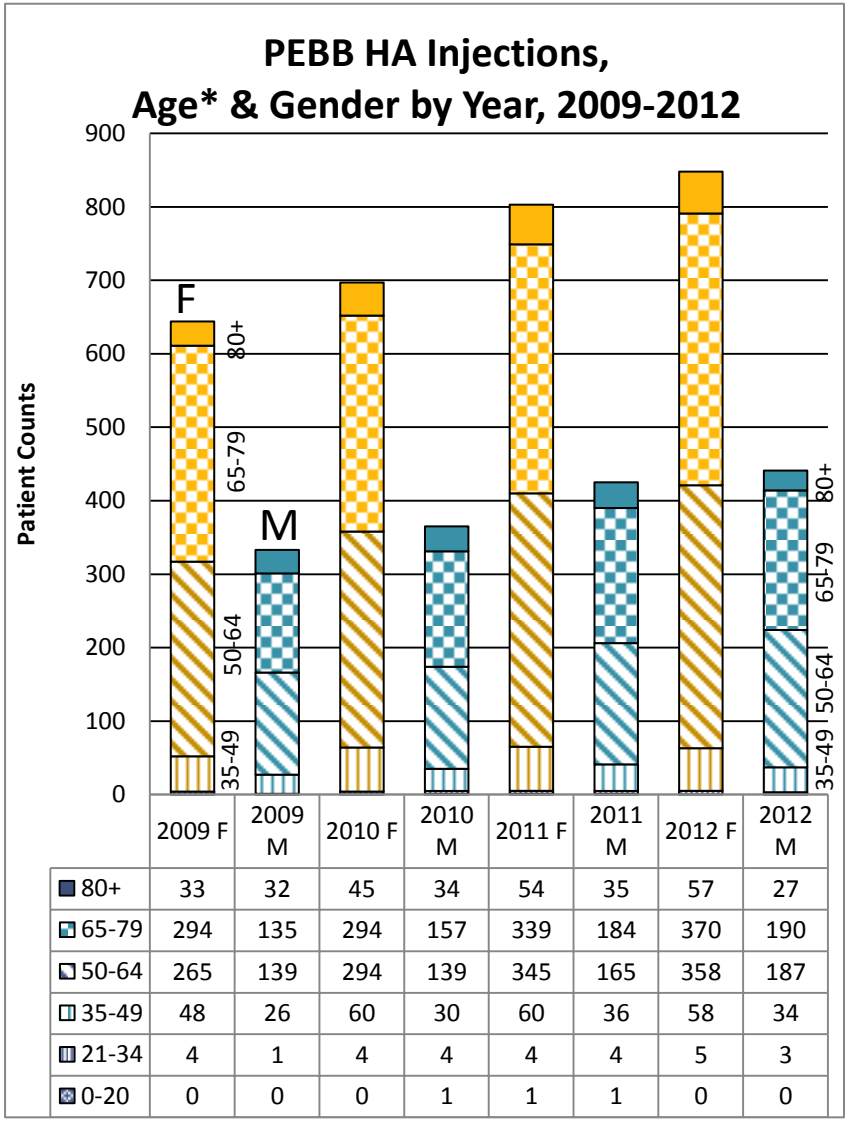
[2] Average % change is calculated over the most recent 4 years.

[3] Average paid per procedure includes the HA injectable and a professional fee for the injection.

Figure 3a PEBB HA Injections for Knee Osteoarthritis: Demographics 2006-2012



	2006 F	2006 M	2007 F	2007 M	2008 F	2008 M
66+	129	74	204	115	253	164
51-65	127	65	186	97	298	168
36-49	24	15	35	21	79	33
19-35	2	0	2	2	4	2
0-18					0	1

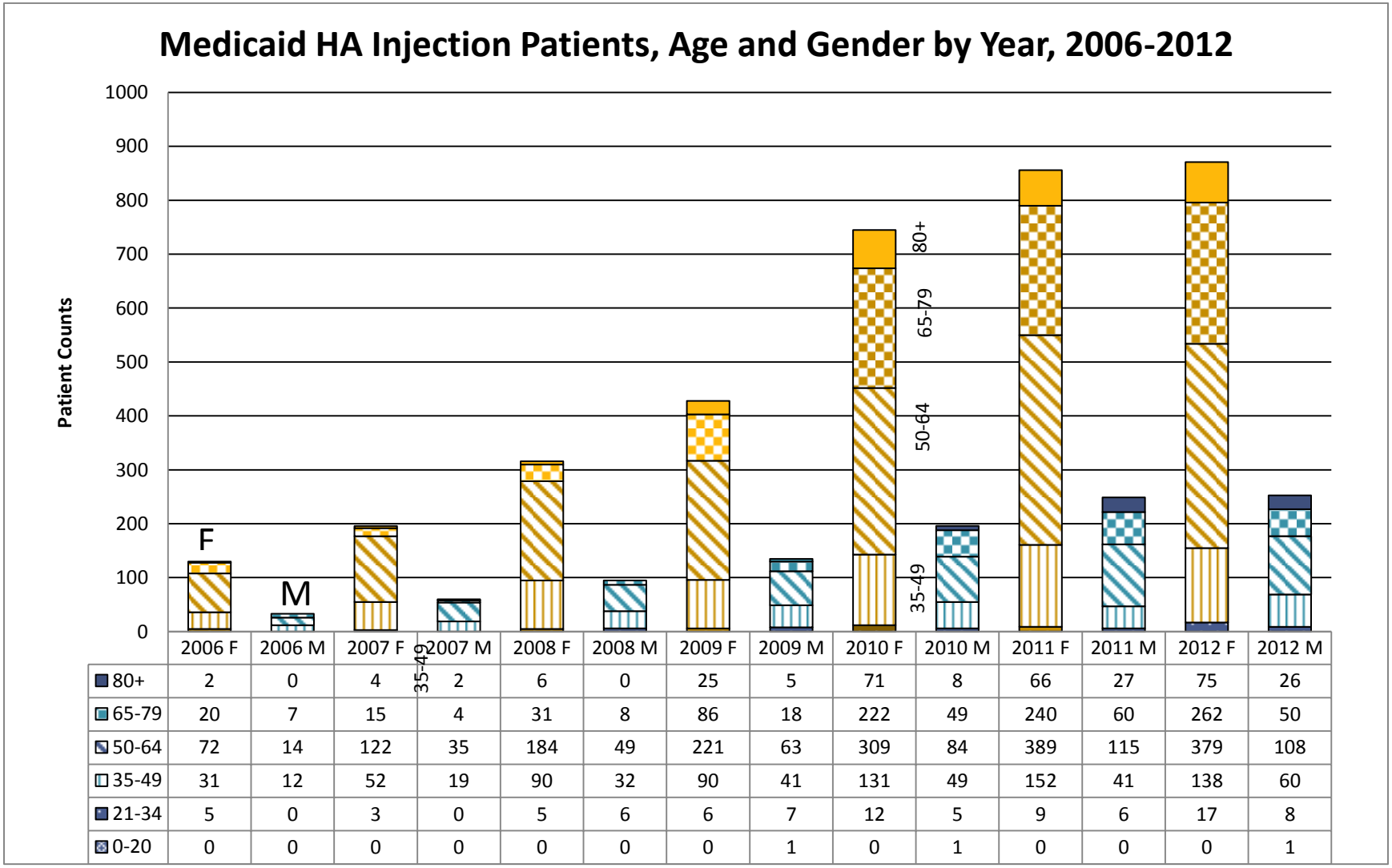


	2009 F	2009 M	2010 F	2010 M	2011 F	2011 M	2012 F	2012 M
80+	33	32	45	34	54	35	57	27
65-79	294	135	294	157	339	184	370	190
50-64	265	139	294	139	345	165	358	187
35-49	48	26	60	30	60	36	58	34
21-34	4	1	4	4	4	4	5	3
0-20	0	0	0	1	1	1	0	0

*Age groupings differ slightly between 2006-2008 vs 2009-1012 data due to differences in data availability.

* HA Knee OA Patient average age is between 64 and 65 for all age groups and genders, 2009-2012.

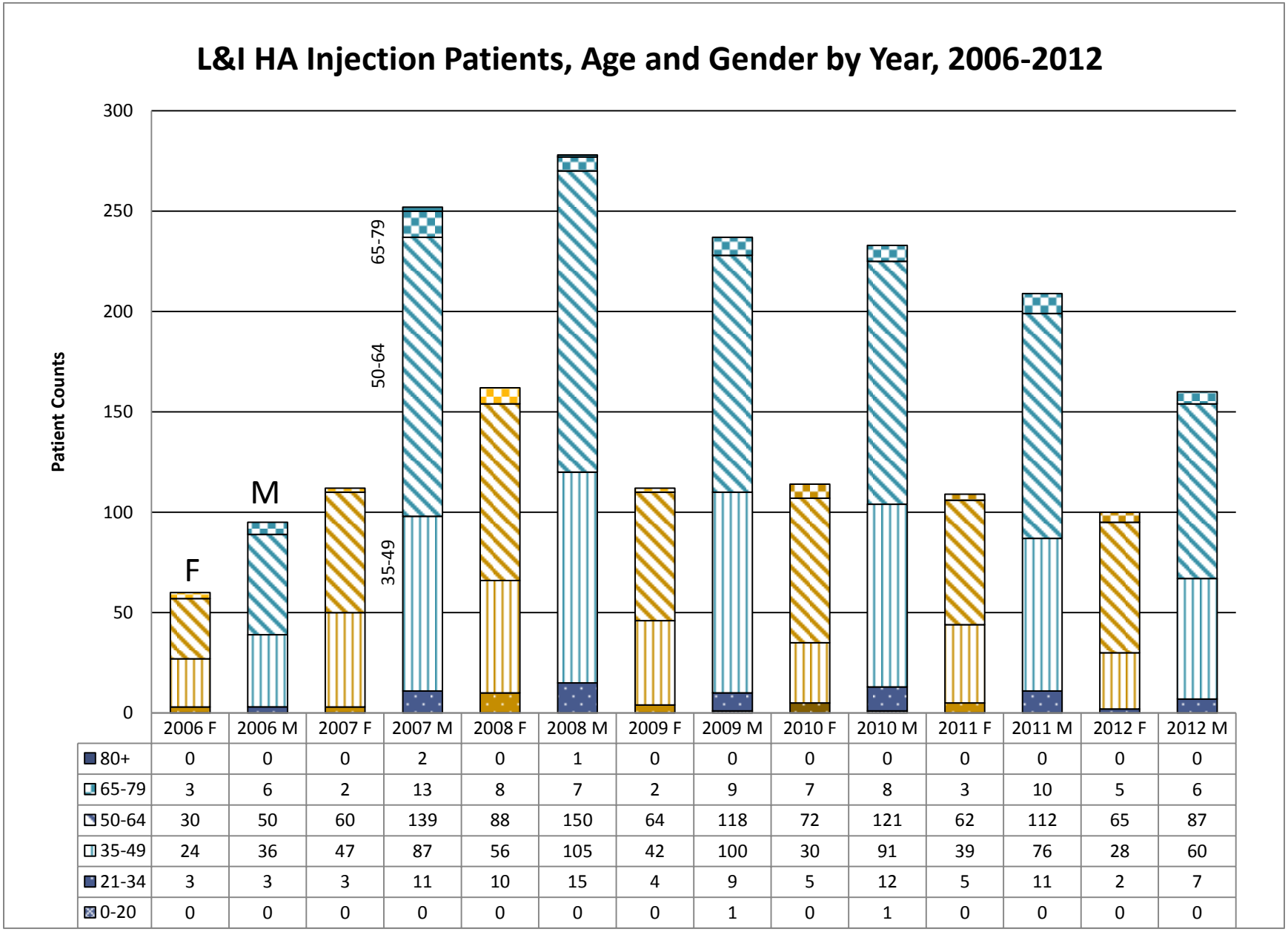
Figure 3b Medicaid HA Injections for Knee Osteoarthritis: Demographics 2006-2012



	2006 F	2006 M	2007 F	2007 M	2008 F	2008 M	2009 F	2009 M	2010 F	2010 M	2011 F	2011 M	2012 F	2012 M
80+	2	0	4	2	6	0	25	5	71	8	66	27	75	26
65-79	20	7	15	4	31	8	86	18	222	49	240	60	262	50
50-64	72	14	122	35	184	49	221	63	309	84	389	115	379	108
35-49	31	12	52	19	90	32	90	41	131	49	152	41	138	60
21-34	5	0	3	0	5	6	6	7	12	5	9	6	17	8
0-20	0	0	0	0	0	0	0	1	0	1	0	0	0	1

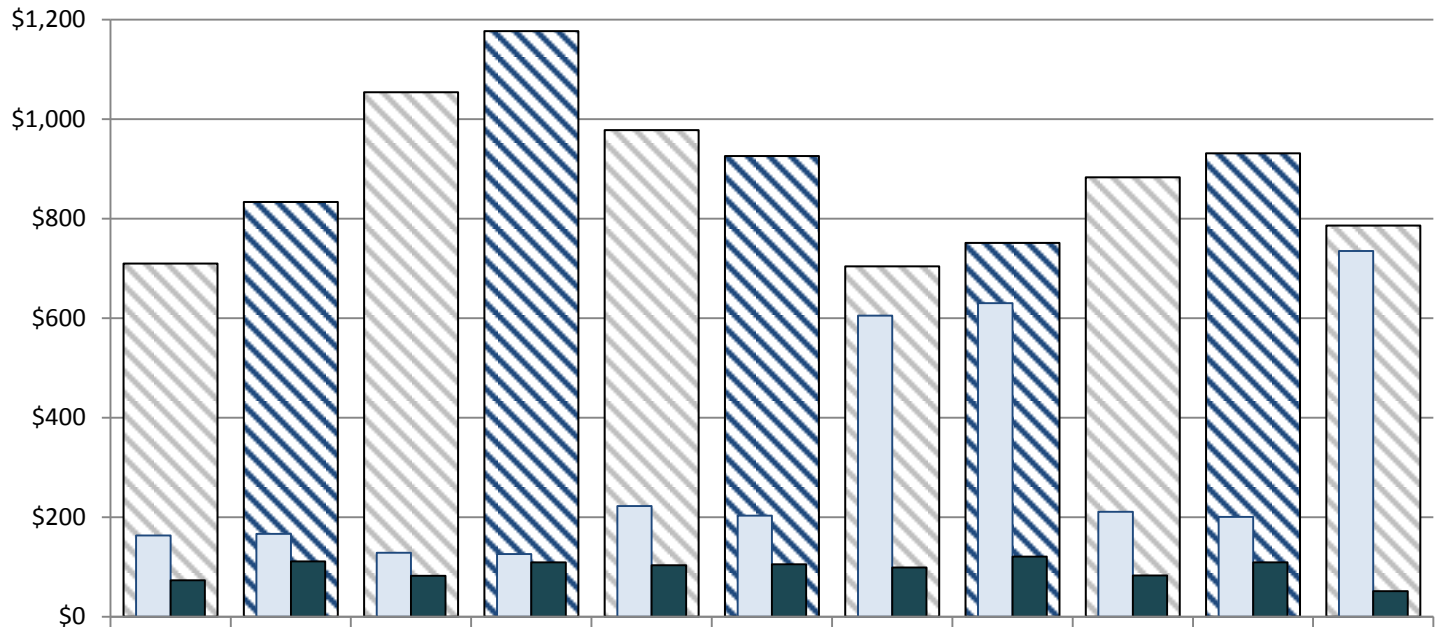
HA Knee OA average age has gradually increased 2009-2012, from 58 to 61 for women, and from 53 to 58 for men

Figure 3c L&I HA Injections for Knee Osteoarthritis: Demographics 2006-2012



	2006 F	2006 M	2007 F	2007 M	2008 F	2008 M	2009 F	2009 M	2010 F	2010 M	2011 F	2011 M	2012 F	2012 M
80+	0	0	0	2	0	1	0	0	0	0	0	0	0	0
65-79	3	6	2	13	8	7	2	9	7	8	3	10	5	6
50-64	30	50	60	139	88	150	64	118	72	121	62	112	65	87
35-49	24	36	47	87	56	105	42	100	30	91	39	76	28	60
21-34	3	3	3	11	10	15	4	9	5	12	5	11	2	7
0-20	0	0	0	0	0	0	0	1	0	1	0	0	0	0

Figure 4a. PEBB Average Allowed Amounts for Injection Courses and Injections, by Product and Payer, 2009-2012



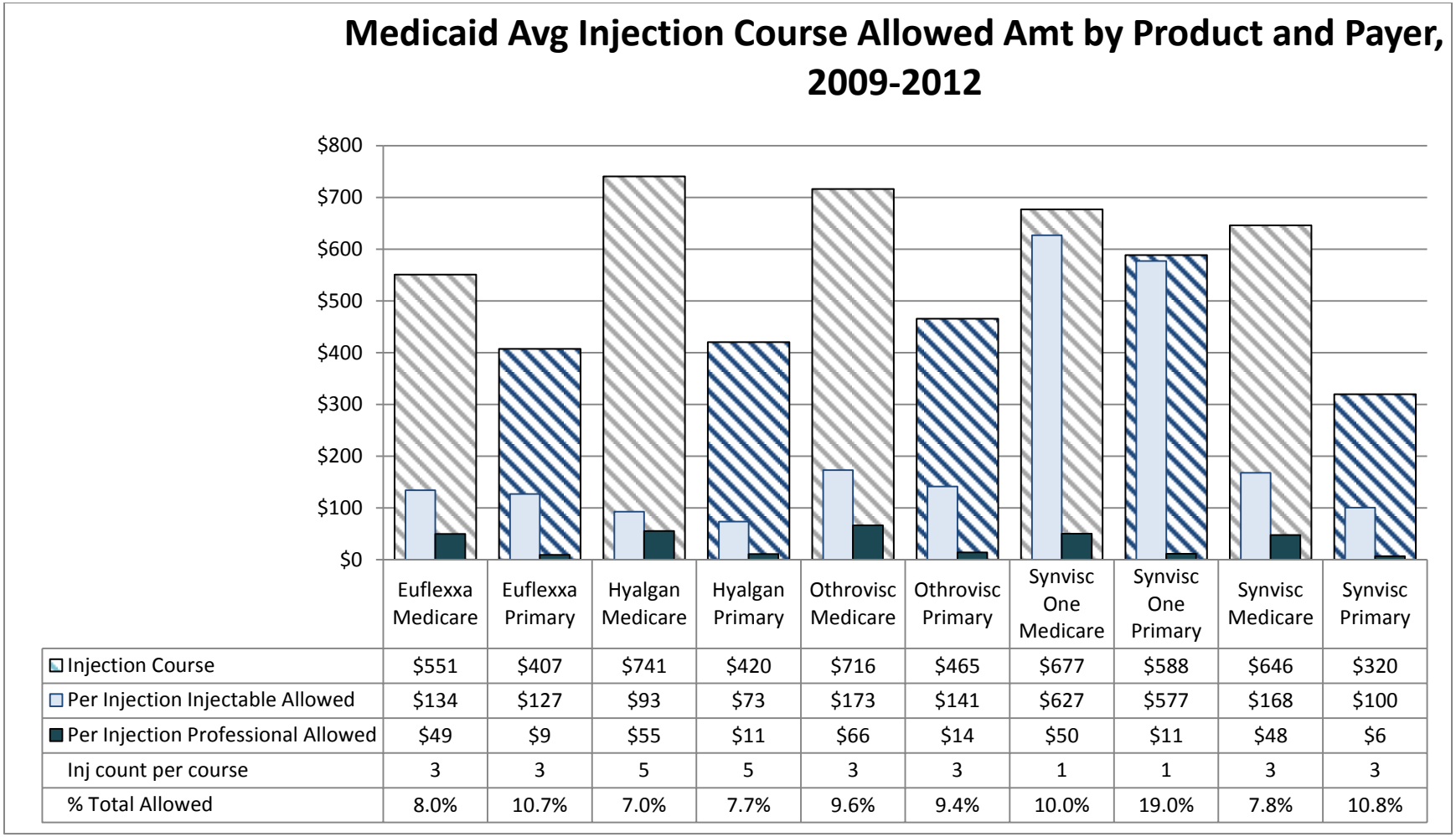
	Euflexxa Medicare	Euflexxa Primary	Hyalgan Medicare	Hyalgan Primary	Othrovisc Medicare	Othrovisc Primary	Synvisc One Medicare	Synvisc One Primary	Synvisc Medicare	Synvisc Primary	Gel One Medicare
Injection Course	$710	$834	$1,054	$1,177	$978	$926	$704	$751	$883	$932	$786
Per Injection Injectable Allowed	$163	$166	$129	$126	$222	$203	$605	$630	$211	$201	$735
Per Injection Professional Allowed	$73	$111	$82	$109	$104	$106	$99	$121	$83	$110	$51
Inj Count per Course	3	3	5	5	3	3	1	1	3	3	1
% Total Allowed	8.3%	12.4%	10.6%	7.8%	10.6%	8.4%	12.2%	12.3%	8.0%	7.1%	0.05%

*Average calculated using most recent 4 years allowed amount.

Note: "Primary" (blue diagonal bars) are calculated for patients where PEBB is the primary payer, in contrast to the Medicare payer pricing shown by the gray diagonal bars.

Note: Synvisc One and Synvisc share a CPT code – they were distinguished using injection count and allowed amount for this and subsequent charts.

Figure 4b. Medicaid Avg Allowed Amounts for Injection Courses and Injections, by Product and Payer, 2009-2012



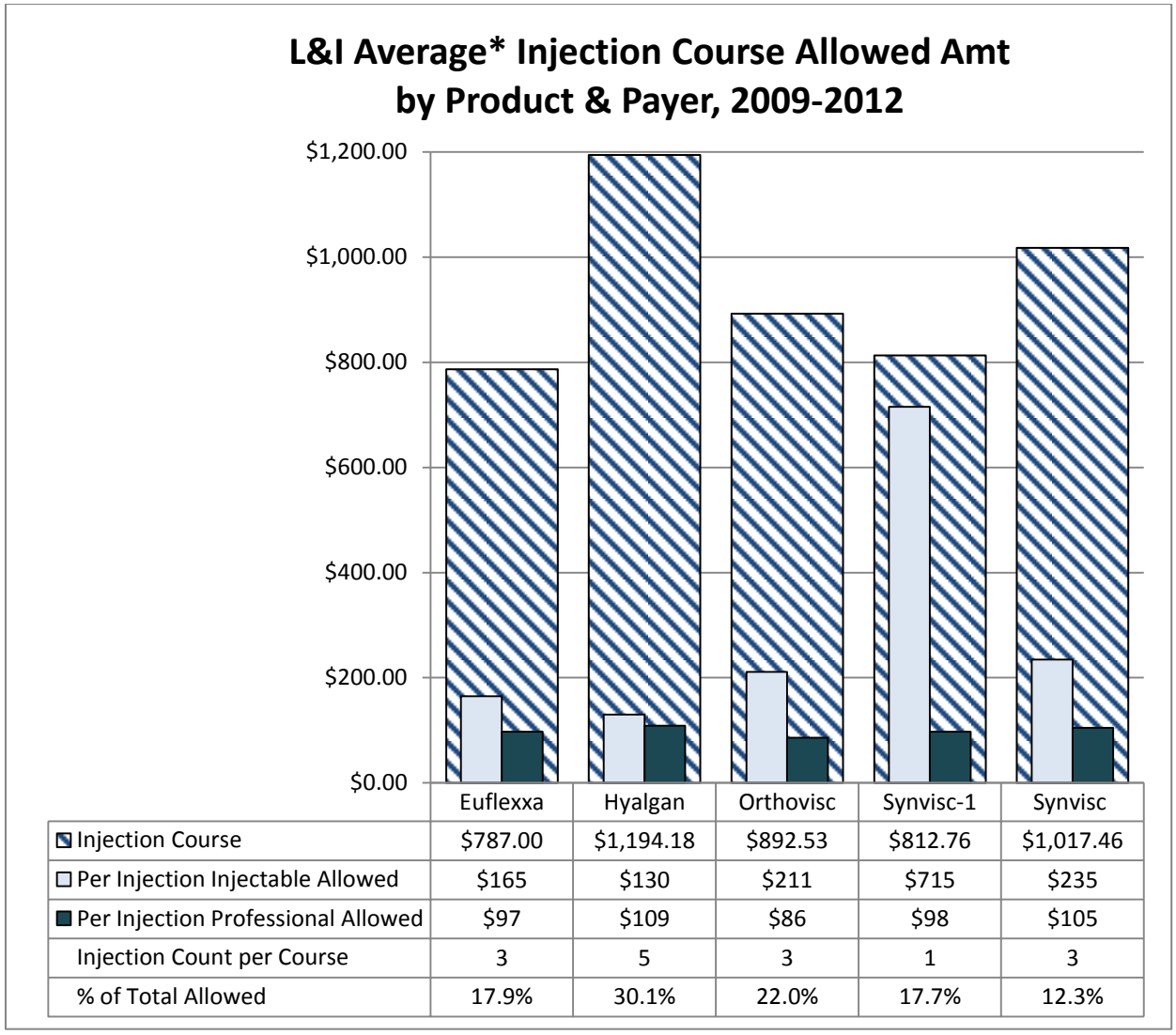
	Euflexxa Medicare	Euflexxa Primary	Hyalgan Medicare	Hyalgan Primary	Othrovisc Medicare	Othrovisc Primary	Synvisc One Medicare	Synvisc One Primary	Synvisc Medicare	Synvisc Primary
Injection Course	$551	$407	$741	$420	$716	$465	$677	$588	$646	$320
Per Injection Injectable Allowed	$134	$127	$93	$73	$173	$141	$627	$577	$168	$100
Per Injection Professional Allowed	$49	$9	$55	$11	$66	$14	$50	$11	$48	$6
Inj count per course	3	3	5	5	3	3	1	1	3	3
% Total Allowed	8.0%	10.7%	7.0%	7.7%	9.6%	9.4%	10.0%	19.0%	7.8%	10.8%

*Average calculated using most recent 4 years allowed amount.

Note: "Primary" (blue diagonal bars) are calculated for patients where Medicaid is the primary payer, in contrast to the Medicare payer pricing shown by the gray diagonal bars.

Note: Synvisc One and Synvisc share a CPT code – they were distinguished using injection count and allowed amount for this and subsequent charts.

Figure 4c. L&I Average Allowed Amounts for Injection Courses and Injections, by Product and Payer, 2009-2012



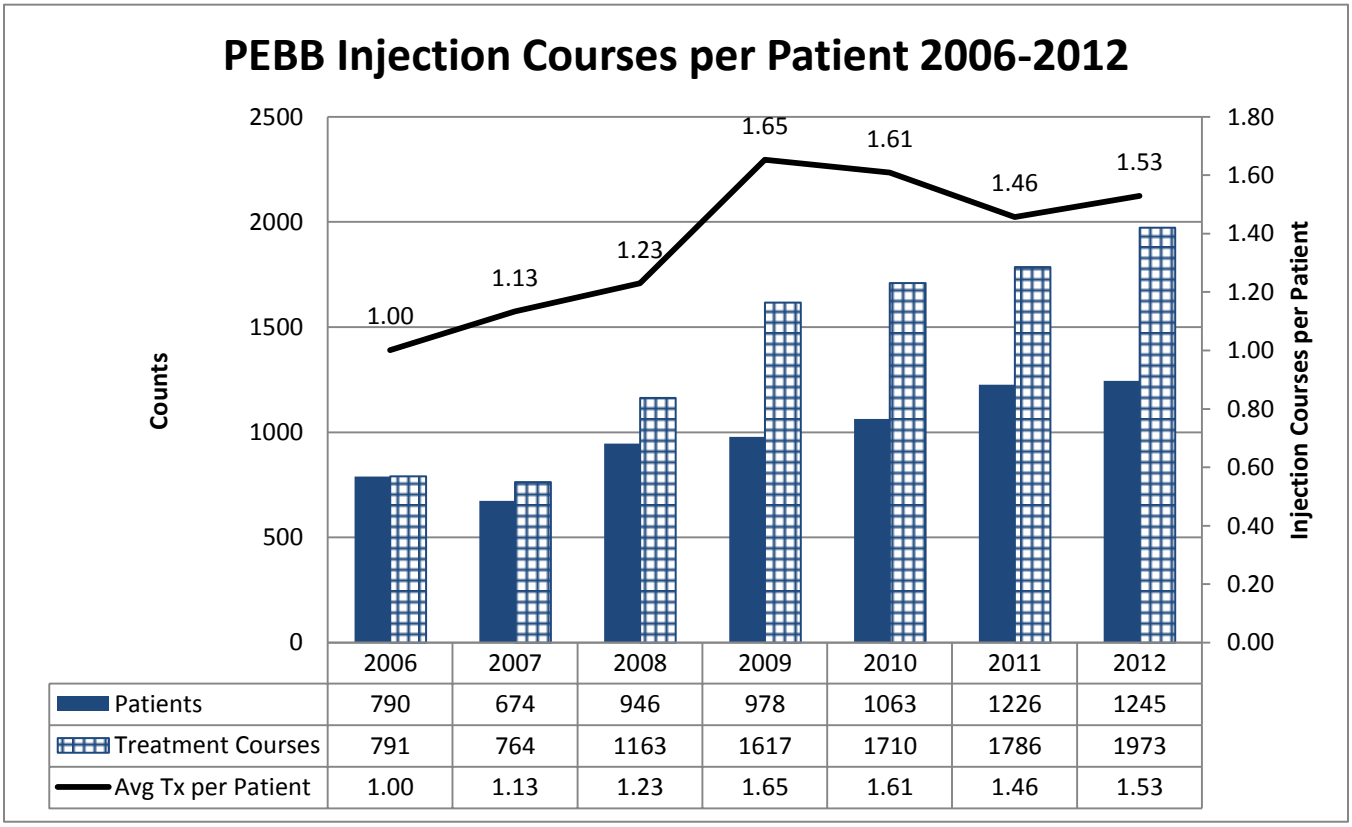
	Euflexxa	Hyalgan	Orthovisc	Synvisc-1	Synvisc
Injection Course	$787.00	$1,194.18	$892.53	$812.76	$1,017.46
Per Injection Injectable Allowed	$165	$130	$211	$715	$235
Per Injection Professional Allowed	$97	$109	$86	$98	$105
Injection Count per Course	3	5	3	1	3
% of Total Allowed	17.9%	30.1%	22.0%	17.7%	12.3%

*Average calculated using most recent 4 years allowed amount

Note: % of Total is included to show the overall impact of each product within the L&I total paid.

Note: Synvisc One and Synvisc share a CPT code – they were distinguished using injection count and allowed amount for this and subsequent charts.

Figure 6a PEBB HA Injection Courses for Knee OA: Series by Patient



	2006	2007	2008	2009	2010	2011	2012
Patients	790	674	946	978	1063	1226	1245
Treatment Courses	791	764	1163	1617	1710	1786	1973
Avg Tx per Patient	1.00	1.13	1.23	1.65	1.61	1.46	1.53

Note Injection courses may be under-reported due to inconsistent reporting of bilateral procedures, 2006-2009 treatment courses were not available from the original report and were calculated from total injection count and product type, while 2009-2012 treatment courses were modeled using claims data.

Figure 6e L&I HA Injection Courses for Knee OA: Series by Patient

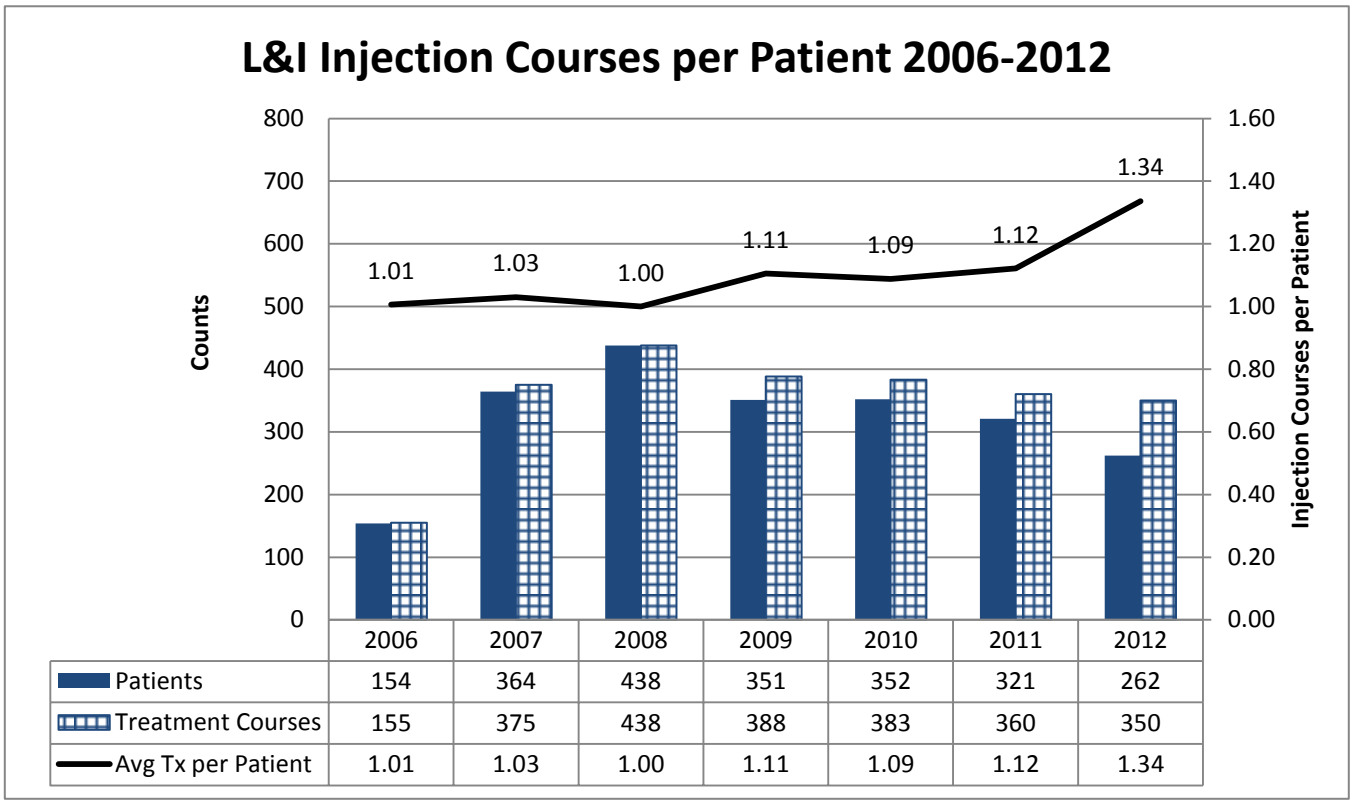
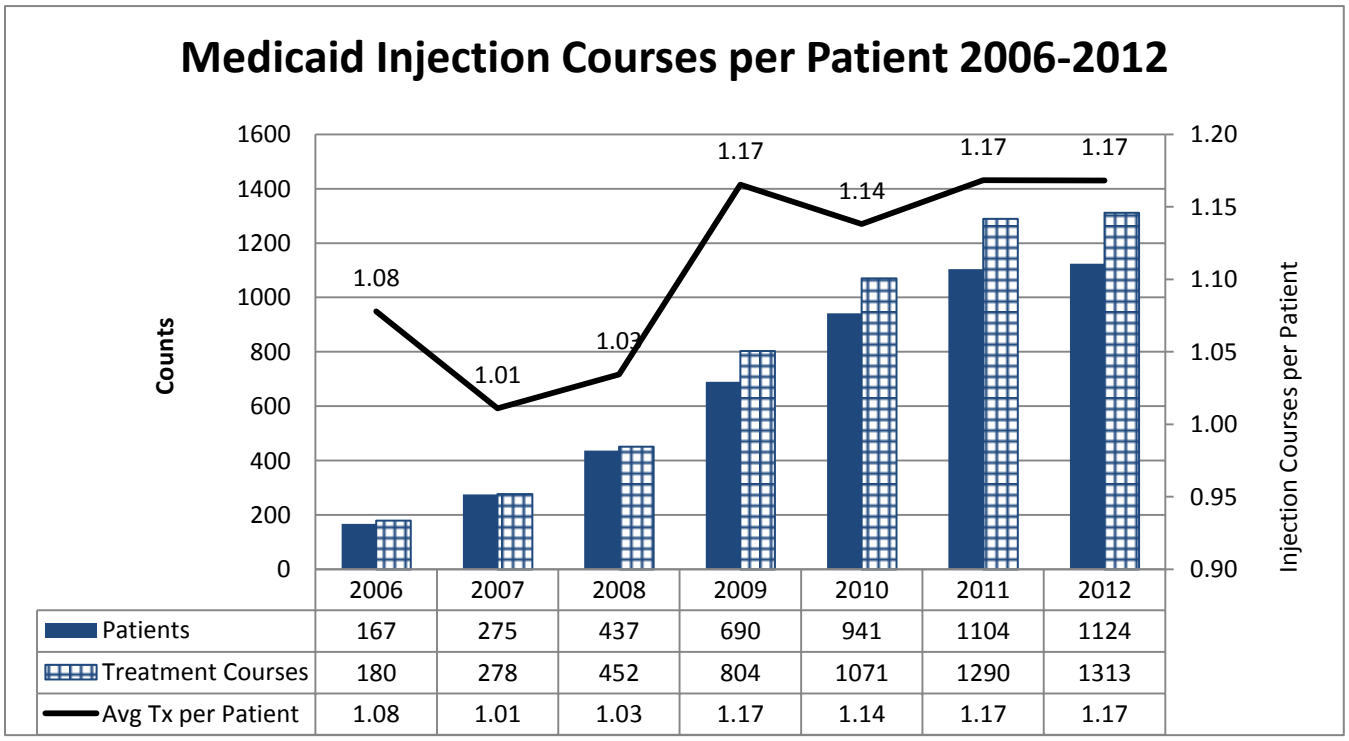
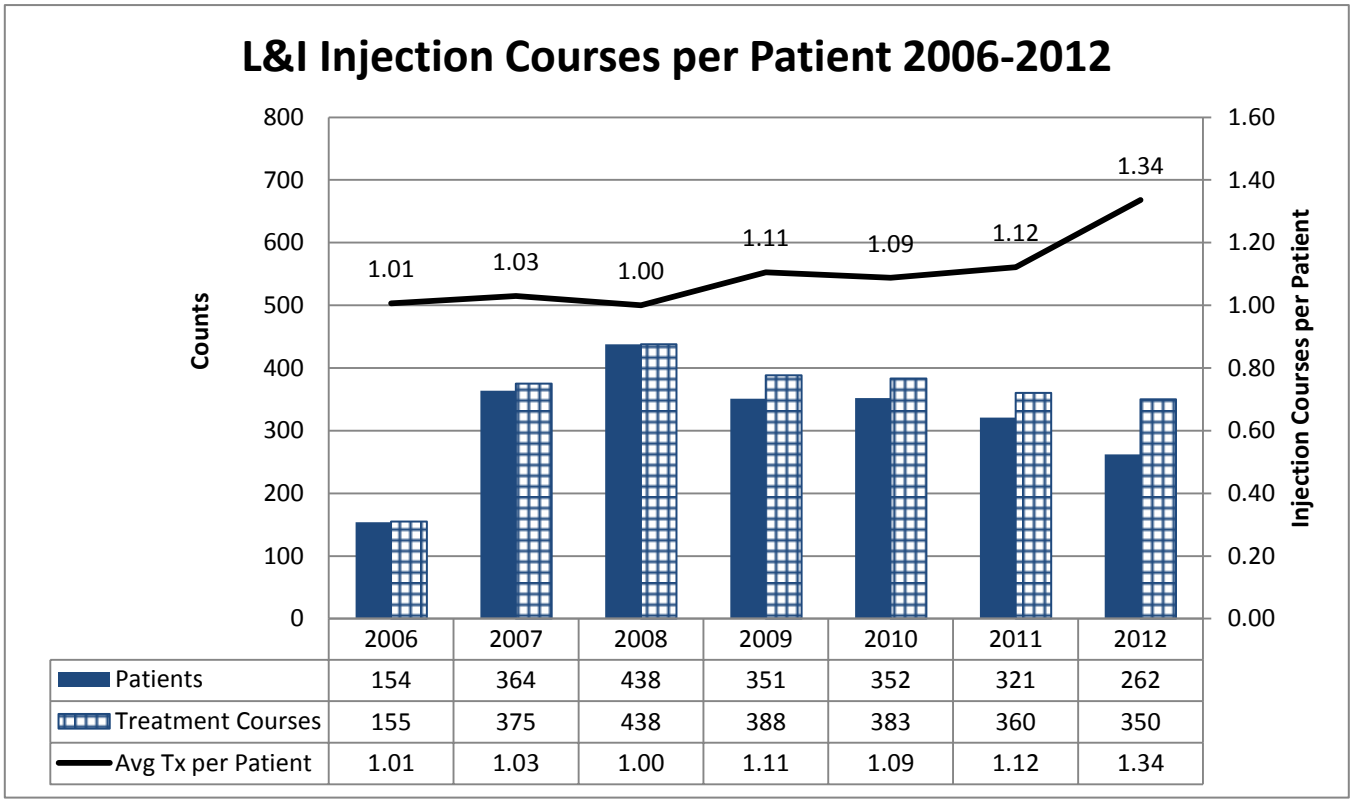


Figure 6g Medicaid HA Injection Courses for Knee OA: Series by Patient





Note Injection courses for L&I and Medicaid may be under-reported due to inconsistent reporting of bilateral procedures, 2006-2009 treatment courses were not available from the original report and were calculated from total injection count and product type, while 2009-2012 treatment courses were modeled using claims data.

Related Medical Codes

Codes	Number	Description
CPT	20610	Arthrocentesis, aspiration and/or injection, major joint or bursa, evaluation and management
ICD-9-Proc	81.92	Injection of therapeutic substance into joint or ligament
ICD-9 Diagnosis	715–715.9	Osteoarthrosis code range. A fifth digit of "6" in the ICD-9 code indicates osteoarthrosis of the knee
	715.16	Osteoarthrosis, localized, primary, lower leg
	715.26	Osteoarthrosis, localized, secondary, lower leg
	715.36	Osteoarthrosis, localized, not specific whether primary or secondary. lower leg
	717.9	Unspecified internal derangement of knee
	719.46	Pain in joint, lower leg
	719.56	Stiffness of joint, not elsewhere classified, lower leg
	719.96	Unspecified disorder of joint, lower leg
HCPCS 2008-2009	J7321	Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose (new code 1/1/08)
	J7322	Hyaluronan or derivative, Synvisc, for intra-articular injection, per dose (new code 1/1/08)
	J7323	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose (new code 1/1/08)
	J7324	Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose (new code 1/1/08)
HCPCS 2010**	J7325	Synvisc and Synvisc-1 (single injection tx)
	J7326	Gel-One Cross-linked Hyaluronate, Zimmer
HCPCS 2007	Q4083	Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose (new code 1/1/07)
	Q4084	Hyaluronan or derivative, Synvisc, for intra-articular injection, per dose (new code 1/1/07)
	Q4085	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose (new code 1/1/07)
	Q4086	Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose (new code 1/1/07)
HCPCS 2006	J7320	Hylan G-F 20, 16 mg for intra-articular injection [i.e., Synvisc]
	J7317	Sodium hyaluronate, per 20 to 25 mg dose for intra-articular injection [i.e., Hyalgan or Supartz]
CPT Knee Surgery	27437	Arthroplasty, patella; without prosthesis 17.30
	27438	Arthroplasty, patella; with prosthesis 22.04

Codes	Number	Description
	27440	Arthroplasty, knee, tibial plateau; 19.08
	27441	with debridement and partial synovectomy 20.23
	27442	Arthroplasty, femoral condyles or tibial plateau(s), knee; 22.99
	27443	with debridement and partial synovectomy 21.60
	27445	Arthroplasty, knee, hinge prosthesis 33.52
	27446	Arthroplasty, knee, condyle and plateau; medial OR lateral compartments 29.88
	27447	Arthroplasty, knee, condyle and plateau; medial AND lateral compartments with or without patella resurfacing

HA Product Information

Orthovisc ® is a registered trademark of DePuy Mitek, Inc., a Johnson&Johnson company.
Synvisc and Synvisc 1 are trademarks of Genzyme Corporation.
Hyalgan® is a registered trademark of Sanofi-Synthelabo.
Supartz® is a registered trademark of Seikagaku Corporation.
Euflexxa™ is a trademark of Ferring Pharmaceuticals, Inc.
GEL-ONE ® is a registered trademark of Zimmer, Inc. (FDA approved for use 12/2012: minor component of agency data).

Centers for Medicare and Medicaid Hyaluronic Acid Injectable Information (1)

HCPCS	Description	Price Basis	Medicare Price	Dosing/Injection Counts	Per Dose*	Treatment Cost*
J7321	Hyalgan/supartz inj per dose	per dose	85.133	2 mL, 5 doses	85.133	$425.65
J7323	Euflexxa inj per dose	per dose	152.880	2 mL, 3 doses	152.880	$458.64
J7324	Orthovisc inj per dose	per dose	172.197	2 mL, 3 doses	172.197	$516.60
J7325	Synvisc	1 MG (8 mg/mL)	12.570	2 mL, 3 doses	201.12	$603.36
	Synvisc-One	1 MG (8mg/mL)	12.570	6 mL/dose, 1 dose	603.36	$603.36
J7326	Gel-One	per dose	620.104	3 mL, 1 dose	620.10	$620.10

*calculated from columns 2, 3, and 4.

References:

1) CMS.gov Centers for Medicare and Medicaid . Accessed at http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2013ASPFiles.html on 8/26/2013. Page last updated 06/07/2013 9:16 AM.
2) SynviscOne. Accessed at http://www.synviscone.com/ on 8/26/2013. Page last updated 9/2011.
3) Biologics Gel-One Crosslinked Hyaluranate. http://www.zimmer.com/en-US/hcp/contact-us-information.jspx on 8/26/2013. Page last updated 12/2011.
4) Orthovisc, accessed at http://orthoviscline.com/ on 8/26/2013. Page last updated 2013.
5) Euflexxa, accessed at http://www.euflexxa.com/physician/ordering-euflexxa on 8/26/2013,. Page last updated 2012.

Review Objectives

The scope of this report is defined as:

Populations: Adults with OA of the knee

Interventions: Viscosupplementation (hyaluronic acid injection – Hyalgan, Synvisc, Supartz, Orthovisc, Euflexxa, Gel-One)

Comparators: NSAIDs, corticosteroid injection, physical therapy, oral pain medications, placebo, arthroscopic lavage and/or debridement

Outcomes: Pain, function, quality of life, adverse events

Key Questions

The following key questions will be addressed:

1. (a) What is the clinical effectiveness of viscosupplementation for treatment of OA of the knee? (b) Do different viscosupplementation products vary in effectiveness?

2. What are the adverse effects associated with viscosupplementation in patients with OA of the knee?

3. Does the effectiveness of viscosupplementation vary by subpopulation, defined by these factors: age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), and prior treatments?

4. What are the cost implications and cost-effectiveness of this type of product?

Methods

Search Strategy and Selection Criteria

Systematic Reviews and Guidelines

For the 2010 version of this report, the following core sources were searched for systematic reviews, technology assessments, and guidelines published from January 2000 through December 2009: BMJ Clinical Evidence; Hayes, Inc.; Cochrane Library; UK National Library for Health (NLH), including National Institute for Health and Care Excellence (formerly National Institute for Health and Clinical Excellence) (NICE); Canadian Agency for Drugs and Technologies in Health (CADTH); Institute for Clinical Systems Improvement (ICSI); Agency for Healthcare Research and Quality (AHRQ); Veterans Affairs/Department of Defense (VA/DoD); Washington State Health Technology Assessment (HTA) program; and the Blue Cross/Blue Shield HTA program. The following search terms were used: *viscosupplementation, hyaluronan, hyaluronate*. A search of the following sources helped identify additional guidelines published in the last 10 years: American Academy of Family Physicians, American Association of Orthopedic Surgeons, American Pain Society, American College of Rheumatology, and the National Guidelines Clearinghouse. The following search phrase was used: *viscosupplementation or hyaluronan or hyaluronate*.

For the current update, systematic reviews and guidelines published since December 2009 were considered, and searches were conducted in February and May of 2013. See **Appendix I** for further detail.

Primary Studies

PubMed and Embase searches were conducted to identify RCTs published after the last search dates of the latest systematic review; thus, the search dates were December 2009 to May 13, 2013. Another search was conducted covering the time frame December 2009 to June 4, 2013 for non-RCT studies that might provide supplemental safety data and evidence regarding differential effectiveness/safety. The reference lists of included systematic reviews and primary studies were manually searched. An update search for new publications was conducted on July 5, 2013. Search strategies are described in **Appendix I**.

Eligible Studies

- Randomized controlled trials (RCTs) reporting pain, function, quality of life (QOL), or safety outcomes and comparing patients treated with hyaluronic acid (HA) injection for osteoarthritis (OA) of the knee with patients who receive usual treatment, an alternative to HA injection, or sham treatment.
- Randomized comparator trials (also referred to as RCTs) comparing 2 forms of HA and reporting outcomes of interest.
- Systematic reviews of eligible RCTs.
- Large observational studies with safety data or data relevant to differential effectiveness and safety.
- English language.

Exclusion Criteria

- Nonstandard treatment regimen (e.g., < 3 injections unless the product was approved for single injection, sodium hyaluronate combined with other substances).
- < 1-month follow-up.
- Studies evaluating intermediate outcomes such as cartilage preservation, gait, and muscle activity.
- Studies evaluating HA for treatment of postsurgical pain, although ≥ 1 such study was included in 1 of the systematic reviews (Colen et al., 2012).
- Studies designed primarily to compare HA with nonconventional treatments, such as various blood products. One such trial (Baltzer et al., 2009) included in the 2010 WA HTA report has not been included in subsequent systematic reviews and is also omitted from this update report.

Quality Assessment

Appendix II outlines the process used by Hayes for assessing the quality of primary studies and bodies of evidence. This process is in alignment with the methods recommended by the GRADE Working Group. Quality checklists for individual studies address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Individual studies are labeled as *good*,

fair, *poor*, or *very poor*. For individual studies included in systematic reviews, this report relies on the quality assessment by review authors; to aid in interpreting the assessment by review authors, a systematic review quality checklist was used.

> **NOTE:** For this update report, modified NICE and Scottish Intercollegiate Guidelines Network (SIGN) quality checklists adapted by the Oregon Health Sciences University (OHSU) Medicaid Evidence-based Decisions (MED) Project were used to maintain consistency with the previous version of this report. These tools included a checklist for evaluating systematic reviews, as well as checklists for primary studies.

The Evidence-Grading Guides assure that assessment of bodies of evidence takes into account the following considerations:

- Methodological quality of individual studies.
- Applicability to the population(s), intervention(s), comparator(s), and outcome(s) of interest, i.e., applicability to the PICO statement.
- Consistency of the results across studies.
- Quantity of data (number of studies and sample sizes).
- Publication bias, if relevant information or analysis is available.

> NOTE: Two terms related to applicability are *directness* and *generalizability. Directness* refers to how applicable the evidence is to the outcomes of interest (i.e., surrogate or intermediate outcomes versus health outcomes) or to the comparator of interest (indirect comparison of 2 treatments versus head-to-head trials). *Generalizability* usually refers to whether study results are applicable to real-world practice. If the setting is not specified in a PICO (population-interventions-comparator-outcomes-setting) statement, the issue of generalizability to real-world settings is not typically treated as an evidence quality issue. Another term used by some organizations is *imprecision*, which refers to findings based on such a small quantity of data that the confidence interval surrounding a pooled estimate includes both clinically important benefits and clinically important harms or that any results other than large statistically significant effects should be considered unreliable.

Bodies of evidence for particular outcomes are labeled as being of *high*, *moderate*, *low*, or *very low* quality. These labels can be interpreted in the following manner:

> **High**: Suggests that we can have high confidence that the evidence found is reliable, reflecting the true effect, and is very unlikely to change with the publication of future studies.
>
> **Moderate**: Suggests that we can have reasonable confidence that the results represent the true direction of effect but that the effect estimate might well change with the publication of new studies.
>
> **Low**: We have very little confidence in the results obtained, which often occurs when the quality of the studies is poor, the results are mixed, and/or there are few available studies. Future studies are likely to change the estimates and possibly the direction of the results.
>
> **Very low**: Suggests no confidence in any result found, which often occurs when there is a paucity of data or the data are such that we cannot make a statement on the findings.

Guidelines

The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool (AGREE Enterprise, 2012), along with a consideration of commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines.

Evidence Selection

Systematic Reviews

Two qualitative systematic reviews (Campbell et al., 2007; Hayes, 2009) that were included in the 2010 report are not reviewed in this update report. The review by Campbell et al. was primarily a commentary on existing meta-analyses and is now outdated. The 2009 Hayes report, a qualitative review, serves the current update report as a source of study data missing from other systematic reviews but its conclusions are not covered. Three systematic reviews with meta-analyses have been retained from the 2010 report (Reichenbach et al., 2007; Samson et al., 2007; Bannuru et al., 2009), and another 3 systematic reviews with meta-analyses have been added (Bannuru et al., 2011; Colen et al., 2012; Rutjes et al., 2012). The Samson review was actually a review of 6 previously published meta-analyses, the most comprehensive of which was a Cochrane Review (Bellamy et al., 2006). Pooled estimates reported in the Bellamy review are highlighted in this update report; pooled estimates from the other meta-analyses covered in the Samson review appear primarily in Appendix V. All systematic reviews included only RCTs or pseudo-randomized trials. See **Appendix IV** for an overview of the included reviews, **Appendix V** for results of meta-analyses of randomized (generally placebo-) controlled trials, and **Appendix VI** for results of meta-analyses of randomized comparator trials.

Three of the 6 systematic reviews covered in this update were concerned primarily with the general efficacy of viscosupplementation (Samson et al., 2007 [represented primarily by Bellamy et al, 2006]; Colen et al., 2012; Rutjes et al., 2012). Of the other 3 systematic reviews, 1 evaluated the relationship between efficacy and time, i.e., peak effect and duration of effect (Bannuru et al., 2011), 1 analyzed trials comparing hylan with non–cross-linked HA (Reichenbach et al., 2007), and 1 analyzed trials comparing viscosupplementation with intraarticular corticosteroid injection (Bannuru et al., 2009). The Bellamy and Colen reviews also included analyses of trials comparing different forms of HA and comparing viscosupplementation with other treatments.

In their primary analyses of efficacy, the 3 general reviews covered disparate sets of RCTs, not only because of different publication dates but also because of differences in selection criteria: the meta-analyses reviewed by Samson et al., including the Bellamy meta-analysis, included RCTs published as conference abstracts as well as in full and the authors of the Bellamy review additionally solicited information on unpublished trials; the Colen review selected only studies that were published in full; and the Rutjes review, like the Bellamy review, included studies published in full, conference abstracts, and unpublished studies. Lastly, the Rutjes review included trials comparing viscosupplementation with nonplacebo controls as well as placebo-controlled trials, while the other 2 general reviews included only placebo-controlled trials in their efficacy analyses. There were also variations in the databases searched. Between the 2 most comprehensive meta-analyses, 5 of 32 placebo-controlled trials in the 2006 review by Bellamy were missing from the 2012 Rutjes review, and 37 of 68 placebo-controlled trials in the

Rutjes review were missing from the Bellamy review (16 due to the date of publication). Appendix VII shows which trials were included in which reviews for analyses of efficacy.

Three reviews included comparator trials of hylan versus non–cross-linked HA viscosupplementation. The special-focus 2007 Reichenbach review and the more general 2012 Colen review overlap due to differences in publication date and inclusion (Reichenbach) versus noninclusion (Colen) of conference abstracts and unpublished studies. The comparator trials in the 2006 Bellamy review are all included in the Reichenbach review, and the Bellamy analysis includes no unique trials; thus, the Bellamy analysis of hylan versus non–cross-linked HA is excluded from this update report. A qualitative review (Migliore et al., 2010) of Synvisc versus placebo or other HA was also excluded since it included no unique trials and did not provide pooled estimates.

Two reviews (Bellamy and Bannuru [2009]) also included comparator trials of viscosupplementation versus intraarticular corticosteroids. The comparator trials in the 2006 Bellamy review are all included in the Bannuru review, and the Bellamy analysis includes no unique trials; thus, the Bellamy analysis of hylan versus non–cross-linked HA is excluded from this update report.

Randomized Controlled/Comparator Trials (RCTs)

The update literature search yielded 5 RCTs that were not included in any systematic review, but only 4 (5 publications) are included in the update report. A pilot trial comparing a single injection of Synvisc (hylan) with a single injection of Hyalgan (non-hylan), was excluded because it was not clear whether the single-injection form of Synvisc was used and, as acknowledged by the authors, Hyalgan has not been approved for single-injection use (Khanasuk et al., 2012). Three of the 4 included trials were double-blind placebo-controlled RCTs (Altman et al., 2011; Navarro-Sarabia et al., 2011; Strand et al., 2012a; Strand et al., 2012b). The fourth compared HA products of 3 different molecular weights (Petrella et al., 2011). Study details are presented in **Appendix VII**.

Supplemental Studies and Reviews

Information provided in the 2007 Samson review on 3 large case series was retained from the previous report. A large multicenter case series evaluating the effectiveness and tolerability of a non–cross-linked HA product (Hyalubrix; Fidia Farmaceutical SpA; not available in the U.S.) was selected for additional safety and patient preference data (Foti et al., 2011). A narrative review article (Goldberg and Coutts, 2004) was selected for additional data on the risk of pseudosepsis.

Cost Studies and Economic Evaluations

No new economic evaluations or cost studies were identified in the literature published since the 2010 report. The original publications of 4 studies described in the 2010 report have been re-reviewed and the summary of their findings for Key Question #4 has been edited for better clarity. These include 4 economic evaluations (Torrance et al., 2002; Kahan et al., 2003; Yen at al., 2004; NICE, 2008). Two studies that were briefly reviewed in the 2010 report have been omitted because study weaknesses did not allow meaningful conclusions. One omitted study was a retrospective cost analysis showing that when HA was ineffective and surgery was necessary, HA contributed only 6% of the total direct medical costs of treatment. However, there was no analysis of how often the cost of surgery could be avoided altogether by HA injection or how long it could be delayed in patients who responded to HA (Turajane et al., 2007). Another omitted study, an RCT, included a cost-effectiveness analysis to test the hypothesis

that Synvisc is cost-effective compared with Artz. However, the RCT was considered to be of poor quality (Chou et al., 2009).

Practice Guidelines

Searches of the core sources and relevant specialty groups identified current guidelines from 4 organizations: the American College of Rheumatology (ACR) (Hochberg et al., 2012), the American Academy of Orthopaedic Surgeons (AAOS) (AAOS, 2013), the National Institute for Health and Care Excellence (formerly the National Institute for Health and Clinical Excellence) (NICE) (NICE, 2008), and the Osteoarthritis Research Society International (OARSI) (Zhang et al., 2007; Zhang et al., 2008; Zhang et al., 2010). American Pain Society (APS) guidelines on management of pain in arthritis, published in 2000, were reviewed in the 2010 report but have since been archived by the APS and thus were omitted from the update report. Also omitted was a 2008 Drug Class Review on viscosupplementation by the Veterans Administration Pharmacy Benefits Management Service; the review no longer appears on the VA website.

Literature Review

Key Question #1a: What is the clinical effectiveness of viscosupplementation for treatment of OA of the knee?

Outcome Measures and Analytic Approaches

See **Appendix III** for a description of the scales commonly used to assess pain and physical function in osteoarthritis (OA) research. When different studies used the same outcome measures, pooled estimates were expressed in terms of weighted mean differences (WMDs), referring to the between-group difference in pain or function score at follow-up or difference in improvement, depending on the particular meta-analysis. When different studies used different outcome measures, standardized mean differences (SMDs), also referred to as effect sizes, were calculated in lieu of WMDs. Heterogeneity was typically assessed according to the *I* statistic (I^2) was interpreted as follows: 25% = low heterogeneity, 50% = moderate, and ≥ 75% = high (Colen et al., 2012). In the Rutjes review, heterogeneity was measured by τ^2 and interpreted as follows: 0.04 = low; 0.09 = moderate, 0.16 = high. Individual randomized controlled trials (RCTs) reported change in pain and function score for each group, or showed how scores compared between groups at follow-up.

Findings: Efficacy of Viscosupplementation

Study and Patient Characteristics

Quantitative synthesis of the evidence for efficacy came from 4 main systematic reviews, all considered to be of good quality: an Agency for Healthcare Research and Quality (AHRQ) Technology Assessment (2007 Samson review) that was included in the 2010 report, and 3 newer systematic reviews with meta-analysis (Bannuru [2011], Colen, and Rutjes reviews). See **Appendix IV** (overviews) and **Appendix VI** (detailed findings). As previously noted, the Samson review was actually a review of 6 previously published meta-analyses, the most comprehensive of which was a Cochrane Review (Bellamy et al.,

2006). Thus, a total of 9 meta-analyses (6 in the Samson review and 3 new) of the efficacy of viscosupplementation are included in this report, representing a total of 81 generally placebo-controlled trials and > 10,000 patients. In addition to the 9 meta-analyses, 3 recent RCTs (4 publications) evaluated the placebo-controlled efficacy of viscosupplementation (Altman et al., 2011; Navarro-Sarabia et al., 2011; Strand et al., 2012a; Strand et al., 2012b).

Patients included in earlier reviews varied in age (mean age, 45 to 72 years by study) and in baseline pain severity (mean, 42 to 80 on a 100-mm visual analog scale [VAS]); study groups included 28% to 100% women (Samson et al., 2007). Patients represented by the most recent and comprehensive review (Rutjes et al., 2012) were similar in age (mean age, 50 to 72 years) and sex (27% to 100% women). Rutjes et al. reported that severity of OA was grade 2 on the Kellgren-Lawrence scale in 44% of patients and grade 3 in 39% of patients. (The Kellgren-Lawrence scheme classifies severity, i.e., progression of OA, on a 0 to 4 scale according to the presence of several radiographic changes. Grades 3 and 4 represent moderate and severe OA, respectively [Kellgren and Lawrence, 1957].) The review by Colen et al. (2012) did not report patient characteristics.

In the 3 recent placebo-controlled trials (1114 participants), mean age was 61 to 63 years, and 60% to 84% of participants were women. Patients in the trial by Navarro-Sarabia et al. (2011) had a baseline OA severity of Kellgren-Lawrence grade 2 to 3 and pain ≥ 55 millimeters (mm) on a 100-mm VAS, while patients in the trial by Strand et al. (2012a) had Kellgren-Lawrence grade 1 to 3 OA and baseline pain of ≥ 40 on a 100-mm Western Ontario and McMaster Universities Index (WOMAC) scale. The trial by Altman et al. (2011) involved 433 willing completers of the 2009 FLEXX trial (Altman et al., 2009). They were given the option, at 6 months following the first treatment cycle, of a second cycle of injections of the same treatment to which they had originally been randomized; patient blinding, but not assessor blinding, was maintained.

Since minimal detail regarding patient characteristics and protocol specifications was provided by systematic review authors, RCTs with ≥ 200 patients were reviewed for detail to help define the population to which the evidence applies. The larger trials were felt to be representative since by virtue of larger sample sizes and smaller variances they would have contributed more heavily to WMDs and SMDs. Indeed, for those few patient characteristics that were reported in the systematic reviews, ranges for all selected studies were very similar to the following ranges that apply to the larger trials. Detail from 21 RCTs, including the newer RCTs by Navarro-Sarabia et al. (2011) and Strand et al. (2012a), can be summarized as follows:

- Mean age: 53 to 71 years
- Percentage women: 35% to 84%
- Mean BMI: Where reported, 29 to 33 kilograms per square meter (kg/m^2)
- Mean duration of OA: Where reported, 6 to 9 years
- OA severity: Generally, Kellgren-Lawrence (0 to 4 scale) grade 2 to 3
- History of trauma: Not mentioned except in 1 study (Rolf et al., 2005); no analysis according to this factor.
- Mean baseline pain: Generally, 42 to 60 on 100-point scales, or the equivalent; 4 studies reported means of 64 to 71 (Karlsson et al., 2002; Navarro-Sarabia et al., 2011; Strand et al., 2012a).
- Compliance with treatment regimens prior to trial enrollment: Not reported.

- Previous use of nonsteroidal anti-inflammatory drugs (NSAIDs): Generally not reported. Where reported, most patients had tried NSAIDs and no distinction was made between Cox-2 inhibitors and traditional NSAIDs.
- Previous intraarticular corticosteroid injection: Almost all studies excluded patients who had received a recent corticosteroid injection, with the cutoff typically being the previous 3 months. Most studies did not report how many patients had tried corticosteroid injections before that time.
- Concomitant medications allowed: Most protocols allowed acetaminophen (paracetamol) but not NSAIDs as a rescue medication. Approximately one third of the studies allowed any type of rescue medication. Some study reports mentioned that a short washout period prior to each assessment was required. Studies allowing medications other than acetaminophen represented a mix of positive and negative outcomes.
- Concomitant intraarticular corticosteroid injection allowed: Generally not reported.

Mean Group Differences

Mean Difference in Pain

The earlier meta-analyses generally calculated different pooled estimates for different follow-up intervals and sometimes calculated separate estimates for pain in different situations (e.g., at rest or walking). The results consistently favored hyaluronic acid (HA) but were sometimes nonsignificant, particularly at follow-up intervals < 4 weeks or for analyses involving a small number of trials. The 2 newer meta-analyses (Colen et al., 2012; Rutjes et al., 2012) analyzed data for pain at 3 months (or the measurement time closest to 3 months), with the Colen review giving preference to visual analog scale (VAS) pain and the Rutjes review giving preference to the WOMAC pain scale. In every analysis, pooled mean pain scores at follow-up were lower for HA groups than for placebo groups, or improvement in pain was greater in HA groups than in placebo groups. The following pooled estimates for an effect on short-term pain relief, all favoring viscosupplementation, were reported by the 3 most comprehensive meta-analyses:

- *At 5-13 weeks (weight-bearing pain, VAS):* WMD –11.0 (95% confidence interval [CI], –17.8 to –8.2; I^2=82%); 21 RCTs, 2090 patients (Bellamy et al., 2006).
- *At 5-13 weeks (weight-bearing pain, WOMAC):* SMD 1.0 (CI, –1.6 to –0.5; I^2=88%; 7 RCTs, 639 patients (Bellamy et al., 2006).
- *At 5-13 weeks (WOMAC pain):* SMD –1.0 (95% CI, –1.6 to –0.05; I^2=88%); 7 RCTs, 639 patients (Bellamy et al., 2006).
- *At 3 months:* WMD –10.20 (95% CI, –15.97 to –4.42; I^2= 2%); 18 RCTs involving 20 comparisons, all published in full, 2801 patients (Colen et al., 2012).
- *At 3 months:* SMD –0.37 (95% CI, –0.46 to –0.28; *P*<0.001; τ^2=0.09, *P*<0.001 for heterogeneity); 68 RCTs involving 69 comparison, 50 RCTs published in full, 9617 patients (Rutjes et al., 2012). Approximately one fifth of the RCTs (14 of 68) included in this analysis involved a nonplacebo control group.

Statistical heterogeneity was moderate to high, and the results across individual studies were inconsistent. Mean differences in the individual trials included in the Colen analysis ranged from –36.00 to 3.30, and only 7 of 20 study-specific comparisons showed a statistically significant, positive effect. Similarly, in the Rutjes review, individual study SMDs ranged from –1.90 to 0.17, and only 13 of 69

comparisons showed a statistically significant, positive effect. The Samson review presented 3-month pain results for 3 meta-analyses that were less comprehensive than the Bellamy review in terms of included studies; the results were conflicting.
To explore observed heterogeneity, the Rutjes review conducted numerous subset analyses. Pooled estimates were significantly larger in the set of trials with inadequate or unclear assessor blinding (25 RTCs, SMD –0.66) versus trials with adequate assessor blinding (46 RCTs, SMD –0.25; *P*=0.003) and for trials with < 100 participants per treatment group (50 RCTs, SMD –0.52) versus trials with ≥ 100 participants per group (21 RCTs, SMD –0.16; *P*=0.002). Given these findings, the authors analyzed the 18 RCTs with adequate assessor blinding and large sample sizes (≥ 100 per group); the SMD at 3 months was –0.08 (compared with 0.37 for all 68 RCTs). There was a trend (*P* value 0.053 to 0.099) toward a significantly larger effect when allocation concealment was inadequate or unclear, 1 to 2 injections as opposed to ≥ 3 injections were administered, and follow-up was < 3 months. Subgroup analysis according to the following factors revealed small and nonsignificant differences: placebo versus nonplacebo control, adequate patient blinding, intention-to-treat (ITT) analysis, freedom from industry funding, and multiple cycles of treatment versus a single cycle. (NOTE: Although the Rutjes review used the term *subgroup* in this context, the term *subset* has been substituted to clarify that this analysis is at the study level, i.e., involves groups of studies, as opposed to patient-level analyses within individual trials, which are referred to in this report as subgroup analyses.)

Mean group differences were not reported for the trial by Navarro-Sarabia et al. (2011). In the trial by Strand et al. (2012a), the difference in mean improvement at approximately 3 months (13 weeks) was 6.39 (*P*=0.037) to 7.10 (*P*=0.005), depending on the analytic model, and favored HA injection.

Mean Difference in Physical Function

There were fewer analyses of functional outcomes than of pain outcomes. The Colen review did not address functional outcomes. The Bellamy and Rutjes analyses show improvement in physical function at 3 months to be slightly smaller than pain improvement:

- *At 5 to 13 weeks (WOMAC function):* SMD –0.9 (95% CI, –1.3 to –0.4; I^2=84%); 7 RCTs, 639 patients (Bellamy et al., 2006).
- *At 3 months:* SMD –0.33 (95% CI, –0.43 to –0.22; *P*<0.001; τ^2=0.10, *P*<0.001 for heterogeneity); 48 RCTs involving 49 comparisons, number of patients not reported (Rutjes et al., 2012).

As was the case in the corresponding meta-analyses of pain at 3 months, statistical heterogeneity was moderate to high, and the results across individual studies were inconsistent. In the Rutjes review, individual SMDs ranged from –2.16 to 0.30, and only 17 of 49 comparisons showed a statistically significant, positive effect. A funnel plot was asymmetrical. An analysis restricted to the 15 RCTs with large sample size and adequate assessor blinding yielded an SMD of –0.09 (95% CI, –0.17 to 0.00, τ^2=0.01), considerably smaller (–0.33) than the estimate for all trials. The Samson review presented estimates of the effect on function from 2 meta-analyses other than that in the Bellamy review; the results were conflicting. No subset analyses were reported for functional outcomes by any of the systematic reviews. Differences favoring viscosupplementation in physical function improvement of 5.42 (nonsignificant) and 5.29 (*P*=0.049), depending on the analytic model, were observed in the trial by Strand et al. (2012a).

Improvement in Quality of Life (QOL)

Six placebo-controlled trials with sample sizes of n ≥ 200 and adequate assessor blinding, according to Rutjes and colleagues, measured the effect of HA injection on QOL scales (Karlsson et al., 2002; Altman et al., 2004; Lundsgaard et al., 2008; Altman et al., 2009; Baltzer et al., 2009; Jorgenson et al., 2010). Most of the studies reported no effect on QOL measures, i.e., no difference in scores or change scores at follow-up between HA and placebo groups. The 2 studies with positive conclusions (Karlsson et al., Altman et al., 2009) reported improvement in the HA arms but provided no information about the placebo arm.

Mean Difference in Composite Measures

The Bellamy review included pooled estimates of improvement difference on the Lequesne Index, which measures a combination of pain and function on a 0 to 24 scale. For Lequesne score at 3 months, the WMD was –1.4 (–2.0 to –0.7; I^2=16%) (4 RCTs). One of the other meta-analyses (Strand et al., 2006) reviewed in the Samson report produced a WMD of –0.58 or –0.68 (both significant, 5 RCTs) on the Lequesne Index. Both estimates favored viscosupplementation. Differences in improvement in total WOMAC score in the trial by Strand et al. (2012a) were calculated according to 2 different analytic models as 5.64 (*P*=0.058) and 5.59 (*P*=0.035), both favoring viscosupplementation. The Strand study used Gel-One, which was not approved at the time of the Bellamy and Strand meta-analyses.

Repeat Courses

Three RCTs evaluated repeat courses of treatment (Jubb et al., 2003; Altman et al., 2011; Strand et al., 2012b). In the FLEXX extension trial, pain improvement continued slightly in both groups after the second treatment cycle (administered at 6 months following randomization). In the original trial, the pain improvement favored HA injection (difference 5 points on a 100-point VAS at 6 months), while in the extension trial, pain improvement at 6 months from initiation of the second treatment cycle favored the placebo group (difference, 5.5 points) (Altman et al., 2011). Since < 75% of the original study group participated in the extension trial, these findings may not be representative. In an earlier double-blind placebo-controlled trial, a significant effect was observed after both a first and second course of treatment, but after a third course, the difference was nonsignificant, although favorable to HA (Jubb et al., 2003). Courses were administrated every 4 months. As in the FLEXX extension trial, the dropout rate was high (22%). The 2012 Gel-One trial (Strand et al., 2012a) was followed by an extension and treatment trial in which patients remained blinded to their original treatment allocation (Strand 2012b). Within a time frame of 3 to 6 months from the time of the initial injection, patients from both randomized groups could obtain a second Gel-One injection or a Gel-One injection stead of another saline injection if their symptoms increased to the levels that defined inclusion criteria for the original trial. Patients originally randomized to HA were 25% less likely to need retreatment (hazard ratio, 0.75; *P*=0.040) after adjustment for baseline scores and covariates. During the retreatment phase, which extended up to 13 weeks from the beginning of the extension trial, there was no difference in improvement or response rate according to original treatment allocation.

Clinical Relevance of Mean Group Differences

Pain

According to the Samson review, the authors of meta-analyses included in that review offered no definition of clinical importance. The following sources suggest that clinically relevant *improvement from baseline* is in the range of 10 to 30 points on a 100-point scale:

- The 2007 Samson review cited a source suggesting that a 20- to 40-point improvement in WOMAC pain (100-point scale) is considered a positive response.
- RCT authors have considered a 20-point improvement on 100-point pain scales to denote a clinical response (Altman and Moskowitz, 1998; Raynauld et al., 2002; Neustadt et al., 2005).
- Two very recent trials have measured clinical response according to criteria adopted by the Osteoarthritis Research Society International (OARSI) (Navarro-Sarabia et al., 2011; Strand et al., 2012a). These are called the Outcome Measures in Rheumatology Clinical Trials (OMERACT)-OARSI criteria. Patients are considered to have a clinical response if: (1) pain *or* physical function score decreases ≥ 50% relative to baseline *and* ≥ 20 mm on a 100-mm VAS ("strict responders" according to Strand et al.); *or* (2) scores on a 100-mm VAS decrease by ≥ 20% or by ≥ 10 mm on *2* of the following: (a) WOMAC pain, (b) WOMAC physical function, or (c) patient global assessment.
- Two consensus statements issued by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group have *provisionally* defined a *minimal clinically important difference (MCID)* in chronic pain intensity to be either a 10% to 20% relative improvement from baseline *or* an absolute change of 1 cm on a 10-cm VAS, which translates to a 10-mm change on a 100-mm VAS; *moderate* (clinically important) improvement to be ≥ 30% relative improvement from baseline *or* an absolute change of 2.0 to 2.7 cm (corresponding to 20 to 27 mm); and *substantial* improvement to be ≥ 50% improvement relative to baseline. The authors cite several studies to support these benchmarks. However, the consensus document advises that further research is needed. The IMMPACT statement also points out that group differences in controlled trials will always be smaller than mean improvement within treatment arms since the group difference reflects a downward adjustment for placebo effect. The group maintains that the clinical meaningfulness of group differences in a trial depends on the balance of harms and benefits of a treatment and its alternatives, including differences in rapidity and durability of benefit. The group favors evaluating group differences in terms of responder rates (Dworkin et al., 2008; Dworkin et al., 2009). See following discussion of *Likelihood of Clinically Relevant Benefit (Responder Rates)*.
- The Colen review cited studies reporting MCID values of 10 to 30 points on a 100-point scale, but these studies were not generally specific to OA.

Thus, for knee OA a 20-point improvement *from baseline* on a 100-point scale seems to have widest recognition as being clinically meaningful, although concurrent observation of a 50% relative improvement would be required to assume a large benefit. These thresholds relate to within-group improvements. According to reasoning presented by the IMMPACT statement, a *group* difference may be clinically meaningful at *less than* 20 points. For the key endpoint of pain at 3 months, WMDs were 11.0 (Bellamy review) and 10.20 (Colen review); neither review offered a basis for interpreting the clinical relevance of these results. The Colen review included pooled within-group estimates of relative improvement: from 30% to 66% for specific HA products, and 30% for placebo.

The authors of the Rutjes review prespecified an effect size of 0.37 as representing a trial-based MCID. One source cited by Rutjes and colleagues stated that the median threshold for clinically meaningful improvement found in uncontrolled studies in patients with OA was a 0.9 difference on a 10-cm VAS, corresponding to an effect size of 0.37 (Wandel et al., 2010). Another source cited in the Rutjes review described an effect size of 0.40 as *moderate* for OA pain relief and stated that this value corresponds to a difference of 1 cm on a 10-cm scale in a 2-arm trial (Nuesch et al., 2010). Thus, the MCID assumed in the Rutjes review for a *between-group difference* was smaller than the typical 2-cm (20-mm) definition of MCID for *improvement from baseline* (see preceding discussion), which would seem to be consistent with the arguments made in the IMMPACT statement by Dworkin et al. (2010). Across all meta-analyses covered in this report, pooled estimates expressed as effect sizes ranged from 0.10 to 1.2 for different types of analyses. For pain effect at 3 months, the 2 estimates reported by key reviews were statistically large in 1 review (1.0, Bellamy) and statistically small to moderate in the other more recent and larger review (0.37, Rutjes).[1] For the particular Bellamy analysis that yielded an effect size of 1.0 (weight-bearing pain measured on the WOMAC scale), data were available from only 7 trials. (The Bellamy review presented numerous analyses based on different outcome measures rather than synthesizing data from trials that used different measures.)

In conclusion, the 3 key meta-analyses suggest that the placebo-controlled effect of viscosupplementation on pain at approximately 3 months just meets or slightly exceeds an MCID.

Physical Function

The OMERACT-OARSI criteria suggest that a clinically meaningful improvement in function is on the same order of magnitude as a clinically meaningful improvement in pain (Navarro-Sarabia et al., 2011; Strand et al., 2012a). No meta-analyses reported functional outcomes in terms of WMDs. Effect sizes for function outcomes ranged from 0 to 1.0 across the 5 meta-analyses reporting estimates of physical function effects. For effect at 3 months, reported estimates in the key meta-analyses were slightly smaller than effect sizes for pain improvement: 0.9 (Bellamy review) and 0.33 (Rutjes review).

Composite Measures

The Samson review cites a source suggesting that 20% is the minimum clinically important improvement for the Lequesne Index. It is not possible to map the 3-month WMD of –1.4 reported in the Bellamy review to relative improvement, but a difference of 1.4 on a 0- to 24-scale would likely be considered small.

Effect over Time

A systematic review published in 2011 focused on the therapeutic trajectory of viscosupplementation (Bannuru et al., 2011). Study eligibility criteria were very similar to those followed for the Rutjes review (no exclusions based on publication status), but the Bannuru literature search ended approximately 2 years earlier than the Rutjes literature search. A total of 54 RCTs (6545 patients) were included in the

[1] According to the Samson and Bellamy reviews, SMDs (effect sizes) are conventionally interpreted as follows: 0.2 or 0.3 = small, 0.5 = moderate (i.e., clinically recognizable), and 0.8 = large. These effect size categories are generic and do not necessarily translate to clinical importance for particular health problems.

2011 Bannuru review. The greatest effect size was found at 7 to 10 weeks (selected to correspond to 2 months): SMD, 0.46 (95% CI, 0.28 to 0.65; I^2 = 75%; 26 trials). The SMD at 3 to 6 weeks was 0.31, and effect sizes at intervals exceeding 10 weeks ranged from 0.21 to 0.25. All SMDs were statistically significant. In the 14 RCTs (2570 patients) deemed to be of high quality, a similar pattern was observed, but the effect was somewhat smaller: SMD at 7 to 10 weeks was 0.34 (95% CI, 0.02 to 0.67). Subgroup analyses yielded findings similar to those reported in the Rutjes review: adequate allocation concealment, double-blinding, > 100 participants, unpublished status (5 of 49 trials), and publication after the year 2000 were associated with substantially smaller effects. Generally, high study quality and intention-to-treat (ITT) analysis were associated with slightly smaller effects. Effect sizes for physical function outcomes did not follow as clear a pattern and were derived from smaller numbers of trials; functional effect seemed peak early (at 3 to 6 weeks) and to begin to decline after 10 weeks. Improvement in stiffness seemed to begin to decline after 6 weeks.
Analysis in the Rutjes review also suggested a possible peak pain effect at < 3 months: SMDs were –0.54 at < 3 months of follow-up, –0.23 at 3 to 6 months, and –0.36 at > 6 months (global *P* across estimates, 0.078; each estimate was statistically significant). Likewise, effect sizes in the Bellamy review were greater at 5 to 13 weeks than at 1 to 4 weeks or at 14 to 26 weeks.

Likelihood of Clinically Relevant Benefit (Responder Rates)

Placebo-Controlled Trials

A small mean effect does not convey whether only a few patients or a substantial proportion of patients experienced clinically meaningful improvement. The Samson review found that most placebo comparisons in individual trials failed to report the results in useful terms such as the proportion of patients in each arm who experienced clinically meaningful improvement. Samson and colleagues referred to the number-needed-to-treat (NNT) calculations carried out in the Bellamy review for individual studies. These NNT estimates were not only conflicting but tended to be tied to nonspecific definitions of improvement or success.

Table 4 presents responder rates in 11 trials (total, n=4029) that defined response in terms of mean individual improvement *within* groups (not to be confused with minimal clinically important group differences). These studies were identified in the Hayes, Colen, and Rutjes reviews, as well as by the update literature search. The findings were variable. Only 3 studies (Neustadt et al., 2005; Chevalier et al., 2010; Navarro-Sarabia et al., 2011) reported positive and statistically significant findings according to intention-to-treat (ITT) or modified ITT analysis. One study found a significant difference favoring viscosupplementation in patients treated with hylan but not in patients treated with non–cross-linked HA (Rolf et al., 2005). Two studies reported findings that favored placebo (Altman et al., 2004; Jorgensen et al., 2010); the definitions of clinically important benefit used in these 2 studies were least like the recently defined OMERACT-OARSI criteria. It should be noted that the OMERACT-OARSI criteria are composite measures and do not allow an assessment of whether pain, function, or both improve. The other 5 studies reported small and nonsignificant differences according to ITT analysis or did not report significance testing.

Table 4. Responder Rates in Randomized Placebo-Controlled Trials with ≥ 200 Participants

Key: CI, confidence interval; f/u, follow-up; HA, hyaluronic acid; ITT, intention-to-treat (analysis); MCID, minimal clinically important difference; N/A, not applicable (NNT could not be calculated); NNT,

number-needed-to-treat (for 1 patient to have a clinically meaningful response); NR, not reported; NS, (statistically) nonsignificant; OMERACT-OARSI, Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Society International; OR, odds ratio; RR, relative risk; tx, treatment; WOMAC, Western Ontario and McMaster Universities Index

NOTE: Trials were placebo-controlled except where noted. All trials were considered, either by authors of the Rutjes review or by direct assessment for this report, to have adequate assessor blinding. **Bolding** is used to highlight significant, positive results.

Study	n	F/u	Definition of Response	Responder Rates (HA vs placebo unless otherwise noted)	Absolute Difference	NNT*
Altman and Moskowitz, 1998	495	5-26 wks	≥20 points on a 100-point scale (pain)	**Per protocol: 56% vs 41% (*P*=0.031)** ITT: 36% vs 28% (NS)	**Per protocol:** 0.08 ITT: 0.14	**Per protocol: 7** ITT: 13
Altman et al. (2004)	347	13 wks	≥40% improvement in pain (WOMAC) and ≥5 points improvement	Per protocol: 38.1% vs 40.3% (NS) ITT: 32.0% vs 35.1% (NS) (NS differences at 26 wks)	Per protocol: –0.02 ITT: –0.03	Per protocol: –46 ITT: –33
Neustadt et al. (2005)†	372	8 wks	≥20 points on a 100-point scale (pain)	**76% vs 62% (*P*=0.0346)** (modified ITT analysis)	**0.14**	**8**
Rolf et al. (2005)	272	26 wks	Symptom free at 26 wks	****Hylan (Synvisc)**: 44% vs 30% (*P*=0.048)** Non–cross-linked HA: 43% vs 30% (NS)	****Hylan**: 0.14** Non–cross-linked HA: 0.13	****Hylan**: 8** Non–cross-linked HA: 8
Lundsgaard 2008	251	26 wks	OMERACT-OARSI	30% vs 27% (NS)		34
Altman et al. (2009) (FLEXX trial)	588	12 wks, 26 wks	OMERACT-OARSI, pain on 50-foot walk	12 wks: OR, 1.3 (CI, 0.9-1.8) (NS) 26 wks: OR, 1.4 (CI, 1.0-2.1) (NS) (HA vs placebo)		N/A
Altman et al. (2011) (Extension of FLEXX Trial)	433	26 wks from 2nd tx	OMERACT-OARSI, pain on 50-foot walk	67% vs 59% (significance testing NR) (modified ITT analysis)	0.06	13 (significance NR)
Chevalier et al. (2010) ***Hylan***	253	26 wks	OMERACT-OARSI	26 wks: OR, 0.69 (CI, 0.41-1.16) >26 wks: OR, 0.66 (0.44-1.02) (placebo vs hylan) (ITT analysis)		N/A
Jorgensen et al. (2010)	337	3 mos	Improved Lequesne score at any time ≤3 mos	69.7% vs 72.4% (NS) (ITT analysis)	–0.03	–38
Navarro-Sarabia et al. (2011)	306	≤40 wks	OMERACT-OARSI	**34 wks: 81% vs 65% (*P*=0.002)** Similar findings at 14, 21, and 27 mos; small and NS differences at 7 mos; earlier f/u results NR. (Substantial loss to f/u at 34 mos, somewhat greater and more likely to be due to lack of efficacy in	**0.16**	**7**

Study	n	F/u	Definition of Response	Responder Rates (HA vs placebo unless otherwise noted)	Absolute Difference	NNT*
				placebo grp.) (modified ITT analysis for this and all other results)		
			OMERACT-OARSI	Last f/u: 81% vs 66% (*P*=0.004); RR, 1.22 (CI, 1.07-1.41)	0.16	7 (CI, 4.1-20.5)
			Pain *or* function reduction ≥50% and 20 mm	**Last f/u: 65% vs 52% (*P*=0.02)**	**0.13**	**8**
			Pain reduction ≥20% or 10 mm	Last f/u: 79% vs 68% (*P*=0.025)	0.11	10
			WOMAC function improvement ≥20% or 10 mm	**Last f/u: 71% vs 56% (*P*=0.023)** (Substantial loss to f/u at 34 mos, somewhat greater and more likely to be due to lack of efficacy in placebo grp.)	0.15	**7**
Strand et al. (2012a) (AMELIA trial) *** (cross-linked HA: Gel-One)***	375	13 wks	OMERACT-OARSI (all criteria met)	6 wks: 51.1% vs 39.5% 9 wks: 54.1% vs 46.6% 13 wks: 45.9% vs 38.7% 6-13 wks: OR, 1.59 (CI, 1.07-2.37) ITT analysis and significance NR for these and other results.	0.11 0.7 0.17 N/A	9 14 15 N/A
			OMERACT-OARSI (criteria partially met)	6 wks: 66% vs 61.3% 9 wks: 65.4% vs 62.7% 13 wks: 61% vs 54.6% 6-13 wks: OR NR	4.7 2.7 6.4 N/A	22 38 16 N/A

*In most cases, calculated from responder rate data rather than reported by authors.

†Versus arthrocentesis without injection rather than placebo injection.

Viscosupplementation as an Add-on to Usual Treatment

As used in practice, viscosupplementation does not necessarily totally replace other therapies. Thus, some studies have investigated the effect of adding HA injections to the existing treatment plan.

Two pragmatic RCTs with sample sizes ≥ 200, both included in the primary analysis conducted in the Rutjes review, compared viscosupplementation using hylan (Synvisc) plus usual care with usual care alone (Raynauld et al, 2002; Kahan et al., 2003). The results are displayed in **Table 5**. These 2 trials were very similar to placebo-controlled trials with respect to typical patient characteristics and exclusion of patients with a recent corticosteroid injection. In the trial by Raynauld et al., usual care included all forms of nonsurgical management as well as total joint replacement (the number of patients who underwent joint replacement was not reported). In the study by Kahan et al., conventional care was not defined, but patients with previous knee replacement surgery were excluded. In both studies, patients were required to have obtained inadequate relief from acetaminophen and/or NSAIDs, and most patients were taking NSAIDs at the time of randomization. Pain and function change score differences at follow-up favored viscosupplementation but were small (–2.6 for pain, Raynauld study; –12.4 for pain,

Kahan study), as in most placebo-controlled studies. However, NNT values were low: 4 to 6, depending on the different definitions of response. One way to interpret these findings is that approximately 15% to 25% of patients treated with viscosupplementation as an add-on treatment when other measures have failed will experience a clinically meaningful benefit. Both studies used ITT analyses but were hampered by the impossibility of blinding in this type of comparison. It was not clear whether patients in the hylan (Synvisc) group of the Kahan study continued to receive conventional care.

Table 5. Responder Rates in Pragmatic Randomized Controlled Trials (RCTs)

Key: f/u, follow-up; ITT, intention-to-treat (analysis); MCID, minimal clinically important difference; NNT, number-needed-to-treat; NS, (statistically) nonsignificant; WOMAC, Western Ontario and McMaster Universities Index

Study	n	F/u	Definition of Response	Responder Rates (HA vs conventional treatment)	Absolute Difference	NNT
Raynauld et al. (2002) (ITT analysis) ***Hylan (Synvisc)***	255	1 yr	≥20 points on 100-mm VAS	**WOMAC pain: 69% vs 40% (*P*=0.0001)** **WOMAC pain and either stiffness or physical functioning: 62% vs 35% (*P*=0.0001)**	**0.19** **0.27**	**4** **4**
Kahan et al. (2003) (ITT analysis) ***Hylan***	506	1 yr	≥20% decrease in pain on walking and "good" or "satisfactory" on a 4-point Likert scale	**Response according to MCID: 88.1% vs 68.0% (*P*<0.001)** **≥20% increase in Lequesne Index: 65.2% vs 40.3% (*P*<0.001)** **≥50% increase in Lequesne Index: 31% vs 14% (*P*<0.001)**	**0.20** **0.15** **0.17**	**5** **5** (rounded from 4.016) **6**

In the large case series (n=1266 patients, predominantly presenting with knee OA) previously mentioned (Foti et al., 2011), the use of medications for relief of OA symptoms declined from 19% of patients during the interval between the first and second HA injections to 11% of patients during the interval between the third (last) injection and the follow-up visit 2 weeks later. However, baseline data indicate that only 10% of patients were using pain medications *prior* to the HA treatment. Data specific to knees showed pain during motion to decline by 35 points on a 100-mm VAS and pain at rest to decline by 25 points. However, there was no follow-up beyond the 2-week visit. Patients in this series were similar in age to patients in the RCTs but had a shorter duration of OA (mean, 2 years) and were less likely to be using other medications prior to HA treatment.

Viscosupplementation Versus Conservative Alternatives

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The Bellamy review included 4 RCTs comparing the effectiveness of a single viscosupplementation product with NSAIDs. The review authors concluded that the 2 treatments had generally comparable efficacy.

Intraarticular Corticosteroids

In a meta-analysis of 7 RCTs (n=606) comparing viscosupplementation with corticosteroid injection (Bannuru et al., 2009), pooled effect sizes for pain favored corticosteroids in the first few weeks but then began to increasingly favor HA/hylan with time. The differences were significant and favored HA at 11 to 16 weeks. The greatest effect (at 17 to 26 weeks) was modest (–0.39; 95% CI, 0.18 to 0.59). Additional subset and regression analyses based on ITT analysis, use of blinding, and use of methylprednisolone acetate as the corticosteroid confirmed the overall findings. The analysis was based on a hierarchy of pain measures. No functional outcomes were assessed.

Other Alternatives

Trials directly comparing HA or hylan (Synvisc) with treatments other than NSAIDs or intraarticular corticosteroids were too few in number to allow the authors of the Bellamy review to reach conclusions. A fair-quality trial omitted from any of the published systematic reviews compared HA with home exercise and found no difference between groups in reduction of pain or improvement of function (Kawasaki et al., 2009). The Colen review presented a pooled estimate of relative improvement, 33%, in the physical therapy groups of 4 RCTs. This compares with pooled estimates of 30% to 66% for different HA products and 30% for placebo groups. However, these calculations do not allow conclusions about the effect of viscosupplementation versus physical therapy since they are all within-group estimates based on different sets of RCTs.

Quality and Generalizability of Evidence, Key Question #1a

Efficacy: Systematic reviews did not assign quality ratings to individual studies. The Rutjes review reported a mean value of 3.6 (median, 3) on the Jadad scales for study quality. The 2011 Bannuru review reported that 30% of trials were considered to be of "high" quality. Sensitivity analyses conducted in the Rutjes review identified 2 methodological features that were associated with effect size: large sample size (> 100 patients per group) and adequate assessor blinding. Eighteen trials met these criteria. The Rutjes analyses also detected a subset difference in pain at 3 months according to publication type (global *P*=0.040), with 14 nonjournal publications (pamphlet, book, or conference abstract) yielding the greatest effect (SMD, –0.63), 52 journal publications yielding an effect (SMD, –0.36) similar to the overall pooled estimate noted previously (–0.37), and 5 unpublished studies yielding a nonsignificant SMD of –0.03. The authors considered these findings to denote substantial publication bias, which was also suggested by an asymmetrical funnel plot. Study subset analysis according to independence from industry funding showed a nonsignificant difference, and the 4 trials with clear commercial independence actually showed a *larger* pooled effect. Considering the large volume of evidence, including good-quality RCTs; the presence of some inconsistency in the results across studies but high consistency in direction and statistical significance across pooled estimates by authors of the 3 largest meta-analyses; the applicability of findings to the PICO statement; and some suggestion of publication bias, the evidence regarding the efficacy of viscosupplementation versus placebo is of **moderate** quality. The magnitude of benefit may be clinically irrelevant, but this finding is not a reflection of the quality of the evidence showing a small mean effect.

Likelihood of a Clinically Relevant Response: There was a substantial body of evidence (11 RCTs) evaluating whether HA injection, compared with a sham injection, was more likely to result in clinically meaningful improvement. However, the representativeness of these trials is unknown; most of the more than 50 placebo-controlled trials published to date have not reported results in these terms. The

differences in response rates were consistently in favor of HA, except for 2 studies using a definition of clinical improvement least similar to criteria endorsed by the OA research community as appropriate for measuring response rates. However, of the 9 studies with results favoring viscosupplementation, only 4 reported statistically significant results according to ITT or modified ITT analysis.

Quality of Life: Evidence for this outcome is of moderate quality, taking into account the quantity of data (6 RCTs with sample sizes ≥ 200; total, n=2147), the adequacy of assessor blinding in the studies, as reported by the Rutjes review, and the slight inconsistency of findings.

Effectiveness in Usual Practice: Two studies (total, n=773) suggest that viscosupplementation as an add-on treatment, at least when hylan (Synvisc) is used, is effective in real-world practice. These would not be considered high-quality studies in terms of risk of bias because they are, by design; pragmatic trials intended to mirror real-world conditions. Both studies had good completion rates. Given the objectives of the studies, this body of evidence was considered to be of **moderate** quality. However, the lack of recently published pragmatic trials raises the question of the generalizability of these results to current practice patterns; furthermore, they were conducted in non-U.S. settings.

Viscosupplementation Versus NSAIDs: The results were fairly consistent across trials as described in the Bellamy review but the review provided no analysis of trial quality and no studies have been published since 2006 (**no quality rating**).

Viscosupplementation Versus Intraarticular Corticosteroids: The 2009 Bannuru review described trial quality as generally poor; thus, the evidence is considered to be of **low** quality.

Viscosupplementation Versus Glucosamine and/or Chondroitin: Since no studies made this comparison, the evidence was **insufficient** to permit a conclusion.

Key Question #1b: Do different viscosupplementation products vary in effectiveness?

Study Characteristics

Evidence pertaining to Key Question #1b came from 2 meta-analyses with overlapping study lists (Reichenbach et al., 2007; Colen et al., 2012), a meta-analysis evaluating therapeutic effectiveness over time (Bannuru et al., 2011), sensitivity analyses conducted in the context of a more general meta-analysis (Rutjes et al., 2012), 1 earlier trial with a post hoc analysis (Kirchner and Marshall, 2006; Onel et al., 2008), and a recently published RCT (Petrella et al., 2011). All 6 works evaluated the association of molecular weight with effectiveness.

Findings

The Reichenbach review analyzed the effect of viscosupplementation on pain in 13 randomized and quasi-randomized comparator trials (n=2085). The meta-analysis detected a marginally significant and small absolute effect (SMD, –0.27; 95% CI, –0.55 to 0.01; I^2=88%) that favored hylan (highest molecular weight) versus non–cross-linked HA products but that was below the authors' definition of minimally important clinical improvement (–0.30). The effect disappeared when 2 outlier trials were removed from analysis. Furthermore, meta-regression analysis showed no association between molecular weight as a continuous variable and effect size. The inconsistency in the direction of results across the individual

studies appeared to be related to study quality: in stratified subset analysis, effect sizes were near the null value in subsets of trials that had adequate allocation concealment, adequate patient blinding, or ITT analysis. Meta-analysis that also produced an RR of any adverse event suggested increased risks associated with hylan: RR, 1.91 (95% CI, 1.04 to 3.49; 6 RCTs with consistent results favoring HA over hylan).

A post hoc analysis of a comparator trial included in the Reichenbach review evaluated responder rates according to OMERACT-OARSI criteria (Onel et al., 2008). The original trial (Kirchner and Marshall, 2006), had demonstrated noninferiority in a comparison of Euflexxa with Synvisc; those results were confirmed in the responder rate analysis conducted by Onel et al.

The Reichenbach review also included an indirect comparison based on the 31 placebo-controlled trials contributing to 3 of the meta-analyses covered in the 2007 Samson review. The indirect comparison was conducted through meta-regression, with hylan (versus non–cross-linked HA) as the independent variable. The SMD of pain scores at follow-up in the indirect comparison was much larger (SMA, –0.64) than that calculated on the basis of the comparator trials (SMD, –0.27). Further analysis suggested that this discrepancy could be due to the relatively small size of the hylan versus placebo trials, the large effects that they reported, and an association across all 31 trials of smaller sample size with larger effect.

The other meta-analysis addressing this issue was provided in the Colen review. In contrast to the Reichenbach review, the Colen review excluded studies that were not published in full. Analysis of Synvisc (hylan) versus HA yielded an effect even smaller than that reported by Reichenbach et al. (2007): SMD, –0.07 (95% CI, –0.24 to 0.10; I^2=72%; 12 RCTs, 2492 patients). Individual trials had inconsistent results, with only 3 trials demonstrating a statistically significant effect favoring Synvisc. Pooled comparisons of Synvisc with individual non–cross-linked HA products yielded small effects; only the comparison with Hyalgan was statistically significant, possibly due to the small number of trials comparing Synvisc with other products. Consistent with the indirect analysis provided in the Reichenbach review, separate analyses of trials comparing a particular product with placebo suggested that Synvisc had a greater effect than non–cross-linked HA products (–0.89 versus –0.61 for Hyalgan and–0.10 for Orthovisc) but the pooled estimate for Synvisc was nonsignificant, possibly because of the small number (n=3) of trials.

Among the sensitivity analyses conducted as part of the Rutjes review, trials were stratified according to whether they involved cross-linked products, i.e., hylan (19 RCTs) or products that were either non–cross-linked or of uncertain chemical structure (56 RCTs). Effect sizes were significant for each subset of RCTs, but the effect size was somewhat larger for the cross-linked subset, with the difference showing a trend toward significance (–0.53 versus –0.29; *P*=0.099). These equivocal findings are consistent with those reported in the Reichenbach and Colen reviews.

An RCT (n=200) published after the systematic reviews showed that a combination of high and low molecular weight HA led to greater relative improvement from baseline (89.3% at 16 weeks) than what was observed for either low molecular weight (81.3%) or high molecular weight treatment (79.1%); the *P* value for the combination versus the other 2 treatments was <0.001 (Petrella et al., 2011). The difference between high and low molecular weights, which favored *low* molecular weight, was nonsignificant.

In the meta-analysis of hylan/non–cross-linked HA comparator trials, the findings suggested approximately a twofold increase in the risk of any adverse event associated with hylan and low statistical heterogeneity across trials, even though definitions and reporting varied considerably (Reichenbach et al., 2007). The absolute rate of any adverse event in the hylan arms ranged from 0.05% to 18%. The same review estimated that 14 patients would need to be treated with hylan rather than non–cross-linked HA in order for 1 patient to suffer an additional adverse event.

None of the systematic reviews analyzed findings according to whether products were FDA approved. In the 21 RCTs with sample sizes of n ≥ 200, more than half the trials used products that were non-FDA approved or did not specify brand names. Among the trials that specified brands, no pattern of differences in results was apparent between those trials that did and did not use FDA-approved products.

Quality and Generalizability of Evidence, Key Question #1b

The Reichenbach review described the quality of included trials as being generally poor; 6 of the 13 studies reported patient blinding and only 1 reported therapist blinding. The Colen review did not provide an assessment of study quality. There was inconsistency across studies in the direction of the results as well as imprecision in the pooled estimates and lack of significance within subsets. The quality of evidence pertaining to differential effect according to **molecular weight** was judged to be of **low** quality since it was based on direct comparison in poor-quality comparator trials and metaregression (indirect comparison). Differential effectiveness according to **FDA approval** could not be assessed because of **insufficient** evidence.

Key Question #2: What are the adverse effects associated with viscosupplementation in patients with OA of the knee?

Study Characteristics

Safety data were presented by the Samson, Bellamy, and Rutjes reviews. None of the systematic reviews provided information on the duration of follow-up represented by adverse event rates. Safety data were also available in the recently published placebo-controlled trials (Altman et al., 2011; Navarro-Sarabia et al., 2011; Strand et al., 2012a). Additional data were obtained from a narrative review of pseudoseptic reactions following viscosupplementation (Goldberg and Coutts, 2004).

Findings, Viscosupplementation Versus Placebo

Any Adverse Event

According to the 2007 Samson review, as well as the recently published RCTs selected for the update report, the most common adverse events after viscosupplementation include injection site pain, joint pain or swelling, and joint effusion. The Bellamy review found no significant differences in placebo trials for 12 adverse events, but reported a high pooled RR for pain at the injection site: RR, 1.7 (95% CI, 1.19 to 2.44). The largest and most recent meta-analysis (Rutjes et al., 2012) yielded an RR of 1.04 (95% CI, 0.99 to 1.09) for any adverse event (25 RCTs, 5204 patients). The subset of trials identified in the Rutjes review as having ≥ 100 patients in each treatment arm and adequate blinded assessment also showed no increased overall risk: RR, 1.01 (95% CI, 0.96 to 1.06; 11 RCTs, 3214 patients). The patient-level meta-

analysis included in the Samson review (Strand et al., 2006) reported a *lower* rate of adverse events in HA arms (1.8%) than in the placebo arms (3.2%). In recently published RCTs, overall adverse event rates were similar between HA and control arms (Altman et al., 2011; Navarro-Sarabia et al., 2011; Strand et al., 2012a).

Large observational studies may provide more reliable estimates of adverse event rates than are obtained through RCTs. The Samson review cited rates from 3 case series, all of which evaluated the use of hylan. Study populations included a mix of patients receiving first-time and repeat courses of treatment. Patients were apparently not followed beyond the end of a treatment course. Per-patient rates from 2 series (total, n=4589 patients) ranged from 5.3% to 8.3%. Per-injection rates from 2 series (total, n=5468 injections) were 2.1% to 2.7% overall. Two of the series reported that the per-injection or per-person rate was much higher during a repeat course than during an initial course. In a recently published case series involving 47 centers and 1266 evaluable patients receiving HA injections for joint OA, 0.8% of patients experienced ≥ 1 adverse event by the time of follow-up at 2 weeks after the last of 3 injections (Foti et al., 2011). Most of the study participants in this study were being treated for knee OA. The HA product was a non–cross-linked product (Hyalubrix) that is not available in the U.S.

Local Adverse Events

The Rutjes review estimated an RR of 1.51 (95% CI, 0.84 to 2.72; 6 RCTs, 811 patients, no heterogeneity) for flare-up (also called *flares*). Flare-up was considered the primary safety outcome in that review and was defined as hot, painful, swollen knee within 24 to 72 hours after an injection. The Rutjes review also reported estimates of RR, 1.34 (95% CI, 1.13 to 1.60; 31 RCTs, 5241 patients) for any local adverse event and RR, 1.15 (95% CI, 0.38 to 3.54 [nonsignificant]; 61 RCTs, 1337 patients) for effusion. All estimates were free of heterogeneity.

Although not specifically mentioned in any of the clinical trials selected for this report, or in the trial information provided in systematic reviews, pseudosepsis is a possible adverse effect following injection with HA products. Pseudosepsis is a noninfectious reaction that mimics systemic anaphylactoid sepsis. Pseudosepsis following knee injection consists of severe joint inflammation with pain and effusion 24 to 72 hours after injection. It is clinically distinct from local inflammatory reactions attributable to hyaluronan products and from the flares associated with most intraarticular injections. Other terms used for this reaction include *severe acute inflammatory reaction* and *pseudo-septic arthritis.* Pseudosepsis can be distinguished from pseudogout if there are no calcium pyrophosphate crystals present in the synovial fluid, and is suggested if eosinophils are present. Patients are treated symptomatically (Goldberg and Coutts, 2004; Idrissi et al., 2012). One review identified 28 cases of pseudosepsis following hylan injection in the clinical literature published as of February 2004. In these reports, the reaction usually occurred after ≥ 2 injections during a course of treatment. For 4 cases, unscheduled care was required, but this information was not available for the other cases. No incidences of pseudosepsis were reported following injection of non–cross-linked HA products. No life-threatening consequences of pseudosepsis were described, but the review authors averred that if repeated injections resulted in additional reactions, OA progression might be accelerated (Goldberg and Coutts, 2004). An additional case of pseudosepsis following injection with a *non–cross-linked HA* product and treated in the hospital with anti-inflammatory and rehabilitation therapy was identified in the recent literature (Idrissi et al., 2012). The case report by Idrissi et al. suggests that pseudosepsis can be a serious event. Other cases of pseudosepsis have been reported to the FDA following use of non–cross-linked HA products.

Serious Adverse Events

The most comprehensive pooled estimate for serious adverse events came from the Rutjes review: RR, 1.41 (95% CI, 1.02 to 1.97; no heterogeneity; 14 RCTs, 3667 patients). Serious events (n=35) included 10 gastrointestinal (GI) events (2 HA, 8 control), 7 cardiovascular events (5 HA, 2 control), 6 cases of cancer (6 HA, 0 control), and 6 cases of musculoskeletal disorders (4 HA, 2 control). No information on the nature of the musculoskeletal disorders was provided. The authors did not report event rates or number of patients by treatment arm for the overall analysis of serious events, so the absolute risk difference in the incidence of serious adverse events is unknown. However, an overall crude event rate (both arms included) calculated from the numbers provided is very small—0.9% (35/3667). Thus, the absolute difference in pooled rates would be quite small (< 0.9 percentage points). The pooled estimate for 11 large double-blinded RCTs was RR, 1.55 (95% CI, 1.07 to 2.24); study-specific RRs in this subset ranged from 0.34 to 2.00 although no statistical heterogeneity was detected. Rutjes and colleagues stated that the causal mechanism associated with the increased incidence of serious adverse events in patients who received viscosupplementation is unclear. GI events, which are known risks with use of NSAIDs, were *less* frequent in the HA arms. The review authors did not provide an a priori definition of "serious" or provide information on follow-up intervals.

Recently published RCTs reported that no serious treatment-related adverse events were observed (Altman et al., 2011; Strand et al., 2012a) or that no serious adverse events attributable to any cause were observed (Petrella et al., 2011), or did not mention the issue of serious adverse events (Navarro-Sarabia et al., 2011). The trial by Strand et al. did find that serious systemic events, even more wide ranging than those counted in the Rutjes meta-analysis, occurred at a rate of 3.2% in the HA arm and were not observed at all in the placebo arm. Strand and colleagues did not consider these events to be treatment related. Safety outcomes from earlier RCTs with sample sizes ≥ 200 were briefly reviewed; for most trials, no serious adverse events were observed, or the overall rate of serious adverse events was similar between HA and placebo groups. Authors consistently stated that these events were not believed to be related to treatment.
Among the 3 case series included in the Samson review (> 9721 injections), 1 severe adverse event (large effusion with synovitis) was reported. The case series by Foti et al. (2011) reported an incidence of 0.08% of patients for severe adverse events occurring within 2 weeks after the last injection; most of the study population (n=1266) were being treated for knee OA. Severe events included pain at injection site (n=6), swelling at injection site (n=1), and other types of events (n=6). There was no discussion of the relationship to treatment.

Findings, Viscosupplementation Versus Other Alternatives or Usual Care

The Bellamy review observed that, in trials comparing viscosupplementation with systemic treatment, e.g., NSAIDs, there were more local reactions but fewer systemic adverse effects such as GI problems. In an RCT comparing viscosupplementation as an add-on treatment with appropriate care alone, fewer patients in the HA arm (52%) had had adverse events at 1 year compared with the appropriate care group (68%; *P*=0.0116) (Raynauld et al., 2002). In another similar RCT, adverse events occurred in 44.2% of patients in the HA arm and 31.9% in the conventional treatment arm (Kahan et al., 2003). Kahan et al. further reported that GI events, the most common adverse event in the placebo arm, occurred in 3.5% (HA) and 11.9% (placebo) of patients. Statistical testing was not reported by Kahan et al. No serious adverse events were mentioned in the results for the Kahan trial. In the Raynauld trial, no serious events occurred in the HA arm.

Manufacturer and User Facility Device Experience (MAUDE)

The Samson review reported that a review of the FDA MAUDE database revealed that in 236 reports having to do with viscosupplementation from January 2005 to January 2007, 85 patients were hospitalized. Nine of 236 reports mentioned pseudosepsis or pseudoseptic reaction (Hyalgan, 4; Euflexxa, 1; Synvisc, 4).

A search of the MAUDE database for the period January 2007 to May 2013, conducted on June 16, 2013, yielded at least 500 records (search Product Code *MOZ*: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM). Almost all of the records were for hylan, either the original Synvisc product or Synvisc One, which may reflect either a poorer safety profile for these products or greater usage in practice. The most recent 10 records were reports of the following types of events, all occurring after use of Synvisc: mild to severe synovitis, severe knee effusion, knee infection, hypersensitivity (allergic reaction), moderate to severe pain, severe swelling, extreme stiffness leading to inability to walk, nausea, headache, flu, and lack of relief. Four cases involving knee infection, effusion, and/or hypersensitivity required emergency department treatment or hospitalization. One patient with nausea was hospitalized for GI workup but the findings were negative. One case in which an *overdose* of Synvisc was administered involved serum sickness, diarrhea, vomiting, dehydration, skin induration, angiopathy, bruising, weight gain, myalgia, and arthralgia. The eventual outcome of many of the events was not reported. Of the total 500 records for this time period, 2 involved deaths (search Product Code *MOZ and* Event Type *Death*: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM). Both deaths followed injection with Synvisc. In 1 case, the patient was hospitalized for an unreported cause and died before discharge; no information on the relationship of either event to Synvisc was provided. The other case involved an allergic reaction leading to death, and the treating physician thought the allergic reaction was possibly related to a Synvisc injection.

Other Supplemental Data

A PubMed search was conducted using keywords related to the events reported in the MAUDE database and in the new systematic reviews, trials, and observational studies selected for this update report. This search yielded a report of 3 cases of septic arthritis, which were treated surgically (Shemesh et al., 2011), and a report of a single case of pseudoseptic arthritis (another term for pseudosepsis), which was referred to previously (Idrissi et al., 2012). All patients in these 2 case reports were elderly (ages 70 to 87 years). The search was unrestricted by publication date, but RCTs, reviews, systematic reviews, meta-analyses, and practice guidelines were filtered out. Given the low yield on this search, the Eurocentric nature of the Embase database, and the fact that several non–FDA-approved products are used in Europe, a similar search was not conducted in Embase.

Long-Term Safety

The long-term safety of viscosupplementation is unknown. As already noted, the Samson review identified 2 case series showing adverse events to increase with repeat courses of treatment. In the extension phases (Altman et al., 2011; Strand et al., 2012b) of the FLEXX trial (Altman et al., 2009) and the AMELIA trial (Strand et al., 2012a), patients underwent a second round of treatment 6 months or sometime between 3 and 6 months after the first treatment. The incidence of adverse events with the second round of treatment was similar to that observed in the original trial in both cases. None of the

reviews described concerns regarding long-term after-effects from injection of HA, but few studies have followed patients longer than 6 months, and most studies report follow-up period's ≤ 3 months.

Quality and Generalizability of Evidence, Key Question #2

Short-Term Safety: Evidence pertaining to the short-term relative overall safety of viscosupplementation is of **high** quality, given the volume of RCTs, including good-quality RCTs, and the availability of real-world data from large case series. Although there was inconsistency in the direction of findings across trials, pooled estimates were precise, did not reveal statistical heterogeneity, and for overall event rates, were similar between analysis of all trials and analysis of the subset of trials with larger sample sizes and double-blinding. Evidence in the Rutjes review pertaining to *serious* adverse events is difficult to interpret because of a lack of consensus regarding the causal relationship between many of the observed events and viscosupplementation The review did not comment on whether clinical history and the length of time between treatment and the occurrence of cardiovascular and cancer events were sufficient to suspect a possible causal relationship. (Among the study articles retrieved for this report, trials followed patients 3 to 12 months.)

Long-Term Safety: The evidence is insufficient with respect to long-term safety.

Key Question #3: Does the effectiveness of viscosupplementation vary by subpopulation defined by these factors: age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), and prior treatments?

No data pertinent to Key Question #3 were available in the systematic reviews and recent RCTs selected for the update report. The following discussion combines data that were summarized in the 2010 report and data from larger (n≥200) published trials included in the most recent systematic reviews (Colen et al., 2012; Rutjes et al., 2012) but otherwise not reviewed in detail for this report.
The Samson review included a key question regarding subpopulation effects. The authors reported the following (sample sizes exceeded 200 unless otherwise noted):

- A trial comparing intraarticular HA with placebo found no overall treatment effect but did observe a significant effect in a subgroup of patients who were > 60 years of age and had more severe OA (Lequesne Index scores > 10) (Lohmander et al., 1996). This finding was not replicated in a confirmatory study (Karlsson et al., 2002).
- Two RCTs (n=495 and n=120) failed to detect a statistically significant differential effect in walking pain at 26 weeks according to age, sex, or body mass index (BMI)/weight (Altman and Moskowitz, 1998; Petrella et al., 2002). A review of the study report by Altman and Moskowitz showed that although no analyzed subgroup differences were statistically significant, estimates of pain reduction differed by > 10 mm (100-mm VAS) for patients < 65 years of age (change, –12) versus ≥ 65 years (change, –5.5) and for patients with BMI > 30.5 (change, –16.0) versus BMI ≤ 30.5 (change, –6.0). Petrella et al. did not report the value of their subgroup estimates.
- One trial (n=120) failed to detect a differential effect by disease severity or by patient compliance with previous treatment (Petrella et al., 2002).
- However, another trial (n=91) observed a substantial difference in pain improvement in patients with Kellgren-Lawrence grade 3 to 4 disease, whereas no effect was observed in patients with grade 2 disease or in the overall study group (Henderson et al., 1994).

- There were no trials that enrolled only patients with secondary OA. The 2 trials that reported a history of trauma in some patients (Dahlberg et al., 1994; Rolf et al., 2005) did not evaluate outcomes by primary versus secondary disease. Two trials specifically excluded patients with secondary OA or recent trauma (Pham et al., 2004; Altman et al., 2009).
- There were no trials examining race/ethnicity, disease duration, or prior treatment.

Other data not discussed in the Samson review and/or published since include:

- A meta-analysis of 20 trials (Wang et al., 2004) included in the Samson review assessed the influence of patient factors on the treatment effect of HA (versus placebo). Using meta-regression and subset analysis, the authors found younger (< 65 years) mean patient age and less severe OA to be associated with greater treatment effects. The Samson review did not take this into account when addressing their key question regarding subpopulation effects.
- A very small before-and-after study (n=32) reported that a higher HA concentration in the synovial fluid predicted greater clinical response in patients who were treated with injections of hylan (60% sensitivity and 77% specificity at an optimal cutoff) (Anandacoomarasamy et al., 2008).
- In a comparison of HA with home exercise, less severe OA at baseline was an independent predictor of better outcomes after adjustment for age and BMI, which were not independent predictors (Kawasaki et al., 2009). Severity was measured by a continuous measure (joint space width) of progression in joint deformity. Less severe disease was prognostic of better composite pain and function outcome in both HA and home exercise groups, and both groups had similar outcomes. In an earlier trial cited in the Hayes review, outcomes were significantly better in the HA group than the exercise group, perhaps because that trial included only patients with advanced OA.
- In 1 trial, no effect was detected in the overall study group, but a significant difference favoring HA was detected in the subgroup of patients whose OA only affected 1 or both knees (and not other joints) (Altman et al., 2004).
- The meta-analysis conducted by Rutjes et al. (2012) suggested a trend (*P*=0.058) toward larger effects in patients with fewer injections.

An informal comparison of patient and protocol characteristics with primary outcomes and/or the pooled estimates of pain effect at 3 months reported in the Rutjes review revealed no apparent patterns by baseline BMI, OA severity, or pain; by age or sex distribution; or by previous use of NSAIDs. However, a substantial number of trials did not report baseline BMI or previous use of NSAIDs. No difference between trials that permitted NSAIDs as rescue medication and trials that permitted only acetaminophen was apparent; the range of estimates calculated for the Rutjes review was exactly the same in the subset of studies disallowing NSAIDs as for the overall group of trials with sample sizes ≥ 200, and the direction of findings according to authors' primary outcomes was very mixed in the subset disallowing NSAIDs.

Quality and Generalizability of Evidence, Key Question #3

Individual trial data regarding the influence of age and disease severity have been conflicting, but a meta-regression and subset analysis of 20 trials suggested an association of **age ≤ 65 years** and **less severe OA** with greater benefit. Evidence pertaining to age and disease severity is of **low** quality because the review did not present the results in a manner that allows an assessment of the magnitude of

difference or the precision of the estimate, and the 2005 publication date means that a substantial volume of currently published trials were not represented in the analysis. Although 2 trials failed to detect an association between effect and sex or BMI, this evidence is of very low quality due to the small number trials, a substantial, albeit nonsignificant, difference according to BMI in 1 of the trials, and the lack of quantitative estimates in the other trial. For other factors, no evidence was available, the results were conflicting between 2 trials, or the issue was evaluated in only 1 trial. Thus, evidence pertaining to differential effects according to **race/ethnicity**, **gender**, **primary versus secondary OA, disease duration**, **weight (body mass index)**, **and prior treatments** is **insufficient**.

Key Question #4: What are the cost implications and cost-effectiveness of this type of product?

Costs

An online site lists these U.S. prices for various viscosupplementation products (PharmacyChecker.com, 2013):

- Euflexxa (1 kit, 3 syringes): $200 to $330 for most U.S.-vetted sources. Standard course of treatment is 3 injections.
- Gel-One: No information available.
- Hyalgan (1 syringe): $55 to $80. Standard course of treatment is 5 injections.
- Orthovisc (1 syringe): $64 to $75 from most sources. Standard course of treatment is 3 to 4 injections.
- Supartz (1 box or 5 syringes): $300 to $350 for U.S.-vetted sources. Standard course of treatment is 3 injections according to Prescribing Information; it is unclear why the product would be sold in 5-syringe sets.
- Synvisc (1 kit or 3 syringes): $300 to $360 from most U.S.-vetted sources. Standard course of treatment is 3 injections.
- Synvisc One (1 syringe, 6 mL/syringe): $355 to $414. Standard course of treatment is 1 injection.

Economic Evaluations

Four economic evaluations were reviewed in the 2010 report. Two of these studies were based on pragmatic trials (Raynauld et al., 2002; Kahan et al., 2003), which are presented in this update report under the heading ***Findings: Viscosupplementation as an Add-on to Usual Treatment*** in the discussion of Key Question #1a. No additional economic evaluations have been published since the 2010 report.

NOTE: In the following discussion, currency conversions represent *approximate* translations of results to current U.S. values. They are based on June 29, 2013, use of the CCEMG-EPPI-Centre web-based cost converter with the International Monetary Fund (IMF) dataset for Purchasing Power Parity (PPP) values, available at: http://eppi.ioe.ac.uk/costconversion/. Monetary values reported in the Taiwanese study represented conversions already made by the authors from Taiwanese to U.S. currency, so further conversions may have distorted these results.

Canadian Study

A trial-based cost-utility study from a Canadian societal perspective and based on 1999 costs yielded a cost-utility ratio of CAD 10,000 per quality-adjusted life-year (QALY) (USD 11,273, year 2013), comparing the use of *hylan* plus appropriate care with appropriate care alone (Torrance et al., 2002). This study represented a further analysis of data collected in the pragmatic trial by Raynauld et al. (2002). Appropriate care was defined as care consistent with guidelines published by the American College of Rheumatology, with instructions to clinicians to treat conservatively. ACR guidelines current at the time recommended use of nonpharmacological treatment, e.g., exercise or physical therapy, to minimize reliance on NSAIDs and acetaminophen, according to the source available at the time of the 2010 report. The study time frame was 1 year. Utilities for calculating QALYs were derived from trial participants' responses to a generic, validated health status questionnaire, which showed a utility value of 0.13 for patients who received viscosupplementation and a value of 0.03 for patients who received usual care alone over a 1-year time frame; the difference of 0.10 units was significant (P<0.001). This finding translated to the cost-utility ratio of CAD 10,000/QALY, which was described as falling under the suggested Canadian adoption threshold. The authors also reported a cost-effectiveness ratio of CAD 2505 (USD 2824, year 2013) per patient improved (see **Table 5** for criteria) over the 1-year time frame. Clinical results in the supporting trial are similar to those reported by the only other pragmatic trial (Kahan et al., 2003) identified in the published peer-reviewed literature.

French Study

Authors of the other pragmatic trial reported economic outcomes along with clinical results (Kahan et al., 2003). The economic evaluation revealed similar per-patient medical and sick leave costs (societal perspective in France) over a 9-month time frame for patients treated with hylan plus conventional treatment, and greater effectiveness in the hylan group**.** Since costs were similar between the 2 groups, no cost-effectiveness ratio was calculated. The observed mean improvement was 11 to 13 points greater in the hylan arm on 100-point WOMAC and VAS scales. Although differences in mean improvement were not clinically significant according to the previously described 20-point threshold, event rates showed clinically important improvement to be more likely in the HA arms. More patients in the HA arm (65%) than in the conventional treatment arm (40%; P<0.0001) experienced ≥ 20% improvement in Lequesne Index score. The proportion of patients who experienced a 20-point or greater decrease in pain with walking (100-point scale) and rated the effectiveness of the treatment as "good" or "satisfactory" was 88% in the hylan group and 68% in the conventional care group. QALYs were not calculated (see **Table 5**). NOTE: Conventional care was not defined, and it was not clear whether patients in the hylan arm continued to receive conventional care. However, all patients in the study had failed at least 2 courses of NSAID therapy.

Taiwanese Study

A modeling study suggested that compared with a reference treatment of conventional treatment excluding NSAIDs, HA would be both more expensive and more effective, in terms of QALYs gained, than either naproxen or celecoxib (Cox inhibitor) in patients who have a poor global knee assessment, have not tried NSAIDs, and have declined surgery (Yen et al., 2004). The study was conducted from a societal perspective (costs to public payer plus productivity losses) in Taiwan. The time frame was 26 weeks and costs were based on average reimbursement during the time period July 2001 to February 2002. The utility values for translating the clinical effect into QALYs were derived from a panel of physicians, rather than patients with knee OA; representativeness is unknown. The estimate of clinical effect was based on

the active treatment arms of placebo-controlled trials of each of the 3 products; in other words, the placebo effect was not subtracted. In the referenced HA trial, 36% of patients in the HA arm achieved clinical success (20-point improvement in pain with walking on a 100-point VAS) at 26 weeks (Altman et al., 1998) (see **Table 4**). The HA product used in the trial is not available in the United States. In addition to utilities and clinical outcomes, QALY estimates also took into account the probability of GI complications from the NSAIDs and related mortality, as well as injection pain from HA. The incremental cost-effectiveness ratio (ICER) reported for celecoxib versus naproxen was $21,226 ($27,312 in 2013 dollars) per QALY gained. The authors did not report the corresponding ratio for HA versus naproxen, which would be $33,148 ($42,652 in 2013 dollars) per QALY according to data supplied in the article. The authors reported an ICER of $42,000 ($54,042 in 2013 dollars) per QALY for HA versus celecoxib. The authors concluded that celecoxib had reasonable cost-effectiveness, while HA might not be economically feasible in Taiwan. (NOTE: The cost-effectiveness threshold suggested by the World Health Organization [WHO] for the year 2005, the latest year for which data are available, was $119,849 for countries in the Americas with the lowest child and adult mortality (WHO, 2013). Thus, conclusions from this study might be different for a U.S. setting.) Sensitivity analysis showed that cost utility was very sensitive to estimates of both the cost and effectiveness of HA. As noted in a review by NICE (NICE, 2008), the cost-effectiveness study did not take into account the possibility of cardiovascular events associated with NSAIDs, which created a bias in favor of the NSAIDs.

UK Study, National Institute for Health and Care Excellence (formerly National Institute for Health and Clinical Excellence) (NICE)

An economic analysis was conducted during development of the NICE guidelines on OA (NICE, 2008). To informally estimate the cost-effectiveness of HA versus placebo, the health economist first constructed a cost consequence table showing health benefits at 26 weeks for each of 2 trials assessing viscosupplementation for OA of the knee; costs came from other sources. Cost and benefit consequences for each trial were considered separately. One cost-effectiveness ratio exceeded the National Health Service cost-effectiveness threshold and the other analysis showed placebo to be both more effective and less expensive. Neither analysis considered the adverse side effects of viscosupplementation compared with those of other treatments. Both trials used products that are not available in the United States.

Quality and Generalizability of the Evidence, Key Question #4

Cost-effectiveness studies do not typically include placebo control since their intention is to compare the technology of interest with real-world alternatives. The Canadian and French evaluations made a real-world comparison and expressed effectiveness in terms of QALYs, thus reflecting the balance of benefits and harms of adding viscosupplementation to and potentially replacing other conservative therapies, which also have placebo effects and negative side effects. These 2 analyses also reflect findings that proportionately more individual patients may experience clinically important effects in a group receiving HA injection compared with a placebo group, even if the mean difference is not clinically important. The Taiwanese evaluation was based on placebo-controlled trials but simulated real-world comparisons by not taking the placebo effect into account. The NICE analysis evaluated cost-effectiveness with placebo injection as the comparator, which does not reflect a real-world use. Evidence pertaining to the cost-effectiveness of viscosupplementation has numerous deficiencies:

- The number of cost analyses and cost-effectiveness studies is very small, methodological limitations have been noted for most of these studies, and the more meaningful studies are > 10 years old.
- Evaluations were not conducted in the United States; the results may not apply to the U.S. due to differences in prices, reimbursement policies, standards of care, and definitions of cost-effectiveness limits.
- The most meaningful studies used hylan and the results may not be generalizable to non–cross-linked HA products.
- There were no cost data or cost-effectiveness data specific to single-injection treatments, now possible for 2 products (Synvisc One, Gel-One).
- There was no cost-effectiveness analysis of HA versus intraarticular corticosteroid injection.
- Three of the economic evaluations were performed from a societal perspective, taking productivity losses into account, and thus may not be generalizable to a payer perspective.

Practice Guidelines

The 4 guidelines selected for this update report were considered to be of good quality. Two organizations—the American College of Rheumatology (ACR) (Hochberg et al., 2012) and the American Academy of Orthopaedic Surgeons (AAOS) (AAOS, 2013)—have replaced the guidance described in the 2010 report with more negative recommendations regarding viscosupplementation for OA of the knee. Both organizations' guidelines referred to the incorporation of more formal methods into their guideline development processes since previous guidelines were issued; the AAOS also described the use of methodologists rather than clinicians to conduct the literature search and study appraisal. The National Institute for Health and Care Excellence (NICE) previously made a negative recommendation that has not been updated (NICE, 2008). Guidance issued by the Osteoarthritis Research Society International (OARSI) now provides an update literature review unavailable at the time of the 2010 report, but OARSI has not changed the previous positive although weak endorsement of viscosupplementation for knee OA (Zhang et al., 2007; Zhang et al., 2008; Zhang et al., 2010).

American Academy of Orthopaedic Surgeons (AAOS)

The American Academy of Orthopaedic Surgeons (AAOS) published a guideline on the treatment for OA of the knee that was rated as good quality (AAOS, 2008). The physician work group responsible for development of the guideline used an Agency for Healthcare Research and Quality (AHRQ) technology assessment (Samson et al., 2007) as the evidence base for the recommendation pertaining to the use of intraarticular HA for treatment of OA of the knee. The authors of the guideline concluded that they could not recommend for or against the use of intraarticular HA as treatment for OA of the knee. This inconclusive rating was due to conflicting evidence in pooled effects from poor-quality trials relative to higher-quality trials, as well as unclear clinical significance of the results. There was no explicit consideration of comparative safety. The AHRQ report did not consider viscosupplementation versus conventional care or cost-effectiveness.

In 2013, revised guidelines on the treatment for OA of the knee were published (AAOS, 2013). These guidelines were also considered to be of good quality. In contrast to the 2008 guidelines, these guidelines were based on an analysis of primary studies only and did not consider secondary analyses such as published systematic reviews. Only studies published in full in peer-reviewed journals were

eligible, and sample sizes had to include ≥ 30 participants in each treatment group. The work group selected 20 RCTs; some were placebo-controlled trials and others were comparisons of different HA formulations. A number of RCTs that would seem to meet the report's selection criteria are missing. Consistent with more inclusive systematic reviews, meta-analyses conducted by the guideline work group showed improvement in both pain (5 RCTs) and function (5 RCTs) to be statistically significant but considerably smaller than prespecified levels of minimum clinically important improvement (MCII). The reported analyses were not specific to a particular follow-up interval, but study selection criteria required a follow-up of ≥ 4 weeks. The guideline authors prespecified definition of MCID was an effect size of 0.39 and was based on some of the same research serving as the basis of the MCID used in the Rutjes review. The final conclusion was that the work group could *not* recommend using hyaluronic acid for patients with symptomatic OA of the knee, and the recommendation was characterized as *strong.* No harms analysis was conducted. There was also no analysis of viscosupplementation as an add-on treatment to usual care alone and no cost-effectiveness analysis.

American College of Rheumatology (ACR)

New guidelines, *Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee*, were published by the ACR in 2012 (Hochberg et al., 2012). The new guidelines were based on a systematic search of the literature extending through December 2010. For each modality and indication, the best available systematic review, meta-analysis, or RCT was selected. The guidelines for knee OA are predicated on the following base case:

> An adult with symptomatic knee OA without cardiovascular comorbidities, current or past upper GI problems, or chronic kidney disease presents to her primary care provider for treatment. She experiences pain in and/or around her knee(s) and has not had an adequate response to either intermittent dosing of OTC (over-the-counter) acetaminophen, OTC NSAIDs, or OTC nutritional supplements (e.g., chondroitin sulfate, glucosamine (Hochberg et al., p. 469).

The guidelines panel concluded that it could make *no recommendation r*egarding the use of intraarticular hyaluronates. This represents a substantial modification of the guidance issued in 2000, which suggested that intraarticular hyaluronan therapy is indicated for use in patients who have not responded to a program of nonpharmacological therapy and simple analgesics (ACR, 2000). In addition to the main statement about HA, the 2012 document *conditionally* recommends the use of tramadol, duloxetine, or intraarticular HA in lieu of oral NSAIDs for elderly individuals (≥ 75 years of age). Conditional recommendations apply to treatments that most but not all informed patients would be expected to choose. No evidence was cited for the conditional recommendation. The guideline document further advises that oral NSAIDs should not be used in patients with advanced chronic kidney disease; no statement about HA injections in this population is made (Hochberg et al., 2012).
National Institute for Health and Care Excellence (formerly National Institute for Health and Clinical Excellence) (NICE)

The NICE guideline covers the care and management of OA in adults (NICE, 2008). The quality of this guideline was rated as good. The authors note that the evidence suggests that intraarticular hyaluronan may provide a treatment benefit for pain reduction up to 3 months after a series of 3 to 5 injections, but with a generally small effect size. A limited cost-effectiveness analysis led to the conclusion that hyaluronans are not within the realm of affordability. The guidance from NICE states that intraarticular hyaluronan injections are not recommended for the treatment of OA.
Osteoarthritis Research Society International (OARSI)

The 2007 and 2008 versions of OARSI guidelines on management of hip and knee OA (Zhang et al., 2007, 2008) were reviewed in the 2010 report. Those guidelines provided a critical evaluation of existing systematic reviews and treatment guidelines (published from 1945 to October 2005) and a systematic review of research evidence from recent studies (up to January 2006). One specific recommendation pertaining to viscosupplementation was issued: that injection of intraarticular hyaluronate may be useful in patients with OA of the knee (level of evidence Ia, strength of recommendation 64% on a 100-point VAS). The authors noted that these injections are characterized by delayed onset, but prolonged duration, of treatment benefit compared with intraarticular injections of corticosteroids. The 2008 guidelines cited the meta-analyses by Lo et al. (2003) and Arrich et al. (2005) (both included in the Samson review) as evidence. Zhang and colleagues report a pooled estimate of the effect size for pain at 2 to 3 months as 0.32 (CI, 0.17 to 0.47). It is not clear how this pooled estimate was derived.

The 2010 guidelines (Zhang et al., 2010), which focused on literature published from January 31, 2006 to January 31, 2009, selected the Cochrane review (Bellamy et al., 2006) on the basis of quality and comprehensiveness as the most representative new evidence for the efficacy of viscosupplementation for knee OA. This document assigns a level of evidence of Ia to the Bellamy review and does not provide a revised overall statement about viscosupplementation. The authors cite the findings of Reichenbach et al. (2007) (no significant difference between hylan and standard HA) and Bannuru et al. (2009) (superior durability of effect, comparing HA with corticosteroid injection) but otherwise do not add to the recommendation stated in 2008. An updated pooled estimate for effect size regarding pain is reported: 0.60 (CI, 0.37 to 0.83). Again, the methods for deriving that estimate are not described.

The OARSI guidelines were considered to be of good quality in terms of rigor of development but the organization includes corporate members, and most of the guideline authors, other than the lead author, had financial ties to manufacturers of HA products. The corporate influence on conclusions was unclear.

Selected Payer Policies

At the direction of Washington State Health Care Authority, the coverage policies for the following organizations were reviewed:

Aetna: Aetna considers viscosupplementation medically necessary for members with symptomatic osteoarthritis (OA) of the knee according to American College of Rheumatology (ACR) criteria when all of the following conditions apply:

- Conservative therapy (including physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen and/or topical capsaicin cream) have not resulted in functional improvement after ≥ 3 months.
- There has been inadequate response to aspiration and injection of intraarticular steroids.
- The member reports pain that interferes with physical function.
- The pain cannot be attributed to other forms of joint disease.
- There are no contraindications.

Aetna considered ultrasound guidance for viscosupplementation injections to be experimental and investigational.

Aetna considers additional series of injections as medically necessary when it has been ≥ 3 months since the last series of injections and the medical record documents a reduction in analgesics or anti-inflammatory medication during the 3 months following the previous series as well as an improvement in pain and function.

See Viscosupplementation: Aetna Clinical Policy Bulletin No. 0179.

Centers for Medicare & Medicaid Services (CMS): No CMS National Coverage Determination (NCD) was identified for viscosupplementation on June 19, 2013 (search National Coverage Documents, National Coverage Determinations, by keywords *viscosupplementation, hyaluronic acid, hyaluronan, hyaluronate* and in entire document at: CMS Advanced Search Database). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Oregon Health Evidence Review Commission (HERC): The Oregon HERC has concluded that viscosupplementation should not be covered for the treatment of pain associated with OA of the knee. The Commission's overall summary states that although viscosupplementation has been shown to result in lower mean pain scores and may lead to improved mean function scores a few weeks after treatment, the magnitude of benefit may be too small to be clinically important. This conclusion is based on a review of 2 reports prepared in 2010 by Hayes, Inc. for the Medicaid Evidence-based Decisions (MED) Project and for the Washington Health Technology Assessment Program and a review of a 2007 Evidence Report prepared for the Agency for Healthcare Research and Quality (AHRQ). Coverage guidance decisions by HERC are intended to guide public and private purchasers in Oregon in making informed decisions about healthcare services.

See Viscosupplementation for Osteoarthritis of the Knee: HERC Coverage Guidance October 11, 2012.

GroupHealth: No coverage policy for viscosupplementation was identified on the GroupHealth website (GroupHealth: Provider) on June 19, 2103 (search by keywords *viscosupplementation, hyaluronic acid, hyaluronan, hyaluronate*). GroupHealth's Office-Administered Prior Authorization Drug List (https://provider.ghc.org/open/referralsAndClinicalReview/list-officeinject.pdf) indicates that medical necessity review is required for intraarticular injection of hyaluronic acid. Medical necessity review requires physician certification of radiological evidence of significant OA of the knee and failure of or intolerance to all conservative treatments (acetaminophen, any NSAID, and corticosteroid injection). Coverage is limited to 2 courses of treatment per year.

Regence BCBS: No coverage policy for viscosupplementation was identified on the Regence Group website (Regence Group Medical Policy) on June 19, 2103 (search by keywords *viscosupplementation, hyaluronic acid, hyaluronan, hyaluronate*). However, Regence does have Medication Policies (http://blue.regence.com/policy/medication/contents.html) that can be accessed by product names (Gel-One, Hyalgan, Orthovisc, Supartz); these policies indicate that most plans require prior authorization for sodium hyaluronate injection. Coverage is limited to 2 courses of treatment per year.

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APPENDICES

APPENDIX I. Search Strategy

Search for New Systematic Reviews and Practice Guidelines (conducted February 20-25, 2013)

Initially, evidence for this report was obtained by searching for systematic reviews and guidelines that had been published since December 2009. Searches were conducted in the following databases: Agency for Healthcare Research and Quality (AHRQ), Blue Cross Blue Shield TEC Assessments, Canadian Agency for Drugs and Technology in Health (CADTH), Centre for Reviews and Dissemination (York University), Cochrane Library, Hayes Knowledge Center, Institute for Clinical Systems Improvement (ICSI), National Institute for Health Services Health Technology Assessment (NIHR HTA) Program (UK), National Guidelines Clearinghouse, VA/Department of Defense Clinical Practice Guidelines, and VA Technology Assessment Program (VA TAP).

The websites for the American Academy of Family Physicians (AAFP), American Academy of Orthopaedic Surgery (AAOS), American College of Rheumatology (ACR), American Pain Society (APS), and Osteoarthritis Research Society International (OARSI) were searched for guidelines.

Additional systematic reviews were selected from a search of the PubMed database using filters for Guidelines, Meta-analyses, and Systematic Reviews.

A repeat search of PubMed and the Centre for Reviews and Dissemination was conducted on May 29, 2013, and the website of AAOS was monitored until a previously announced update of its guidelines on knee osteoarthritis were posted (May 18, 2013).

Searches for Primary Clinical Studies Published After the Systematic Reviews

Databases Searched: MEDLINE (PubMed), Embase

Search Strategy (for PubMed search) for RCTs (May 13, 2013)

#1	Search viscosupplementation or hyaluronic acid or HA or hyaluronate or hyaluronan or hylan or Hyalgan or Synvisc or Supartz or Orthovisc or Euflexxa or Gel-One
#2	Search osteoarthritis or knee
#3	Search (#2) AND #1
#4	Search (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))
#5	Search (#4) AND #3
#6	Search (#4) AND #3 Filters: Publication date from 2009/12/01 to 2013/12/31

Search Strategy for Supplemental Studies (June 4, 2013)

Exploratory searches for observational studies reporting data pertinent to Key Questions #2 and #3 were conducted in MEDLINE (PubMed) and Embase by filtering out randomized controlled trials (RCTs),

systematic reviews, reviews, meta-analyses, and practice guidelines. An additional search string that included terms such as *adverse event*, *complications*, and *side effects*, as well as specific terms for all adverse events mentioned in the selected RCTs, the systematic reviews, and the most recent 10 reports in the Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database was used, and no date restriction was applied. Additionally, a search for non-RCT clinical studies published since December 2009 was conducted.

Searches for Cost Studies or Economic Evaluations (February 20-25, 2013)

The National Health Service Economic Evaluation Database (NHS-EED) was searched on February 20, 2013, with the search string *Viscosupplementation or hyaluronan or hyaluronic acid or sodium hyaluronate* restricted to Title.

In addition, PubMed was searched on February 25, 2013:

#1	Search viscosupplementation or hyaluronic acid or HA or hyaluronate or hyaluronan or hylan or Hyalgan or Synvisc or Supartz or Orthovisc or Euflexxa or Gel-One
#2	Search osteoarthritis or knee
#3	Search (#2) AND #1
#4	Search ((((economic analysis) OR (economic evaluation)))) OR (((((cost AND (analysis OR benefit OR effective* OR consequence OR minimization)))) OR (("Costs and Cost Analysis"[MeSH] OR "Cost-Benefit Analysis"[MeSH]))))
#5	Search (#4) AND #3
#6	Search (#4) AND #3 Filters: Publication date from 2009/12/01 to 2013/12/31

Update Search (July 5, 2013)

#1	Search viscosupplementation or hyaluronic acid or HA or hyaluronate or hyaluronan or hylan or Hyalgan or Synvisc or Supartz or Orthovisc or Euflexxa or Gel-One
#2	Search osteoarthritis or knee
#3	Search (#2) AND #1
#6	Search (#1) AND #1 Filters: Publication date from 2013/5/13 to 2013/7/5

APPENDIX II. Overview of Evidence Quality Assessment Methods

Tools used include internally developed Quality Checklists for evaluating the quality (internal validity) of different types of studies, a checklist for judging the adequacy of systematic reviews used instead of de novo analysis, and Hayes Evidence-Grading Guides for evaluating bodies of evidence for different types of technologies. Hayes methodology is in alignment with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system, which was developed by the GRADE Working Group, an international collaborative body.

Step 1	Individual study appraisal a. Initial rating according to study design *Good:* Randomized Controlled Trials *Fair:* Nonrandomized Trial (controlled, parallel group, quasi-randomized) *Poor:* Observational Analytic Studies (prospective or retrospective trials involving historical controls, pretest posttest control trial [patients legitimately serve as their own controls], case-control, registry/chart/database analysis involving a comparison group) *Very Poor:* Descriptive Uncontrolled Studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data]) b. Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist c. Repeat for each study
Step 2	Evaluation of each body of evidence by outcome, key question, or application a. Initial quality designation according to *best* study design in a body of evidence b. Downgrade/upgrade *Downgrade factors:* Study weaknesses (Quality Checklists), small quantity of evidence, lack of applicability, inconsistency of results, publication bias *Possible upgrade factors:* Strong association, dose-response effect, bias favoring no effect c. Assign final rating: High-Moderate-Low-Very Low d. Repeat for each outcome/question/application
Step 3	Evaluation of overall evidence a. Rank outcomes by clinical importance b. Consider overall quality of evidence for each *critical* outcome c. Assign overall rating based on lowest-quality body: High-Moderate-Low-Very Low
Step 4	Evidence-Based Conclusion Overall quality of evidence + Balance of benefits and harms

APPENDIX III. Common Measurement Instruments for Pain and Function in Studies of Osteoarthritis Treatments

The primary outcomes for this report were reduction in pain and improvement in function. The osteoarthritis research community recognizes the following outcome measures (Bannuru et al., 2009):

- Pain (visual analogue scale [VAS] or Likert scale) in the index joint—at rest, during walking, or during activities other than walking.
- Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. This validated scale is specific to the knee or hip and measures symptoms related on 3 subscales: pain, stiffness, and physical function. There are 24 items per subscale. A higher score represents less severe symptoms. The WOMAC is available in 5-point Likert scale form and in 100-mm VAS form (ACR, 2013).
- Lequesne Index. The Lequesne scale is specific to the knee and assesses pain with walking and with activities of daily living (ADL). Higher scores on this scale signify greater pain-induced impairment; scores range from 0 to 24 (About.com, 2013).

APPENDIX IV. Overview of Systematic Reviews, Key Questions #1 and #2

(See Appendix V for more specific findings.)

Key: ACR, American College of Rheumatology; ADL, activities of daily living; AE, adverse event; FDA, Food and Drug Administration; BL, baseline; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HA, hyaluronic acid; IA, intraarticular; ITT, Intention-to-treat; MA, meta-analysis; MAUDE, Manufacturer and User Facility Device Experience; MCID, MD, (unstandardized) mean difference; MOOSE, Meta-analyses of Observational Studies (reporting guidelines); NS, not (statistically) significant; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; pt(s), patient(s); PT, physical therapy; QOL, quality of life; RCT, randomized controlled trial; SMD, standardized mean difference; SR, systematic review; VAS, visual analogue scale; WMD, weighted mean difference; WOMAC, Western Ontario and McMaster Universities (Index)

Authors and Methods	Studies and Patients; Outcomes and Comparisons Evaluated	Main Findings; Authors' Conclusions	Quality of the Evidence; Comments
Bellamy et al. (2006) SR of RCTs with MA MEDLINE through mid-July 2003, Embase through week 29 2003, Current Contents to mid-September 2000, and Cochrane Central Register of Controlled Trials Published conference proceedings through 2005 and additional studies solicited from industry representatives and investigators	***Studies:*** 76 blinded RCTs published in full, published as abstracts, or unpublished; 32 RCTs were placebo-controlled; 30 RCTs included in pooled analyses. Blinding was not a selection criterion. Studies selected if pts were diagnosed with OA according to ACR criteria, a published algorithm, or detailed clinical or radiographic information. ***Pt characteristics:*** Not summarized. ***Outcomes:*** Pain, physical function, pt global assessment, joint imaging. (Selected studies had to assess ≥1 of first 3 outcomes.) ***Comparison:*** All comparisons	***Efficacy/effectiveness*:** At 5-13 wks, relative pain difference ranged from 28% to 54% (favoring HA), and relative function, from 9% to 32% (favoring HA). Effect size in placebo comparisons was moderate to large for some products on some variables. In comparison with corticosteroids, HA/hylan may have more prolonged effects. Compared w/ NSAIDs, comparable effects. ***Safety:*** No major safety issues; in some analyses HA/hylan was comparable in efficacy to systemic forms of active intervention with more local reactions but fewer systemic AEs. Almost all AEs were relatively transient. ***Authors' conclusion***: HA is effective, especially at the 5- to 13-wk postinjection period. Authors noted that analyses suggest differential efficacy for different products on different variables and at different time points.	***Quality of included RCTs*:** Mean quality of RCTs was 3.6 on Jadad scale (1-5), median 3. ***Quality of SR:*** Good This report was an update of an earlier report that had received manufacturer funding. NOTE: Although the methodological quality of this review was considered to be good, the narrative synthesis of the large number of pooled estimates was lacking.
Reichenbach et al. (2007) SR with MA of RCTs or quasi-randomized comparator trials (hylan vs HA) with MA plus	***Studies:*** 13 RCTs (n=2085) or quasi-randomized trials published in full (11 RCTS) or as abstracts (2 RCTs); no unpublished trials selected ***Pt characteristics by trial:*** Mean age 54-71 yrs, median 61; mean duration symptoms 4-7.7 yrs,	***Efficacy/effectiveness:*** Absolute effect had CI near null, did not meet authors' definition of clinical importance, and was characterized by high heterogeneity. Stratified analysis suggested poor quality of some	***Quality of RCTs:*** Generally poor quality and/or incomplete reporting. 2 clearly reported allocation concealment; 6 clearly reported pt blinding; 1 clearly reported therapist blinding; 4 were clearly not supported by industry.

Authors and Methods	Studies and Patients; Outcomes and Comparisons Evaluated	Main Findings; Authors' Conclusions	Quality of the Evidence; Comments
indirect comparison using results from previous MAs MEDLINE, Embase, and CINAHL to November 2006 Unpublished trials from these sources: textbooks, FDA advisory panel proceedings, and additional studies solicited from industry representatives	median 5 ***Outcomes:*** Pain (global, with walking, WOMAC, Lequesne, or with activities other than walking, in order of decreasing preference). AEs (flares, effusions, any) ***Comparisons:*** Hylan vs HA	trials inflated the overall effect and was largely responsible for the high heterogeneity. Metaregression of placebo-controlled trials included in other MAs showed inverse association between trial size and effect size. ***Safety:*** Robust evidence of an approximately 2-fold increase in risk of local adverse events associated with use of hylan as opposed to HA. ***Authors' conclusions:*** (a) Because of lack of clear superior effectiveness over that of HAs, and increased risk of local adverse events, use of hylan should be discouraged in research and clinical practice. (b) Heterogeneity appears to be due more to trial quality than to different HA comparators, as assumed by the Bellamy review. (c) Large effect size in formal, indirect comparison of placebo-controlled trials in comparison with estimate based on direct comparison trials suggests that previous implicit indirect comparisons were misleading.	***Quality of SR:*** Good
Samson et al. (2007) SR of MAs with supplemental analyses MEDLINE (through March 2007, Embase (November 2006), and Cochrane Central Register of Controlled Trials(November 2006) Conference proceedings, including: American Association of Orthopedic Surgeons, American College of Rheumatology, and Osteoarthritis Research Society International (2004-2006)	***Studies:*** 6 MAs (41 trials) plus 1 additional RCT (42 RCTs total; n=5843 pts); mean age 54 yrs, predominantly men, early-stage OA 5 of 42 RCTs published as abstracts only 5 MAs analyzed study-level data; 1 MA, pt-level analysis ***Pt characteristics by trial:*** Mean age 45-72 yrs; 28%-100% women; mean BL pain (100-point VAS) with movement was 44-79 in hyaluronan arms and 42-80 in placebo arms ***Additional literature:*** 3 case series (articles or abstracts), MAUDE (FDA), and 1 physician survey reviewed for AE data. ***Outcomes:*** Overall review targeted pain, function, AEs, and QOL. Individual MAs analyzed pain (5 MAs), physical function (3 MAs), pt global assessment (1 MA),	***Efficacy/effectiveness:*** MA authors conclusions: (a) effective at 5 wks and beyond; (b) comparable with other treatments; (c) no proof of clinical effectiveness and possible increased risk of AEs; (d) moderately effective at 5-7 and 8-10 wks; (e) effective and safe but questions remain about differential effectiveness; and (f) small effect but caution about potential publication bias. ***Safety:*** AE profiles were not consistent across trials, but when reported, were generally similar in frequency between HA and placebo arms. Most common events included injection site pain, injection site infection, and local joint pain/swelling. MAUDE data suggested rare serious AEs associated with Hyalgan, Euflexxa, and hylan. Survey of rheumatologists: Pseudoseptic arthritis may not be as rare as thought (no denominator,	***Quality of RCTs in study-level MAs:*** Quality ratings for 37 evaluable RCTs: good (9 RCTs), fair (16 RCTs), poor (12 RCTs). ITT results reported in 17 RCTs; 9 RCTs reported ≥20% loss to f/u; double blinding reported by 35 RCTs. ***Industry involvement:*** Funding (23 RCTs [55%]), statistical analysis (8 RCTs), coauthor (8 RCTs). ***Industry sponsorship:*** 30% RCTs (1 MA), 65%-73% RCTs (3 MAs), not reported (1 MA). ***Quality ratings for MAs*:** Major flaws (3 MAs); minor flaws (2 MAs). Primary flaws were failure to search Embase and language restrictions. Impact of language restrictions was minimal; impact of omission of Embase was not elucidated). *Conclusions considered to be supported:* Fully (1 MA with negative conclusions), partially (3 MAs), not supported (1 MA). NOTE: No quality assessment of pt-level MA due to lack of a validated instrument; also no

Authors and Methods	Studies and Patients; Outcomes and Comparisons Evaluated	Main Findings; Authors' Conclusions	Quality of the Evidence; Comments
	composite Lequesne Index (1 MA) ***Comparisons:*** Placebo	low survey response rate, not published). Case series, hylan only: 2.1% (82/3931) AE rate per injection; 1% (34/3367) for single course, and 8.5% (48/564) for second course. (Waddell 2003) Case series, hylan only: 5.3% pts (n=4253), most commonly arthropathy; 1 severe AE (large effusion and synovitis); 2-fold increase in subgroup with previous HA treatment. (Kemper 2005) Case series, hylan only: 2.7% injections (n=1537) and 8.3% pts (n=336). (Lussier 1996) ***W/in-study subgroup analysis:*** No evidence of differential effect by age, sex, primary/secondary OA, BMI/weight, or disease severity (see Findings, Key Question #3, for more detail). ***Supplemental analysis:*** (a) Smaller effect sizes associated with higher-quality trials, use of non–cross-linked HA vs hylan, and larger sample size (>100). Further analysis added uncertainty to conclusions regarding differences associated with hylan. (b) Positive, underpowered studies more likely than negative studies to be published. 15.5% pts in unreported studies and 9.7% pts in abstracts only. Suggests publication bias in overall body of research. ***Authors' conclusions:*** Evidence does not clearly demonstrate clinical benefit. Variations in the approaches and characteristics of the 5 study-level MAs provide multiple perspectives that permit broad synthesis of evidence.	assessment of validity of the MA's conclusion. ***Quality of SR***: Good
Bannuru et al. (2009) SR with MA Searched MEDLINE, Embase, CINAHL, BIOSIS, and Cochrane Controlled Trial Register to February 2009. No language restrictions.	***Studies:*** 7 RCTs (606 participants, 610 knees). All trials published in full. ***Patient characteristics by study:*** Mean age 49-72 yrs; 53%-100% women ***Outcomes:*** Studies had to report ≥1 of a hierarchy of outcome measures recommended for OA clinical trials (WOMAC, OA Index Pain Subscale*, knee pain when walking*, knee pain during activities other	***Efficacy/effectiveness:*** Pooled effect sizes favored corticosteroid up until 3 to 6 wks and significantly favored HA by 11-16 wks. Effect size reached 0.39 at 17-26 wks. Several types of analysis ruled out any influence of covariance between outcomes and time points, trial quality, BL differences, or type of HA product and corticosteroid.	***Quality of included RCTs according to Bannuru et al.:*** No formal assessment tool; 1 trial clearly reported allocation concealment; 3 were open label, 3 single-blind, and 1 double-blind; 5 had industry sponsorship and 2 were unclear; 8%-30% withdrawal rates. 5 trials judged to be of "low quality", 2 of "higher quality." ***Quality of SR:*** Fair to good. Rationale for not including Lequesne Index as an outcome measure not

Authors and Methods	Studies and Patients; Outcomes and Comparisons Evaluated	Main Findings; Authors' Conclusions	Quality of the Evidence; Comments
Conference proceedings, including: American College of Rheumatology, British Society for Rheumatology, Osteoarthritis Research Society International (1990 to February 2009), additional unpublished studies solicited from experts and manufacturers	than walking*, spontaneous joint pain*) *VAS or Likert ***Comparison:*** HA vs corticosteroids	***Efficacy by product:*** Uncertain superiority of Synvisc over HAs; very small NS SMD favoring Synvisc. ***Safety:*** Not assessed. ***Authors' conclusions:*** Corticosteroids are more effective than HA in the short term (up to approximately 4 wks), whereas HA is more effective in the long term (4-26 wks).	explained. Authors were unclear whether all reported outcomes were extracted from each study or only the outcome highest in the hierarchy.
Bannuru et al. (2011) SR with MA to assess therapeutic trajectory (interaction of time and effect) Searched MEDLINE, Embase, CINAHL, BIOSIS, Web of Science, Google Scholar, and Cochrane Controlled Trial Register to March 2010. No language restrictions. Conference proceedings, including package inserts and correspondence with authors.	***Studies:*** 54 trials (49 reports) (n=6545) 45 trials (83%) published in full, 5 as abstracts only, 3 unpublished (1 study, Chevalier 2010, has since been published). Trials not published in full comprised 18% of total participant population. Pain: 49 trials (6962 participants) Function: 16 trials (2571 participants) Stiffness: 15 trials (2488 participants) (19 trials w/ <100 participants) Same study inclusion criteria as in Bannuru et al. (2009) (see eligible Outcomes) ***Patient characteristics by study:*** Mean age 45-72 yrs; 28%-100% women; clinical heterogeneity across trials for age, sex, knee radiographic grade, and BL pain. ***Outcomes:*** Pain, function, stiffness ***Comparison:*** Placebo	***Efficacy/effectiveness:*** Peak effect at 7-10 wks. ***Safety:*** Not evaluated. ***Authors' conclusions:*** Intraarticular HA injection is effective for pain due to OA of the knee; the magnitude of benefit is modest but exceeds a MCID. Overall cost-utility should be reevaluated.	***Quality of included RCTs according to Bannuru et al.:*** No formal assessment tool. 16 trials (30% of total) were high quality. Adequate concealment in 28 trials (52%); ITT analysis, 28 (52%); double-blinding, 38 (70%) (single-blinding or unclear in others); dropout 0%-50% and ≥20% in 11 trials. ***Quality of SR:*** Good ***Other comments:*** 4 studies had >1 HA arm; review authors treated the different comparisons as separate trials; explanation for how the common control grp was treated was unclear. High statistical heterogeneity for pain at ≤10 wks. Included studies were not identified. Industry involvement in 98% of trials.
Colen et al. (2012) SR with MA to assess efficacy of HA Published randomized or pseudorandomized studies indexed in MEDLINE, Cochrane Database of systematic	***Studies:*** 74 RCTs Vs placebo: 37 RCTs Vs no tx: 6 RCTs Vs IACS: 13 RCTs Vs PT: 5 RCTs Vs regular tx (home exercises, NSAIDs, etc.): 5 RCTs Different types/doses of HA: 13 RCTs ***Pt characteristics by study:*** NR	***Efficacy/effectiveness (3-mo between-grp pain difference):*** WMD –10.20 (CI, –15.97 to –4.42; 18 RCTs, 2801 pts). Relative improvement from BL for several products exceeded that for placebo, PT, and no tx. ***Safety:*** Not addressed ***Authors' conclusions:*** (1) A statistical effect was demonstrated but its clinical relevance is	***Quality of included RCTs according to Colen et al.:*** No individual study quality assessment (MOOSE *reporting* guidelines were cited for use in study selection; this may be an error since MOOSE guidelines are for observational studies). ***Quality of SR:*** Good. High statistical heterogeneity across studies and authors acknowledge known clinical heterogeneity (blinding, BL OA grade,

Authors and Methods	Studies and Patients; Outcomes and Comparisons Evaluated	Main Findings; Authors' Conclusions	Quality of the Evidence; Comments
Reviews, Cochrane Clinical Trial Register, and Embase; English and, if translation possible, non-English (inception to June 2011)	***Outcomes:*** Primary, pain (VAS) at 3 mos. Secondary, any outcome (VAS pain, WOMAC pain or Lequesne Index) at 3 mos divided by BL value (findings regarding relative improvement all referred to pain). (3 mos selected because of the frequency of this endpoint in trials, and previous research showing superiority of HA over IACS at f/u intervals >3 mos) ***Comparison:*** Primary research objective was to compare HA w/ IA injection of placebo (saline). ***MCID:*** Studies reporting values of 10-30 were cited, but these were not generally specific to OA.	debatable. (2) Future evaluation requires a determination of the exact mechanism of action or saline infiltrations if they are to be used as sham treatments. (3) Due to conflicting evidence, unable to conclude that 1 brand of HA has better efficacy over another; large multicenter trials are needed to address this question.	treatment strategies) but no sensitivity analyses. No well-supported assumption regarding MCID. ***Other comments:*** Colen et al. reported that 59.5% of RCTs were industry sponsored; sponsorship was unknown in 27.4% of RCTs. Review based on published studies only.
Rutjes et al. (2012) SR and MA Published trials; search conducted in Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and manual searches; last search January 31, 2012. Unpublished trials identified conference proceedings and trial registries.	***Studies:*** 89 RCTs (12,667 pts) ***Studies:*** Full publication: 57 RCTs Conference proceedings: 23 RCTs In pamphlet: 2 RCTs In book chapter: 1 RCT Total published: 83 RCTs (11,310) Total unpublished: 6 RCTs (1357 pts) ≥100 pts per grp: 23 Randomized or quasi-randomized trials eligible. ITT results used where possible. ***Pt characteristics (mean values by study):*** Overall: Age 50-72 yrs (median 63 yrs, 69 RCTs); 27%-100% women, median 67%, 71 RCTs); Kellgren-Lawrence grade 2, 44% pts, and grade 3, 39% pts (27 trials). ***Outcomes:*** Effectiveness: Primary, pain intensity; secondary, physical function. If >1 scale was used for measuring pain, data were used according to a hierarchy (e.g., WOMAC pain subscale preferred over VAS pain). Data extracted for time point closest to 3 mos. Safety: Primary, flare-up in injected knee. Secondary (in descending order): serious AEs (inpatient hospitalization, prolongation of hospitalization, persistent or significant disability, congenital abnormality of offspring, life-threatening events, or death,	***Effectiveness/efficacy:*** Pain at 3 mos: SMD –0.37 (CI, –0.46 to -0.28; *P*<0.001; τ^2=0.09 and *P*<0.001 for heterogeneity) (68 RCTs, 9617 pts). Function at 3 mos: SMD –0.33 (CI, –0.43 to –0.22); τ^2=0.1 (for heterogeneity, *P*<0.001) (48 RCTs, # pts NR) NOTE: Some effect sizes were unrealistic (much larger than what would be expected of total joint replacement). Authors emphasized that when analysis was restricted to large trials w/ adequate assessor blinding; only a small, clinically irrelevant effect on pain at 3 mos was detected and no effect on function was detected. Authors also noted that a pooled estimate from the 5 unpublished studies (12% of pts) contributing to the meta-analysis of pain outcomes was SMD –0.03 (NS and w/ low heterogeneity); they interpreted this to signify unethical publication bias. ***Safety:*** Any AE: RR 1.04 (CI, 0.99-1.09). Local AE: RR 1.34 (CI, 1.13-1.60). Serious AE: RR 1.41 (CI, 1.02-1.97). Many studies did not report AEs, which prohibits understanding of causes of the reported AEs. ***Authors' conclusions:*** Benefit on pain and function is minimal or nonexistent; HA injection should be discouraged because of the increased risk of	***Quality of included RCTs according to Rutjes et al:*** Allocation concealment (13 RCTs), adequate blinding of patients (sham control plus syringe identical to that used in HA grp or view of knee obscured by screen during tx; 16 RCTs), use of sham control (injection of saline or minimal HA concentration; 68 RCTs), blinded outcome assessment (either self-reported outcomes + adequate pt blinding + no apparent involvement of investigator in assessment *or* blinded assessment by investigator + attempt to blind pts; 48 RCTs), ITT analysis (17 RCTs), median loss to f/u 8% (as reported in 44 RCTs). Several trials reported insufficient details for calculation of effect sizes; authors had to approximate. ***Quality of SR:*** Good. No reporting of responder rates. ***Other comments:*** ((1) Authors specified a very high standard for adequate pt blinding. (2) Pooled estimates include 18 studies w/ nonplacebo controls, referred to by authors as "nonintervention controls" but including comparators such as usual care; although subset analysis did not detect a significant difference in effect according to placebo or nonplacebo comparator, point estimates were larger for the nonplacebo subset of studies (–0.48 vs 0.–0.32). (3) Some discrepancy between # trials identified for overall pain outcome and # trials across subsets in

Authors and Methods	Studies and Patients; Outcomes and Comparisons Evaluated	Main Findings; Authors' Conclusions	Quality of the Evidence; Comments
	withdrawals/dropouts due to AEs, overall AEs, effusions, any local AE, and overall withdrawals/dropouts. ***Comparisons:*** Placebo (sham) or nonintervention control ***MCID:*** SMD (effect size) 0.37; corresponds to 0.9 on 10-cm VAS; no reference to an official statement but research was cited.	serious AE and local AEs. Authors point out that comparisons were likely overpowered.	sensitivity analysis.

APPENDIX V. Key Results of Meta-analyses of Randomized Placebo-Controlled Trials, Key Questions #1 and #2

Details pertaining to individual meta-analyses of HA/hylan versus placebo, including those conducted by Bellamy et al. (2006), were derived primarily from descriptions provided by Samson et al. (2007); a few details were confirmed or supplemented by referring to the original articles. See **Appendix IV** for overviews of Bellamy 2006, Bannuru 2009, Hayes 2009, Reichenbach 2007, and Samson 2007. See **Appendix VI** for meta-analyses of nonplacebo comparisons. **Estimates in this table with confidence intervals that do not cross the null value are bolded.** Peak effects are asterisked (*). Different outcomes (pain, function, stiffness, pain/function, and adverse events) have been color coded for easier tracking. Analyses specific to hylan (as opposed to non–cross-linked HA) are denoted by ** **. For most trials, difference at follow-up had to be used as a proxy for difference in change from baseline.

Key: AE, adverse event (or effect); ASPID/ASFID, adjusted (for baseline pain/function intensity) SPID/SFID; CI, confidence interval; f/u, follow-up; GI, gastrointestinal; HA, hyaluronic acid; I, I index (statistical measure of heterogeneity); IA, intraarticular; ITT, intention-to-treat; MA, meta-analysis; MCID, minimal clinically important difference; NNT, number needed to treat (harm) (in order for one patient to experience benefit or harm according to related outcome measure and unit); OA, osteoarthritis; OMERACT-OARSI, Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International; PID/FID, pain/function intensity difference; PMA, Premarket Approval (FDA); RCT, randomized controlled trial; RR, relative risk; SE, standard error; SMD, standard mean difference; SPID/SFID, sum of pain/function intensity differences; SR, systematic review; VAS, visual analog scale; WMD, weighted mean difference; WOMAC, Western Ontario and McMaster Universities (Index)

Authors, Design, Comparator	# Studies and Patients; Outcomes and Follow-up	Pooled Estimates	Comments (Including review authors' quality assessment)
Samson 2007 (Study-level MA using data abstracted by Bellamy 2006) Placebo	** Hylan trials only**: 6 RCTs VAS pain (weight bearing or WOMAC) 5-13 wks	Negative WMD favors HA. All trials: –20.2 (CI, –29.5 to –10.9); I^2=82%; Egger test NS Larger effects*: –34 (CI, –37 to –30) (2 RCTs) Smaller effects*: –12 (CI, –14 to –10) (4 RCTs) *Estimated from forest plot. Note that the 2 CIs do not overlap with CI for all 6.	3 poor-quality trials; 3 fair-quality trails (on basis of 7 defined criteria); 24%-29% dropout rates in 2 trials; 1 trial unblinded, double-blinding in others. The 2 trials with larger effects were pooled with others in 4 of the study-level MAs. Samson and colleagues concluded that the pooled effect for hylan should be considered more uncertain than the CI would suggest.
From Samson 2007 Lo et al. (2003) (study-level MA)	22 single-/double-blind RCTs published in full or as abstracts (2949 knees, 2927 pts Pain (global, with walking,	**SMD in change from baseline at: –0.32 (–0.47 to –0.17); significant heterogeneity** **SMD diminished to –0.19 (–0.27 to –	Special RCT inclusion criteria: ≥3 injections, dropout <50%. 77% of RCTs had industry sponsorship; 7 reported ITT data, provided raw data for ITT analysis, or had no dropouts; overall dropout rate 12.4%. Evidence of publication bias (funnel plot asymmetry based on sample size of published trials; very small pooled effect in unpublished trials).

Authors, Design, Comparator	# Studies and Patients; Outcomes and Follow-up	Pooled Estimates	Comments (Including review authors' quality assessment)
Placebo	WOMAC, Lequesne, or with activities other than walking, in order of decreasing preference) 1-4 mos (preference given to measurement at 2-3 mos)	0.10) with no heterogeneity when 3 RCTs of hylan were excluded. Authors considered 2 (Scale 1994, Wobig 1998) of 3 trials to be outliers.** Authors concluded small effect, but publication bias may overestimate.	In a subset of 8 trials that reported change from baseline, the difference in pooled change in each arm suggested that a placebo effect accounted for 79% of the improvement in HA arms (f/u intervals not reported). *Quality (according to Samson and colleagues): M*ajor flaws; conclusions partially supported by data/analysis.
From Samson 2007 Wang et al. (2004) (study-level MA)	20 single-/double-blind RCTs published in full or as abstracts) 1647 knees (pain/function outcomes); 2252 knees (AEs)	Integrated analysis. Positive estimates favor HA. SPID% and SFID% are overall measures of efficacy that standardize different outcome measures, different evaluation time points, and different trial durations across studies; expresses cumulative response. ASPID% and ASFID% are adjusted for baseline values. Peak PID% and peak FID% reflect maximum efficacy observed in each trial as a percentage of the maximum possible on the scale used). Authors concluded that MA confirmed therapeutic efficacy and safety; additional studies needed to resolve uncertainty regarding differential effect by product, clinical situation, and pt population.	English–only. Mean RCT quality score was 19 points (maximum 28); allocation concealment unclear in all; 65% RCTs had industry sponsorship. MA reported no evidence of publication bias (no funnel plot asymmetry, using sample size as ordinate); funnel plots constructed by Samson and colleagues using precision at the ordinate showed asymmetry. No explanation of how the efficacy measures relate to clinical assessment. *Quality (according to Samson and colleagues):* Major flaws; conclusions partially supported by data/analysis.
(Wang 2004 from Samson 2007)	17 RCTs (# pts NR) Pain with activities, non–cross-linked HA trials	**SPID%, 7.90% (CI, 4.10-11.70); I2=84% (17 trials)** **ASPID%, 13.4% (CI, 5.5-21.3); I2=83% (15 trials)** **Peak PID%, 9.9% (CI, 4.8-15.0); I2=91% (16 trials)**	Metaregression and/or subset analysis showed trial quality, sample size, allowing escape analgesics, OA severity, and age to have a negative (inverse) association with pain outcomes. Evidence of the influence of industry sponsorship was mixed.
(Wang 2004 from Samson 2007)	3 RCTs (# pts NR) Pain with activities, **hylan** trials	SPID%, 23.6%; ASPID%, 34.8%; peak PID%, 27.1% (no CIs)	In contrast to non–cross-linked HA trials, no heterogeneity. Greater treatment–placebo differences than those reported for non-hylan trials.

Authors, Design, Comparator	# Studies and Patients; Outcomes and Follow-up	Pooled Estimates	Comments (Including review authors' quality assessment)
(Wang 2004 from Samson 2007)	10 RCTs (# pts NR) Pain without activities	**SPID%, 6.0% (0.7 to 11.2); significant heterogeneity (10 trials)** ASPID%, 11.0% (CI, –3.7 to 25.7); significant heterogeneity (9 trials) Peak PID%, 7.0% (CI, –1.8 to 15.7); significant heterogeneity (9 trials)	Significant heterogeneity for each overall calculation. NOTE: Results for this outcome were not reviewed by Samson and colleagues; data taken from MA article.
(Wang 2004 from Samson 2007)	17 RCTs (# pts NR) Function (any of multiple measures), non–hylan trials	**SFID%, 5.3% (CI, 2.1-8.5); no heterogeneity** **AFPID%, 11.7% (CI, 6.3-16.2) in favor of HA; no heterogeneity** **Peak FID%, 8.2% (CI, 3.8-12.6) in favor of HA; significant heterogeneity**	Metaregression and/or subset analysis showed trial quality, sample size, allowing escape analgesics, and age >65 yrs to be associated with smaller effect on function.
(Wang 2004 from Samson 2007)	3 RCTs (# pts NR) Function (any of multiple measures), **hylan** trials	SFID%, 21.9%; AFPID%, 38.3%; peak FID%, 26.8% (no CIs)	Greater treatment-placebo differences than those reported for non–cross-linked HA trials.
(Wang 2004 from Samson 2007)	20 RCTs (2252 knees) AEs	RR of *minor* AE, 1.2 (1.01–1.41)	*Major* AEs occurred in 3/1002 knees in non–hylan trials (severe swelling, vasculitis, hypersensitivity reaction); 1/139 knees (acute painful local reaction) in hylan trials.
From Samson 2007 Arrich 2005 (study-level MA) Placebo	22 single-/double–blind RCTS, published in full Sample sizes 38-330	Authors concluded that HA has not been proven clinically effective and may be associated with greater risk of AEs. Negative WMD/SMD at f/u favors HA.	RCTs with English or German abstracts included. In general, no evidence of publication bias. No explanation of why some trials, e.g., the 2 hylan trials with large effects (Scale 1994, Wobig 1998), could not be used although other MAs used them. *Quality (according to Samson and colleagues):* Minor flaws; conclusions fully supported by data/analysis.
(Arrich 2005 from Samson 2007)	8 RCTs (468 pts) Pain at rest (100-point VAS)	**WMD –8.7 (CI, –17.2 to –0.2); I^2=94%**	Pooled estimates for trials that did not use ITT analysis, did not clearly report allocation concealment, or were unblinded showed a greater treatment effect.

Authors, Design, Comparator	# Studies and Patients; Outcomes and Follow-up	Pooled Estimates	Comments (Including review authors' quality assessment)
(Arrich 2005 from Samson 2007)	9 RCTs (941 pts) Pain during/after exercise (100-point VAS)	2-6 wks: WMD –3.8 (CI, –9.1 to 1.4); I^2=81% (9 trials) 10-14 wks: WMD –4.3 (CI, –7.6 to –0.0); I^2=0 (5 trials) **22-30 wks: WMD –7.3 (CI, –11.8 to –2.4); I^2=0 (4 trials)**	Omitting an outlier trial in which pain increased among those with more advanced disease resulted in a WMD for 2-6 wks of –4.2 and I2=20%.
(Arrich 2005 from Samson 2007)	9 RCTs (994 pts) Function (multiple measures) 994	2-6 wks: SMD 0 (CI, –0.23 to 0.23); I^2=66% (9 trials) 10-14 wks: SMD –0.11 (CI, –0.31 to 0.09); I^2=59% (7 trials) **22-30 wks: SMD –0.16 (CI, –0.16 to –0.13); I^2=62% (5 trials)**	Pooled estimates for trials that did not clearly report allocation concealment showed a greater treatment effect for first 2 time periods.
(Arrich 2005 from Samson 2007)	15 RCTs (2019 pts) AEs	**RR 1.08 (1.01-1.15)**	Pooled estimates for trials that did not clearly report allocation concealment showed a greater treatment effect for first 2 time periods.
From Samson 2007 Modowal et al. (2005) (study-level MA) Placebo	9 double-blind RCTs, published in full Pain (100-point VAS)	Negative WMD in change favors HA. **1 wk: WMD –4.4 (CI, –7.2 to –1.1); I^2=92% (9 RCTs)** **5-7 wks: WMD –17.6 (CI, –28.0 to –7.5); I^2=92% (6 RCTs)** **8-12 wks: WMD –18.1 (CI, –29.9 to –6.3); I^2=95% (6 RCTs)** 15-22 wks: WMD –4.4 (CI, –24.1 to 15.3); I^2=94% (3 RCTs) Authors concluded that HA is moderately effective at 5-7 and 8-10 wks.	Trials reporting pain as part of WOMAC score were excluded. 73% of RCTs had industry sponsorship. 4 RCTs were considered low quality (score ≤0.75, maximum 1.0); excluding them lowered pooled estimates considerably. In metaregression, the relationships between trial quality and outcomes varied by f/u interval. No publication bias detected (tendency toward significant Eggers test, *P*=0.096). **Metaregression showed hylan to be associated with significantly better outcomes at 5 wks and beyond.** Few studies relative to the literature; no justification for excluding WOMAC pain as an outcome measure. *Quality (according to Samson and colleagues):* Major flaws; conclusions not supported by data/analysis.

Authors, Design, Comparator	# Studies and Patients; Outcomes and Follow-up	Pooled Estimates	Comments (Including review authors' quality assessment)
From Samson 2007 Bellamy 2006 (study-level MA; Cochrane Review) Placebo	32 RCTs published in full, published as abstracts, or unpublished	*SMDs calculated when different measures for pain and function were used. Authors concluded that HA is effective, especially at the 5- to 13-wk postinjection period. No major safety issues, but a review of RCTs are not the best source of AE rates. Negative values for WMD at f/u and SMD at f/u favor HA. Positive values for NNT favor HA; negative values favor placebo.	No language restrictions. 30% all included RCTs had industry sponsorship. Mean RCT quality was 3.5 (Jadad scale, 5 maximum), median 3. No specific analysis of publication bias, but Egger test results consistent with publication bias. Of >850 forest plots, only 38 provide pooled estimates for >3 trials. Analysis by RevMan 4.2.8 software. The following results, except where noted, are presented as comparison 50 in Bellamy 2006. *Quality (according to Samson and colleagues):* Minor flaws; conclusions partially justified by data/analysis. 25% pts and trials were unreported or reported only as abstracts.
(Bellamy 2006 from Samson 2007)	9 RCTs Pain at rest (100-point VAS)	1-4 wks: WMD –3.5 (CI, –9.2 to 2.1); I^2=80% (9 RCTs)	CORRECTION: Comparison 50 in Bellamy 2006 reports –5.37 (–9.90 to –0.85); 12 RCTs, 577 pt.
(Bellamy 2006 from Samson 2007)	16 RCTs Weight-bearing pain (100-point VAS)	**1-4 wks: WMD –7.7 (CI, –11.3 to –4.1); I^2=80% (20 RCTs)** **5-13 wks: WMD –13.0 (CI, –17.8 to –8.2); I^2=82% (16 RCTs)** **14-26 wks: WMD –9.0 (CI, –14.8 to –3.2); I^2=77% (8 RCTs)** 45-52 wks: WMD –2.6 (CI, –7.4 to 2.2); I^2=0 (3 RCTs)	CORRECTION: Comparison 50 in Bellamy 2006 reports 1-4 wks: 27 RCTs, 2542 pts 5-13 wks: –11.00 for 5-13 wks (same CI); 21 RCTs, 2090 pts 14-26 wks: 10 RCTs, 1491 pts
(Bellamy 2006 from Samson 2007)	6 RCTs WOMAC pain	**1-4 wks: SMD –1.2 (CI, –1.9 to –0.5); I^2=88% (6 RCTs)** **5-13 wks: SMD –1.0 (CI, –1.6 to –0.5); I^2=88% (6 RCTs)** **14-26 wks: SMD –1.0 (CI, –1.8 to –0.3); I^2=80% (3 RCTs)**	CORRECTION: Comparison 50 in Bellamy 2006 reports 1-4 wks: 7 RCTs, 412 pts 5-13 wks: 7 RCTs, 639 pts 14-26 wks: 4 RCTs, 275 pts
(Bellamy 2006 from Samson 2007)	6 RCTs Pain on weight bearing (100-point VAS), ***hylan trials***	**1-4 wks: WMD –12.54 (CI, –20.39 to –4.69) (6 RCTs)** **5-13 wks: WMD –22.5 (CI, –35.2 to –9.7); I2=83% (5 RCTs)** 14-26 wks: WMD –20.7 (CI, –35.56 to 5.83) (4 RCTs)	
(Bellamy 2006	6 RCTs	**1-4 wks: SMD –1.0 (CI, –1.6 to –0.4);**	CORRECTION: Comparison 50 in Bellamy 2006 reports

Authors, Design, Comparator	# Studies and Patients; Outcomes and Follow-up	Pooled Estimates	Comments (Including review authors' quality assessment)
from Samson 2007)	WOMAC function	**I^2=85% (6 RCTs)** **5-13 wks: SMD –0.9 (CI, –1.3 to –0.4);** **I2=84% (6 RCTs)** **14-26 wks: SMD –0.8 (CI, –1.4 to –0.2);** **I^2=70% (3 RCTs)**	1-4 wks: 7 RCTs, 412 pts 5-13 wks: 7 RCTs, 639 pts 14-26 wks: 4 RCTs, 275 pts
(Bellamy 2006 from Samson 2007)	Lequesne Index (pain and function, 0-24)	**1-4 wks: WMD –0.8 (CI, –1.4 to –0.2);** **I^2=44% (5 RCTs)** **5-13 wks: WMD –1.4 (CI, –2.0 to –0.7);** **I^2=16% (4 RCTs)** 14-26 wks: WMD –0.1 (CI, –0.8 to 0.9); I^2=6% (3 RCTs) 45–52 wks: WMD –1.1 (CI, –2.7 to 0.5); (1 RCT)	CORRECTION: Comparison 50 in Bellamy 2006 reports 1-4 wks: 7 RCTs, 412 pts 5-13 wks: 7 RCTs, 506 pts 14-26 wks: 4 RCTs, 566 pts
(Bellamy 2006 from Samson 2007)	1 RCT 40% relative or 5-point absolute (20-point scale) improvement in WOMAC pain	1-4 wks: NNT 14 5-13 wks: NNT –33 (favoring placebo) 14-26 wks: NNT –33 (favoring placebo)	
(Bellamy 2006 from Samson 2007)	1 RCT 5-point absolute (20-point scale) improvement in WOMAC pain	14-26 wks: NNT 5.9	Considered by Samson et al. to possibly be related to a definition of clinically important improvement.
(Bellamy 2006 from Samson 2007)	7 RCTs Improvement in global assessment	Generally negative NNT value at 1-4, 5-13, 14-26 wks.	Samson et al. note that these calculations are not tied to a definition of clinically important improvement.
(Bellamy 2006 from Samson 2007)	# RCTs NR Injection site pain	**RR 1.7 (1.19–2.44; *P*=0.004)**	No other significant differences in AE occurrence, e.g., discontinuance of study drug or GI complaint, at any f/u interval.
(Bellamy 2006 from Samson 2007)	5 RCTs AEs, *non–hylan trials*	RR 1.6 (0.54-5.6)	
(Bellamy 2006 from Samson 2007)	5 RCTs AEs, ***hylan** trials*	RR 1.9 (0.51-7.3)	

Authors, Design, Comparator	# Studies and Patients; Outcomes and Follow-up	Pooled Estimates	Comments (Including review authors' quality assessment)
From Samson 2007 Strand 2006 (pt-level MA) Placebo (IA saline)	5 double-blind RCTs; 3 published and 2 unpublished; selected from 18 trials included in PMA application 1155 pts Lequesne Index (pain and function, 0-24)	5 and 13 wks (all trials); 9 wks (4); 17, 20, and/or 25 wks (3); integrated analysis tested for effects of treatment over time Authors concluded that HA is comparable with other treatments, given the magnitude of improvement in HA arms and the significance of HA-saline differences. Negative estimate favors HA. *Group mean change (treatment vs placebo):* Fixed-effects model: **–2.74 vs –2.16** Random–effects model: **–2.68 vs –2.00** *Translates to a difference in mean change (treatment minus placebo):* Fixed-effects model: **WMD –0.58 (–0.95 to –0.20**) Random-effects model: **WMD –0.68 (–0.79 to –0.56)**	Pooled estimate of difference in change (–0.58 or –0.68) is very small compared with magnitude of the scale (0-24). *Quality:* No formal evaluation of quality (lack of validated instrument MAs of pt-level data); no deficiencies noted other than 10% dropout rate in treatment arm and 15% in placebo arm.
(Strand 2006 from Samson 2007)	# trials NR AEs	1.8%, HA; 3.2%, placebo	
Bannuru et al. (2011) (pt-level MA) Placebo	54 RCTs (49 reports) 6545 participants Outcome data selected according to a hierarchy of outcome measures as shown below, each measured according to (VAS or Likert). 5 f/u intervals	Bayesian random effects models and Hedges' g statistic as the effect size for each study. I^2 for heterogeneity (25%, low; 50%, moderate; 75%, high). Overall effects were those occurring at 8 wks, 12 wks, or end of trial, whichever occurred earlier, as suggested by manufacturer estimates of peak effects; calculated by metaregression (study-level data. Positive values for g statistics favor HA.	Data as reported were converted according to published or sensitivity-analysis methods when necessary.

Authors, Design, Comparator	# Studies and Patients; Outcomes and Follow-up	Pooled Estimates	Comments (Including review authors' quality assessment)
	49 RCTs (6962 pts) Pain (primary outcome): WOMAC OA Index Pain Subscale, knee pain when walking, knee pain during activities other than walking, spontaneous joint pain	**3-6 wks: SMD 0.31 (CI, 0.17-0.45); I^2=75% (44 trials)** **7-10 wks: SMD 0.46 (CI, 0.28-0.65); I^2=75% (26 trials)** **11-14 wks: SMD 0.25 (CI, 0.15-0.36); I^2=58% (31 trials)** **15–-8 wks: SMD 0.20 (CI, 0.11-0.30); I^2=15% (15 trials)** **23-26 wks: SMD 0.21 (CI, 0.10-0.31); I^2=33% (20 trials)** At 7-10 wks: 12 trials with NS effect sizes; 0 with negative effect sizes; 14 with significant effect sizes ≥ the pooled effect size of 0.46. **Overall: 0.34 (CI, 0.22-0.46) (I^2=70%)**	High–quality subset (14 trials, 2570 pts): Pain outcomes followed similar trajectory as in overall trials, but peak effect at 7-10 wks was lower (CI, 0.34 [0.02-0.67]). Same pattern when analysis was adjusted for time to correct for multiple outcome assessments at each time point. Metaregression (study-level sensitivity analysis): Substantially smaller effects in trials with adequate allocation concealment, double-blinding, >100 participants, unpublished status, publication after 2000, lower molecular weight, or non-avian source and slightly smaller effects (difference 0.04) in high–quality trials and trials with ITT analysis.
(Bannuru 2011)	16 RCTs (2571 pts) Function: WOMAC OA Index Function Subscale, function score for index joint	**3-6 wks: SMD 0.48 (CI, 0.12-0.84) (10 trials)** 7-10 wks: SMD 0.41 (CI, –0.07 to 0.89) (4 trials) 11-14 wks: SMD 0.16 (CI, –0.04 to 0.36) (11 trials) **15-18 wks: SMD 0.23 (CI, 0.03-0.44) (2 trials)** 23-26 wks: 0.16 (CI, –0.07 to 0.89) (9 trials) **Overall: 0.31 (CI, 0.11-0.51); I^2=79%** With 2 outliers removed: 0.15 (CI, 0.01-030); I^2=58%	NS overall effect in 5 high-quality trials (0.12; CI, –0.04 to 0.27; I^2=51%. Effect size 76% less than in low-quality trials.
(Bannuru 2011)	15 RCTs (2488 pts) Stiffness: WOMAC OA Index Stiffness Subscale, stiffness score for index joint	3-6 wks: 0.64 (CI,0.25-1.04) (8 trials) 7-10 wks: 0.28 (CI, –0.08 to 0.63) (4 trials) 11-14 wks: 0.23 (CI, 0.01-0.45) (11 trials) 15-18 wks: 0.20 (CI, –0.01 to 0.40) (2 trials)	NS overall effect in 4 high-quality trials (0.10, CI –0.11 to 0.31; I^2=67%. Effect size 78% less than in low-quality trials.

Authors, Design, Comparator	# Studies and Patients; Outcomes and Follow-up	Pooled Estimates	Comments (Including review authors' quality assessment)
		23-26 wks: 0.12 (CI, –0.13 to 0.36) (9 trials) **Overall: 0.31 (CI, 0.12-0.49); I^2=74%**	
Colen et al. (2012) (study-level MA) Placebo	WMDs were calculated if the same scales were used; SMDs (effect sizes) if different scales were used. Random effects models if I^2>50%. Relative within-grp improvement was calculated by dividing the outcome by BL value. Authors stated that when possible, sensitivity analyses were conducted with exclusion of trials using quasi-randomization methods, but no results of such analyses were reported.		
	All forms of HA: 18 RCTs (20 comparisons; 3 doses in 1 study; 2801 pts) Pain at 3 mos	**WMD –10.20 (CI, –15.97 to –4.42); I^2=92%**	In individual trials, mean differences ranged from –36.00 to 3.30; 16 of 20 comparisons favored HA and of these, 7 CIs excluded null value (statistically significant).
(Colen 2012) Within-grp relative improvements from BL	Hyalgan: 25 RCTs (1095 pts) Orthovisc: 13 RCTs (1370 pts) Euflexxa: 3 RCTs (608 pts) Synvisc: 35 RCTs (2117 pts) Placebo injection:32 RCTs (2464 pts) PT program:4 RCTs (149 pts) No tx/injections:6 RCTs (558 pts) Pain at 3 mos	43% 30% 66% 41% 30% 33% 20%	
Rutjes et al. (2012) (pt-level MA) All comparators	WMDs were calculated if the same scales were used; SMDs (effect sizes) if different scales were used. Differences in mean values at f/u were used if available; otherwise, differences in mean change. Random effects models. Heterogeneity measured by τ^2 (0.04 = low, 0.09=moderate, 0.16 = high). Prespecified MCID of effect size –0.37, based on studies of OA treatments; corresponds to a 0.9-cm difference on a 10-cm VAS. Of all 89 trials (177 publications), 57 published in full, 23 conference abstracts, 2 published in a pamphlet or book, 6 unpublished. For stratified sensitivity analyses (to assess effect modification), *P* values are for interaction. Total # RCTs reported by Rutjes et al. corresponds to total # comparisons (>1 in some trials) and includes trials reporting data that could not be converted to SMDs. Distribution of missing data across subgrps is unknown. Selection of 100 pts/tx arm (≥200 for a 2-arm study) as trial size cutoff was based on calculations for 80% power to detect a moderate effect size (–0.40) (Nuesch et al., 2010).		
(Rutjes 2012)	68 RCTs (71 possible comparisons,	**SMD –0.37 (CI, –0.46 to –0.28;**	Includes 14 studies w/ nonplacebo (non-sham) controls.

Authors, Design, Comparator	# Studies and Patients; Outcomes and Follow-up	Pooled Estimates	Comments (Including review authors' quality assessment)
	3 not contributing to pooled estimate [none published in full]; hence, 69 comparisons), 9617 pts; 50 RCTs were published in full Pain at 3 mos	***P*<0.001); τ^2=0.09 (*P*<0.001 for heterogeneity)**	In individual trials, SMDs ranged from –1.90 to 0.17; 26 of 69 comparisons favored HA and of these, 13 CIs excluded the null value and 8 CIs included only values exceeding the MCID. Asymmetrical funnel plot (SE vs SMD); no interpretation by authors. In analysis of 18 trials (5094 pts) w/ large sample sizes (100 pts in each grp) and blinded outcome assessment: (1) SMD was –0.11 (CI, –0.18 to –0.04; τ^2=0.01). (2) SMDs across time were –0.02 (1 mo), –0.08 (3 mos), –0.13 (6 mos), 0.02 (9 mos), 0.05 (12 mos).
(Rutjes 2012)	Significant interaction between trial characteristic and effect size (pain, 3 mos) Adequate blinding of assessors (46 RCTs) vs inadequate/unclear (25 RCTs) ≥100 per trial grp (21 RCTs) vs <100 per trial grp (50 RCTs) Full journal article (52 RCTs) vs other publications (14 RCTs) vs unpublished (5 RCTs)	*P* values are for interaction **SMD –0.25 (CI, –0.34 to –0.16) vs SMD –0.66 (CI, –0.84 to –0.44) (*P*=0.003)** **SMD –0.16 (CI, –0.26 to –0.07) vs SMD –0.52 (CI, –0.67 to –0.39) (*P*=0.002)** **SMD –0.36 (CI, –0.46 to –0.26) vs SMD –0.63 (CI, –0.91 to –0.36) vs** SMD –0.03 (CI, –0.14 to 0.09) **(global *P*=0.040)**	No interaction in stratified analysis (small and NS [*P*≥0.10] differences): sham (54 RCTs) vs non-sham intervention (18 RCTs); adequate pt blinding (16 RCTs) vs inadequate/unclear (55 RCTs); ITT analysis (15 RCTs) vs none (56 RCTs); free of industry funding (4 RCTs) vs industry funding or unclear (67 RCTs); ≥1 cycle (8 RCTs) vs 1 cycle (64 RCTs) Global differences were NS for molecular weight, but SMDs were greater for very high (–0.58; 18 RCTs) and high (–0.55, 15 RCTs) than for low (–0.23; 34 RCTs). No comment from authors on why blinded assessment but not pt blinding would modify treatment effect measured by pt–reported outcomes. In stratified analysis of 18 trials (5094 pts) w/ large sample sizes (100 pts in each grp) and blinded outcome assessment, interaction effects were NS. Subgrp-specific point estimates generally favored HA but CIs generally did not extend to the MCID of –0.37. Heterogeneity was low. Analysis according to f/u duration suggested peak effect at 3 mos (–0.16) and no effect after 6 mos (0.02). NOTE: # trials accounted for across some sets of strata exceeded 71, which the authors identified as the total # of RCTs with pain data. For example, there were 73 trials across the 3 publication types. The discrepancy was not explained.
(Rutjes 2012)	Trend toward significant interaction (pain, 3 mos) Adequate allocation concealment (13 RCTs) vs inadequate/unclear (58 RCTs) 1-2 injections (7 RCTs) vs 3 injections (38 RCTs) vs >3 injections (30 RCTs) Cross-linked (19 RCTs) vs Non–cross-linked or unclear (56 RCTs)	*P values are for interaction* SMD –0.18 (CI, –0.36 to –0.01) vs SMD –0.43 (CI, –0.53 to –0.32) (*P*=0.053) SMD –0.52 (CI, –0.85 to –0.18) vs SMD –0.46 (CI, –0.60 to –0.32) vs SMD –0.22 (CI, –0.34 to –0.10) (global *P*=0.58) SMD –0.53 (CI, –0.73 to –0.34) vs SMD –0.29 (CI, –0.39 to –0.20) (*P*=0.099)	

Authors, Design, Comparator	# Studies and Patients; Outcomes and Follow-up	Pooled Estimates	Comments (Including review authors' quality assessment)
	>6 mos f/u vs 3-6 mo vs <3 mos	SMD –0.36 (CI, –0.62 to –0.09) vs SMD –0.23 (CI, –0.33 to –0.12) vs SMD –0.54 (CI, –0.70 to –0.37) (global *P*=0.078)	
(Rutjes 2012)	51 RCTs (52 possible comparisons, 3 not contributing to pooled estimate); # pts NR Physical function at 3 mos	**SMD –0.33 (CI, –0.43 to –0.22); τ^2=0.1 (for heterogeneity *P*<0.001).**	In individual trials, SMDs ranged from –2.16 to 0.30; of 40 comparisons favored HA and of these, 17 CIs excluded the null value and 12 CIs included only values exceeding the MCID. Asymmetrical funnel plot (SE vs SMD); no interpretation by authors. In analysis of 15 trials (4296 pts) w/ large sample sizes (100 pts in each grp) and blinded outcome assessment, SMD was –0.09 (CI, –0.17 to –0.00; τ^2=0.01). SMDs across time were –0.03 (1 mos), –0.11 (3 mos), –0.09 (6 mos), –0.07 (9 mos), 0.05 (12 mos).
(Rutjes 2012)	Flare–ups (primary safety outcome) (6 RCTs, 811 pts) Local (31 RCTs, 5241 pts) Effusions (6 RCTs, 1337pts) Overall withdrawals (40 RCTs, 7277pts) Serious adverse events (14 trials, 3667 pts) Any AE (25 RCTs, 5204 pts) Dropouts due to AE (23 RCTs, 5522 pts)	**RR 1.51 (CI, 0.84-2.72); τ^2=0.00** **RR, 1.34 (CI, 1.13-1.60); τ^2=0** RR 1.15 (CI, 0.38-3.54); τ^2=0 RR 0.97 (CI, 0.87-1.09); τ^2=0 **RR 1.41 (CI, 1.02-1.97); τ^2=0** RR 1.04 (CI, 0.99-1.09); τ^2=0 **RR 1.33 (CI, 1.01-1.74); τ^2=0**	In analysis of trials w/ large sample sizes (100 pts in each grp) and blinded outcome assessment (# trials/pts NR), RR for flare-ups was 2.39 (NS) RRs for local AE, effusions, and any AE were similar to overall results. RR for serious AE was **1.55 (CI, 1.07-2.24; τ^2=0.04; 11 RCTs, 2899 pts**) Rutjes et al. stated that the causal relationship between HA injection and serious AEs was unclear; they did not comment on whether study authors offered an explanation.

APPENDIX VI. Key Results of Meta–analyses of Randomized *Nonplacebo* Comparisons, Key Questions #1 and #2

Key: AE, adverse event; CI, confidence interval; f/u, follow-up; HA, hyaluronic acid; I, I index (statistical measure of heterogeneity); IACS, intraarticular corticosteroid; ITT, intention-to-treat; MA, meta-analysis(es); NNH, number needed to harm; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PT, physical therapy; pt(s), patient(s); RCT, randomized controlled trial; RR, relative risk; SMD, standardized mean difference; VAS, visual analog scale; WMD, weighted mean difference; WOMAC, Western Ontario and McMaster Universities (Index)

Authors, Design, Comparator	# Studies and Patients; Outcomes and F/u	Pooled Estimates	Authors' Conclusions; Other Comments
Bellamy et al. (2006) Exercise, PT, appropriate care, or trigger point injection	11 RCTs (982 pts) Various outcomes and f/u intervals	Mostly nonsignificant differences for outcomes of interest. Largest significant effect favoring HA: WMD –13.20 (CI, –17.02 to –9.38), WOMAC function (100-point VAS) at 36 wks, hylan vs appropriate care (Bellamy comparisons # 9, 16, 17, 25, 26, 29, 27, 28, 39, and 40)	Authors did not comment on these findings or provide study–specific quality assessment.
NSAIDs	6 RCTs (891 pts); 2 RCTs assessed safety only Various outcomes and f/u intervals	Mostly nonsignificant differences for outcomes of interest. Exception: In 3 trials of hylan, significant WMDs favoring HA over NSAIDs in the range of –12 to –19 were observed, but CIs were wide. (Bellamy comparisons 10, 21, 22, 51 (3 trials included in comparison 51)	Authors' conclusions: In general, similar efficacy compared with NSAIDs. Few AEs; compared with systemic interventions, may result in more local reactions but fewer systemic AEs.
Reichenbach et al. (2007) (MA; pt-level unclear) **Hylan vs HA**	MA: 13 RCTs or quasi-randomized trials, publicized or unpublicized; abstracts or in full (2085 pts) Pain (global, with walking, WOMAC, Lequesne, or with activities other than walking, in order of decreasing preference) Last f/u or at 6 mos following last injection, whichever came first	SMD or, if value at last f/u not available, then SMD of change. Negative values favor hylan. **SMD –0.27 (CI, –0.55 to 0.01); *P*<0.001; I^2=88% (13 RCTs)** (SMD –0.10; CI, –0.26 to –0.06; I^2=48% when 2 outlier trials were removed) Individual RCT effect sizes: CI crossed null (7 trials), favoring hylan in 4 trials (SMD, –1.21 to –0.44; 4 trials) and favoring HA in 2 trials (SMD, 0.18-0.26).	A priori determination of –0.30 as threshold for clinical importance. Funnel–plot analysis and univariate metaregression revealed no association between trial size and treatment effect. Cutoff value in metaregression was 200. Univariate metaregression produced effect sizes near null in trials with adequate allocation concealment (2 RCTs and 46% pts), blinding of pts (6 RCTs and 72% pts), ITT analysis. CIs for these estimates did not include the minimally clinically relevant effect size of –0.30, and statistical heterogeneity was reduced to low–moderate range. However, tests for interaction did not reveal statistically significant effect modification, possibly because of small # of trials.

Authors, Design, Comparator	# Studies and Patients; Outcomes and F/u	Pooled Estimates	Authors' Conclusions; Other Comments
			Longer f/u resulted in a clinically important effect size, but test for interaction was again nonsignificant. Metaregression with f/u as continuous variable showed no association. No association between molecular weight (continuous variable in metaregression) and effect size.
(Reichenbach 2007) **Hylan vs HA**	Meta-regression w/ hylan as the independent variable: indirect comparison of pain effect. 31 trials contributing to 3 MAs (Arrich 2005, Bellamy 2006, Lo 2003) Last f/u or at 6 mos following last injection, whichever came first	**SMD –0.64 (–1.25 to –0.02); I^2=72%**	3 of 31 trials compared hylan with placebo, were small, and reported large benefits. The other trials compared non–cross-linked HA with placebo. Metaregression showed a nonsignificant effect size of 0.23 (favoring HAs) in trials ≥200 and a significant effect size of –1.19 (favoring hylan) in trials with <200 pts; test for interaction between effect size and trial size was significant.
(Reichenbach 2007) **Hylan vs HA**	6 RCTs Flares, effusions, or any AE Last f/u or at 6 mos following last injection, whichever came first	Values >1 favor hylan. Flares: RR 7.27 (CI,0.39-1.34) (4 RCTs) **Effusions: RR 2.40 (CI,1.21-4.76) (2 RCTs)** **Any AE: RR 1.91 (CI,1.04-3.49) (6 RCTs)** NNH 14 (5-324) for 1 additional AE.	Variable definitions and reporting detracts from validity of pooled estimate, but RR measure compensates for between-trial differences. Risk increase observed consistently in individual trials. Low statistical heterogeneity across trials.
Bannuru et al. (2009) (study-level MA) IACS	7 RCTs, published in full (606 pts, 610 knees) Hierarchy of outcome measures (WOMAC OA Index Pain Subscale*, knee pain when walking*, knee pain during activities other than walking*, spontaneous joint pain*) *VAS or Likert 5 f/u intervals	Hedges' g statistic as the effect size for each study; represents score change corrected for small samples. (Hedges' g is a particular formula for calculating standardized differences between means. The article provides a textbook reference but no further explanation.) Pooled g statistics (*positive* values favor HA): **1-2 wks: –0.39 (CI, –0.65 to –0.12); I^2=47%** 3-6 wks: –0.01 (CI, –0.23 to 0.21); I^2=37% 7-10 wks: 0.22 (CI, –0.05 to 0.49); I^2=47% **11-16 wks: 0.35 (CI, 0.03-0.66); I^2=49%** **17-29 wks: 0.39 (CI, 0.18-0.59); I^2=0**	General consistency in direction of results across trials. Very similar rates were observed in multivariate analyses, adjusting for within- and between-study covariance (among outcomes and between time points). The same was true in sensitivity analysis, pooling results only for the 5 trials using ITT analysis, for the 4 trials with blinding, for the 4 trials comparing Hyalgan with methylprednisolone acetate. Metaregression revealed no significant interactions with blinding or ITT status. 2 trials had significant baseline differences, but MA of change scores did not reveal these trials to differ from pooled data.

Authors, Design, Comparator	# Studies and Patients; Outcomes and F/u	Pooled Estimates	Authors' Conclusions; Other Comments
Colen et al. (2012) **Hylan vs HA**	All results apply to 3 mos f/u.		
	Synvisc vs other HA: 12 RCTs (14 comparisons; 2492 pts)	SMD –0.07 (CI, –0.24 to 0.10); I^2=72%	In individual trials, SMDs ranged from –0.77 to 0.38; 8 of 14 comparisons favored Synvisc and of these, 3 CIs excluded the null value.
	Synvisc vs Orthovisc: 5 RCTs (627 pts)	SMD 0.25 (CI, –0.15 to 0.64); I^2=70%	
	Synvisc vs Hyalgan: 2 RCTs (422 pts)	**SMD –0.37 (CI, –0.57 to –0.18); I^2=0**	
	Synvisc vs Euflexxa: 2 RCTs (636 pts)	SMD –0.09 (CI, –0.25 to 0.06); I^2=0	
	Hyalgan: 10 RCTs (13 comparisons; 1466 pts)	**SMD –0.61 (CI, –0.92 to –0.29; *P*=0.0002); I^2=86%**	In individual trials, SMDs ranged from –3.33 to 0.05; 10 of 13 comparisons favored HA and of these, 4 CIs excluded null value.
	Synvisc: 3 RCTs (524 pts)	SMD –0.89 (CI, –1.98 to 0.21); I^2=97%	In individual trials, SMDs ranged from –2.31 to –0.16; all 3 comparisons favored HA and of these, 1 CI excluded null value
	Orthovisc: 3 RCTs (498 pts)	SMD –0.10 (CI, –0.27 to 0.08); I^2 NR	In individual trials, SMDs ranged from –0.20 to 0.03; 2 of 3 comparisons favored HA; CIs for all 3 SMDs crossed the null value.

APPENDIX VII. Randomized Controlled/Comparator Trials Published Since December 2009

Key: ACR, American College of Rheumatology; AE, adverse event; BL, baseline; ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; CMW, combined molecular weight; f/u, follow-up; grp(s), group(s); HA, hyaluronic acid; HMW, high molecular weight; IA(CS), intraarticular (corticosteroid); ITT, intention-to-treat; LMW, low molecular weight; LOCF, last observation carried forward; MCID, minimum clinically important difference; MCS, mental component summary; NNT, number needed to treat; NR, not reported; NS, [statistically] nonsignificant; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OMERACT, Outcome Measures in Rheumatology; OR, odds ratio; PCS, physical component summary; pt(s), patient(s); QOL, quality of life; RCT, randomized controlled trial; SF-36 Health Survey (QualityMetric Inc.); sig, [statistically] significant; TEAE, tx-emergent AE; tx, treat/treatment; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities (Osteoarthritis Index)

Authors/Study Design	Study Population	Procedural Protocol	Results (95% CIs and significant level 0.05 unless otherwise noted)	Main Finding/Limitations/Quality/Comments
Altman et al. (2011) Extension of FLEXX Trial (36-site [U.S.] double-blind, placebo-controlled RCT of Euflexxa; superiority trial [Altman et al., 2009]) Open-label RCT to assess repeated injections *F/u:* 26 wks beyond 2nd series of tx (wk 52 measured from randomization) *Time frame:* NR *Funding source:* Ferring Pharmaceuticals	n=433 willing participants of 516 FLEXX Trial completers HA grp: n=219 (mean age 63 yrs; 63% women) Saline grp: n=214 (mean age 61 yrs; 64% women) FLEXX completers represented 88% of originally randomized pts in each grp; Extension Study participants represented 85% (HA)/ 83% (saline) of original grps. (Sample size for original trial based on 90% power to detect 8.0-mm between-grp difference in pain scores at wk 26, assuming 30% dropout rate.) *Inclusion criteria:* OA according to ACR criteria, mean age 61-62 yrs; 63% women; similar prior treatment; moderate	*Tx:* Pts completing the 2009 FLEXX Trial had option of second series (1 injection/wk × 3 wks) in same knee w/ same tx. Pt blinding was continued. *Concomitant tx:* Acetaminophen allowed; otherwise NR *F/u:* Telephone interview at wk 34 or 35 and office visits at wks 41 and 52. AEs recorded during all 4 contacts. *Analysis:* ITT analysis of all pts w/ ≥1 injection and ≥1 post-BL evaluation during Extension Study. Safety analysis included all 433 participants. *Outcome measures:* Primary: Difference in pain on 100-mm VAS following 50-foot walk and compared w/ BL. Secondary: Responder rate according to OMERACT-OARSI Index* (composite), change in WOMAC (100-point scale), # tablets rescue acetaminophen, change in SF-36 (Acute Form Health Survey), Pt Global Assessment (current pain according to 100-mm VAS). Safety: Vital signs, physical examination of target knee following injection, TEAEs, and concomitant	The 2 Extension Study grps had very similar BL characteristics. *Dropouts:* 378 participants (87%) completed Extension Study; no between-grp differences in discontinuation rates due to AEs, use of exclusionary medication, protocol violation, withdrawal of consent, loss to f/u, or other reason. *Change in VAS pain score (HA, saline) (# NR):* –3.5 (–26.5 in FLEXX Trial), –9.0 (–21.5 in FLEXX Trial); improvement maintained at 52 wks. *OMERACT-OARSI response rate at wk 52 (HA, saline) (% pts):* 67%, 59% (significance testing NR); NNT=13 (calculated from event rates) *WOMAC, Patient Global Assessment, use of rescue medication, SF-36 scores:* Further improvements for overall study grp; no HA-saline differences were reported. *Safety outcomes (HA, saline) (% pts):* In general, very similar to FLEXX Trial. ≥1 TEAE: 43.8% (compared w/ 43% in	Pain improvement continued w/ a 2nd trial of 3 HA injections, but no difference in comparison w/ saline injection was demonstrated. *Limitations:* <75% of original FLEXX study grp completed Extension Study; statistical analysis of between-grp differences in pain and pain change scores NR; strict ITT analysis not followed. Lead author and 3 other authors were paid consultants to Ferring. *Quality:* Fair (incomplete analysis)

Authors/Study Design	Study Population	Procedural Protocol	Results (95% CIs and significant level 0.05 unless otherwise noted)	Main Finding/Limitations/Quality/Comments
	baseline pain (mean 55-56 according to primary outcome measure) *Exclusion criteria:* Knee surgery w/in 12 mos (target knee) or 6 mos (contralateral) *Clinical hx/pt characteristics:* Caucasian (77%), African American (10%), Asian (2%), Hispanic (10%), other (1%); mean wt 92 kg; mean BMI 33	medications.	original FLEXX trial), 43.0% Specific events: Nausea (1.8%, 1.4%); diarrhea (1.4%, 0.5%); pain (1.8%, 0.5%); injection site pain (0, 1.4%); hypersensitivity (1.4%, 0.5%); nasopharyngitis (4.6%, 2.3%); upper respiratory infection (2.7%, 3.3%); sinusitis (2.3%, 1.4%); urinary tract infection (1.4%, 0.5%); injury (4.1%, 4.7%); arthralgia (8.7%, 11.2%); joint swelling (2.7%, 1.9%); back pain (2.7%. 0.5%); extremity pain (1.4%, 1.9%); headache (1.4%, 0.9%); cough (1.4%, 0.5%); hypertension (0.5%, 1.9%) Other comments: No detectable pretx or posttx synovitis or synovial effusions. No serious AEs considered tx-related and no deaths. Authors cited arthralgia, joint swelling, peripheral edema, and injection site pain as the most common tx–related AEs.	
Navarro-Sarabia et al. (2011) 5 centers in Spain Osteoarthritis Modifying Effects of Long-term Intraarticular Adant (AMELIA) trial Double-blind RCT to assess repeated injection cycles *F/u:* ≤40 mos *Time frame:* October 2003 – July 2009	n=306 pts (mean age 63.4 yrs; 83.7% women) HA Grp: n=153 Saline Grp: n=153 *Inclusion criteria:* OA of the knee according to ACR criteria; Kellgren-Lawrence grade II to III radiographic stage OA; ≥45 yrs of age; ≥55 mm VAS for pain anytime during wk prior to study; ≥2 mm minimum medial femorotibial joint space *Exclusion criteria:* BMI >32 kg/m^2; hx of trauma or	*Tx:* Pts randomized to HA (Adant [MW 900,000 Daltons], Tedec-Meiji Farma) or placebo (saline). Each tx cycle consisted of 5 wkly injections. Pts received 4 tx cycles **regardless of symptoms at** 0 mos, 7 mos, 14 mos, and 27 mos; 5 injections/cycle. *Concomitant tx:* Rescue medications permitted but no NSAIDs for 8 days prior to each assessment; IACS not permitted. *F/u:* Office visits 6 mos after 1st and 2nd cycles; approx 1 yr after 3rd and 4th cycles *Analysis:* Pts were considered responders if they meet OMERACT-OARSI criteria: (1) pain or physical function scores decreased ≥50% and ≥20 mm on VAS, or	301 pts (149 pts in HA grp and 152 pts in saline grp) had ≥1 efficacy assessment and were included in efficacy analyses. 109 pts (73%) in HA grp and 94 pts (62%) in saline grp completed the study. No between-grp differences in discontinuation rates due to AEs, withdrawal of consent, loss to f/u, or other reason, w/ exception of lack of efficacy (21% of HA grp, 32% of saline grp) (*P*=0.027). *OARSI response rate at last f/u (HA, saline) (% pts):* At last f/u: 81%, 66% (*P*=0.004; RR 1.22; CI, 1.07 to 1.41); NNT was 7 (CI, 4.1 to 20.5)	Viscosupplementation, administered in 4 cycles over a 3-yr period, regardless of symptoms following 1st cycle, was shown to improve pain and function. *Limitations:* High rate of dropouts at 40 mos; short-term outcomes, e.g., at 3 mos, NR; pain measurement condition (resting, walking, standing) NR; strict ITT analysis not followed Study authors were either employees of, or had received research funds from, HA manufacturer. Quality: Fair

Authors/Study Design	Study Population	Procedural Protocol	Results (95% CIs and significant level 0.05 unless otherwise noted)	Main Finding/Limitations/Quality/Comments
Funding source: Tedec Meiji Farma SA	surgery to target knee; arthroscopy w/in 1 yr of study entry; joint inflammatory disease; microcrystalline arthropathies; coagulation/platelet disorders; intraarticular steroids w/in 3 mos, HA injections w/in 1 yr, or NSAID use w/in 2 wks of study entry *Clinical hx/pt characteristics (HA, saline) (mean):* OA pain on 100 mm VAS (69.7, 71.2), WOMAC function on 100 mm VAS (57.1, 59.1), WOMAC stiffness on 100 mm VAS (23.0, 22.4)	(2) 2 of the following occurred: (a) decrease in pain of ≥20% or ≥10 mm on VAS, (b) decrease in physical function of ≥20% or ≥10 mm on VAS, or (c) increase in global assessment by ≥20%. The main study population included all randomized pts w/ ≥1 efficacy assessment (modified ITT grp). LOCF method used for imputation (found to be more conservative than mixed method repeated measures). Study designed to have statistical power of ≥80% to detect a difference of ≥20% of pts responding to tx. *Outcome measures:* Primary: Responder rate according to OMERACT-OARSI Index (composite) at last f/u. Secondary: Clinical response according to OMERACT-OARSI Index* at each visit, pain, function (WOMAC), pt global assessment, use of rescue medication. Safety: Physical examinations and blood laboratory tests.	7 mos (n=209): 71%, 68% (NS) 14 mos (n=213): 77%, 65% (*P*=0.03) 21 mos (n=219): 78%, 68% (*P*=0.049) 27 mos (n=219): 78%, 68% (*P*=0.049) 34 mos (n=220): 81%, 65% (*P*=0.002) *Secondary outcomes at last f/u (HA, saline) (% pts):* Pain or function reduction 50% & 20 mm: 65%, 52% (*P*=0.02) Pain reduction 20% or 10 mm: 79%, 68% (*P*=0.025) WOMAC function improvement 20% or 10 mm : 71%, 56% (*P*=0.023) Pt global assessment improvement 20%: 75%, 58% (*P*=0.002) Mean consumption paracetamol (mg/day): 644, 926 (NS) *Safety outcomes (HA, saline):* Number of pts who had ≥1 AE were same in both grps. **No serious AEs were mentioned.** TEAE: 9.8%, 9.1% Allergic reaction (1.9%, 1.9%); pain at injection site (3.9%, 1.3%); bleeding at injection site (1.3%, 3.9%); arthralgia (1.3%, 1.3%); other (1.3%, 0.7%)	*Comments:* Adant is not approved in the U.S.
Petrella et al. (2011) University of Western Ontario, London, Canada Double-blind placebo controlled and comparative trial *F/u:* 2 yrs *Time frame:* NR *Funding source:* NR	n=200 pts HMW grp: n=50 (mean age 71 yrs; 21 men, 29 women) LMW grp: n=50 (mean age 69 yrs; 23 men, 27 women) CMW grp: n=50 (mean age 68 yrs; 22 men, 8 women) Saline grp: n=50 (mean age 71 yrs; 20 men, 30 women)	*Tx:* Pts randomized to receive injections of HMW HA (6000 kDa), LMW HA (500-1000 kDa), CMW HA (combined LMW and HMW), or saline. Pts received 1 injection wkly for 3 wks. Some pts received a repeat HA injection at 52 wks. Pts in saline grp had option to receive any tx at 52 wks. *Concomitant tx:* Medications taken before trial could be continued but new medications prohibited, as were other IA injections	3 pts (6%) in saline grp, 2 (4%) in CMW grp, 1 (2%) in LMW grp, and 4 (8%) in HMW grp withdrew from study. Repeat injections administered at 52 wks for 39 pts in CMW grp, 41 in LMW grp, and 43 in HMW grp. *Improvement in mean walking pain on VAS (CMW, LMW, HMW) (%):* 16 wks: 89.3%, 81.3%, 79.1% 52 wks: 87.4%, 78.2%, 81.1% 104 wks: 88.1%, 77.0%, 79.4% (Differences from BL were significant	Viscosupplementation was associated w/ improved pain in pts w/ knee OA. A combination of HMW and LMW HA may lead to a quicker and greater improvement in symptoms. *Limitations:* Small # pts in each grp; incomplete reporting of efficacy data for active tx grps; pain measurement condition (resting, walking, standing) NR; efficacy data for saline grp is NR; saline grp discontinued study at 52

Authors/Study Design	Study Population	Procedural Protocol	Results (95% CIs and significant level 0.05 unless otherwise noted)	Main Finding/Limitations/Quality/Comments
	Inclusion criteria: Knee OA; Grade 1-3 medial compartment OA confirmed by x-ray; non-weight bearing VAS ≥45 mm *Exclusion criteria:* End stage OA; planned surgical tx of knee during study period; current tx w/ intraarticular drugs; intraarticular steroids or HA w/in 6 mos of study entry; systemic steroids w/in 3 mos of study entry; anticoagulants (except ≤325 mg/day acetylsalicylic acid); significant venous or lymphatic stasis in the legs; active skin disease or infection at injection site *Clinical hx/pt characteristics (CMW, HMW, LMW, saline) (mean):* BMI (26.9, 26.7, 27.3, 27.2 kg/m^2), # of concomitant OA tx's (2, 2, 3, 3), prior use HA (7, 7, 9, 10)	*F/u:* Evaluations performed at 16, 52, and 104 wks. *Analysis:* Study designed to have statistical power of 90% to detect a difference of 20 mm in weight-bearing VAS. ANOVA w/ repeated measures and Chi-square test were used to detect differences from BL. *Outcome measures:* Primary: 40 meter walking pain on 100 mm VAS at wk 16, 52, and 104. Secondary: Pain at rest (VAS), pt global satisfaction (5-point numerical scale), consumption of concomitant medications, and number of pts w/ <45 mm pain at 52 and 104 wks f/u. Safety: # AEs.	for all HA grps, *P*<0.001) Outcomes in Saline Grp NR. CMW grp had greater response to tx than other HA grps (*P*<0.001); no difference detected between LMW and HMW; unclear whether these findings were for pain at rest or walking. Global satisfaction was significantly higher in the CMW grp compared w/ other grps at 16, 52, and 104 wks (*P*<0.005). Pts in CMW grp received fewer alternative tx's than the other grps (*P* value NR). *Safety outcomes (% of entire study grp, including saline):* There were **no serious AEs**. Overall procedure-related AEs were: pain and swelling at injection site (21%), erythema at injection site (12%), stiffness in index knee (7%). No between-grp differences.	wks; intergrp statistical analyses were NR; AEs not reported separately for tx grps. Quality: Fair *Comments:* Inclusion of a repeat injection of any active tx at 1 yr makes this trial more like an effectiveness (pragmatic) trial rather than an efficacy trial.
Strand et al. (2012a) 28 centers in U.S. Double-blind RCT to evaluate single injection formulation of HA	n=375 pts HA grp: n=247 (mean age 60.9 yrs; 100 men, 147 women) saline grp: n=128 (mean age 60.3 yrs; 51 men, 77 women) *Inclusion criteria:* 40-80 yrs	*Tx:* Pts randomized 2:1 to receive a single intraarticular injection of HA (Gel-One®, Seikagaku Corp.) or saline. Injecting physician was unblinded. *F/u:* Assessments at 1, 3, 6, 9, and 13 wks. *Analysis:* Effectiveness evaluated in modified ITT population (all tx'd pts w/ ≥1 f/u visit) according to 2 models:	16 (6%) pts in HA grp and 9 (7%) pts in saline grp discontinued study. NOTE: All of the following effectiveness outcomes favor HA. *Improvement at f/u, estimated difference (between grps according to Model 1 (100-mm scale):* WOMAC Pain: 6.39 (CI, 0.37-12.41;	A single-injection formulation of hylan was more effective than a placebo injection at relieving pain. The effect on function was more uncertain. *Limitations:* Multiplicity; strict ITT analysis not followed; method of imputing missing values NR; no long-

Authors/Study Design	Study Population	Procedural Protocol	Results (95% CIs and significant level 0.05 unless otherwise noted)	Main Finding/Limitations/Quality/Comments
F/u: 13 wks *Time frame:* August 2006 – December 2007 *Funding source:* Seikagaku Corp.	of age; knee pain ≥4 wks; Kellgren-Lawrence grade 1-3; WOMAC pain score ≥40 mm in index knee and ≤20 mm in contralateral knee; stable ≥4 wks before study entry *Exclusion criteria:* Inflammatory disease of knee other than OA; severe knee effusion; severe malalignment of knee; hx of knee or hip replacement w/in 1 yr before study entry; arthroscopy of either knee w/in 3 mos of study entry; intraarticular injection of steroids w/in 4 wks of study entry; intraarticular HA injections w/in 6 mos of study entry; serious systemic disease; infection or inflammatory disease at injection site *Clinical hx/pt characteristics (HA, saline) (mean):* BMI (28.3, 28.7 kg/m^2), WOMAC pain (70.7, 68), WOMAC physical function (68.9, 67.6), total WOMAC (69.5, 67.8), WOMAC stiffness (71.6, 69.3)	Model 1 assessing differences in improvement from BL to wk 13, using all available data and Model 2 assessing longitudinal differences across assessment times (3-13 wks). Study designed to have statistical power of 90% to detect a difference of 10 mm in WOMAC pain score. Blinded investigators evaluated severity of AEs and potential relationship to tx. *Exploratory analysis:* Responders defined according IMMPACT criteria: MCID (≥10 mm improvement), moderate improvement (30%), substantial improvement (50%) *Outcome measures:* Primary: WOMAC pain subscores by 100 mm VAS at wk 13. Secondary: Responder rate according to OARSI Index (composite); change in total WOMAC, physical function, and stiffness subscores; pt and physician global assessments (VAS); acetaminophen consumption; health-related QOL (SF-36); % pts meeting or exceeding MCID. Pts were considered responders if they met OMERACT-OARSI criteria (see Navarro-Sarabia et al., 2011); "strict" response according to first set of criteria and "response" according to 2nd set of criteria. Safety: AE, physical examination, hematology.	*P*=0.037) Total WOMAC: 5.64 (–0.20 to 11.47; *P*=0.058) WOMAC physical function: 5.42 (CI, –0.47 to 11.31) WOMAC stiffness: 4.91 (–1.31 to 11.14) Physician global assessment: 3.56 (CI, –1.48 to 8.60) Pt global assessment: 0.92 ((CI, –4.63 to 6.47) (All analyses were NS) *Improvement across assessment times, estimated difference between grps according to Model 2 (100-mm scale, global P values):* WOMAC pain: 7.10 (*P*=0.005) Total WOMAC: 5.59 (*P*=0.035) WOMAC physical function: 5.29 (*P*=0.049) WOMAC stiffness: 5.27 (NS) Physician global assessment: 5.97 (*P*=0.012) Pt global assessment: 3.82 (NS) *Strict OARSI responders (HA, saline) (% pts):* 6 wks: 51.1%, 39.5% 9 wks: 54.1%, 46.6% 13 wks: 45.9%, 38.7% (NNT=15; calculated from reported data) OR for strict responders was statistically significant for HA over saline from wks 6-13 (OR=1.59; CI, 1.07 to 2.37; *P*=0.022). *OARSI responders (HA, saline) (% pts):* 6 wks: 66%, 61.3% 9 wks: 65.4%, 62.7% 13 wks: 61%, 54.6% % (NNT=16;	term f/u. All authors were either consultants or employees of Seikagaku Corp. Quality: Fair

Authors/Study Design	Study Population	Procedural Protocol	Results (95% CIs and significant level 0.05 unless otherwise noted)	Main Finding/Limitations/Quality/Comments
			calculated from reported data) (OR for responders was NS) *Safety outcomes (HA, saline):* Any AE: 69.1%, 63.3% Tx-related AE: 26.9%, 25.8% Serious AE: 3.2%, 0. Serious AE reported in 8 pts in HA grp (5 cases of cancer; other serious AEs included cardiac arrest, respiratory arrest, cirrhosis, pulmonary edema, renal failure, transient ischemic attack, exertional dyspnea, transient blurry vision, dizziness, femoral hernia, abdominal pain); none were considered to be tx-related by the authors. There was no statistically significant difference in AEs between grps. *TEAE occurring in ≥5% of pts (HA, saline) (% pts):* Joint swelling: 14.1%, 11.7% Joint effusion: 11.2%, 10.2% Arthralgia: 7.6%, 9.4%	
Strand et al. (2012b) Extension and retreatment phases of trial by Strand et al. (2012a) *F/u:* ≥13 wks after initiation extension phase (26 wks after 1st injection in original trial) for extension results; 13 wks after initiation of retreatment for	n=258 pts Original HA grp: n=162 pts Original Saline grp: n=96 *Inclusion criteria, extension:* Willingness to continue in trial *Inclusion criteria for retreatment:* Same as for entry to original trial (WOMAC pain ≥40 in tx'd knee plus <20-mm improvement from baseline)	Original blinding was maintained. Pts in extension phase were only followed. Pts who met criteria for retreatment all received 1 Gel-One injection. *Outcome measures:* Time to retreatment *Analysis:* Kaplan-Meier curves, Cox proportional hazards model (w/ adjustment for initial VAS scores and covariates) to assess relative risk of Endpoint A (WOMAC pain ≥40 in tx'd knee) and Endpoint B (WOMAC pain ≥40 in tx'd knee plus <20-mm improvement from baseline); response defined as in original trial.	11% of extension/retreatment grp withdrew or were lost to f/u. 196 of 258 extension pts became eligible for retreatment w/in 13 wks. EXTENSION RESULTS *Median time to retreatment (original HA, original saline) (wks):* Endpoint A: 5.3, 3.4 Endpoint B: 12.4, 4.2 *HR (original HA vs original saline):* Endpoint A, 0.74 (*P*=0.023); Endpoint B, 0.75 (*P*=0.040) RETREATMENT RESULTS *Change in WOMAC and PGA scores:* Improvement over time according to	A 2nd injection of Gel-One at 3-6 mos following initial injection in pts whose symptoms returned to pre-injection levels was associated w/ symptom relief comparable w/ that obtained w/ 1st injection. Safety outcomes were similar to those in the original trial. *Limitations:* Only 61% of original study grp participated. All authors were either consultants or employees of Seikagaku Corp. Quality: Fair

Authors/Study Design	Study Population	Procedural Protocol	Results (95% CIs and significant level 0.05 unless otherwise noted)	Main Finding/Limitations/Quality/Comments
retreatment results *Time frame:* March 2007 – May 2008 *Funding source:* Seikagaku Corp.			all measures, no difference between pts receiving 2nd HA injection (originally randomized to HA) and those receiving 1st (originally randomized to saline) *Response rates:* No difference between grps *2nd injection (n=122 who met criteria for retreatment) vs 1st injection (n=247 randomized to HA in original trial):* Improvement over time and responder rates favored retreatment somewhat but differences were not significant. *Safety outcomes (original HA, original saline):* Any AE: 54.4%, 58.1% Tx-related AE: 20.8%, 17.6% Serious AE: 2.4%, 1.4%; none considered to be “device” related.	

APPENDIX VIII. Randomized Trials (Primarily Placebo Controlled) Contributing to Efficacy Analyses

NOTE: This table lists the placebo-controlled trials included in the six meta-analyses reviewed in the report by Samson et al. (2007) and in the systematic reviews published since December 2009. The pooled efficacy estimates reported by Rutjes et al. (2012) were based not only on placebo-controlled trials but also studies that compared HA injection with "nonintervention controls." These non–placebo-controlled studies, where identification was possible, are indicated by gray shading; in some studies, the control groups actually received usual care or treatment such as physical therapy. Color Coding: Not published in full (abstract only or unpublished, including pamphlets). Published in a book. Not included in any meta–analysis. One study (Rolf 2005) was identified by Samson et al. in addition to the studies identified by the meta–analyses authors. (Table continues across 3 pages.)

Trial	Lo 2003	Wang 2004	Arrich 2005	Modowal 2005	Bellamy 2006[1]	Strand 2006	Bannuru 2011	Colen 2012	Rutjes 2012
Rydell 1972									X
Shichikawa 1983a					X		X		X
Shichikawa 1983b					X				X
Bragantini 1987		X	X		X		X	X	X
Grecomoro 1987		X	X	X	X		X	X	X
Dixon 1988	X	X			X		X		X
Ghirardini 1990									X
Russell 1992	X		X				X		X
Dougados 1993	X	X	x		X		X		X
Moreland 1993					X		X		X
Puhl 1993	X	X	X	X	X	X	X		X
Cohen 1994	X	X					X		X
Creamer 1994	X	X			X		X	X	X
Dahlberg 1994	X		X				X		
Henderson 1994	X	X	X	X	X		X		X
Scale 1994	X	X		X	X		X	X	X
Adams 1995									X
Carrabba 1995	X	X	X		X		X	X	X
Corrado 1995	X	X	X		X		X	X	X
Formiguera 1995	X	X			X				

Trial	Lo 2003	Wang 2004	Arrich 2005	Modowal 2005	Bellamy 2006[1]	Strand 2006	Bannuru 2011	Colen 2012	Rutjes 2012
France 1995						X	X		
Sala and Miguel							X		
Guler 1996					X		X		X
Lohmander 1996	X	X		X	X	X	X	X	X
UK 1996						X	X		
Kalay 1997									X
Listrat 1997									X
Schneider 1997									X
Wu 1997		X			X		X		
Altman 1998	X	X	X	X	X		X	X	X
Dickson 1998[2]		X							
Wobig 1998	X	X		X	X		X		X
Hizmetli 1999					X		X		
Huskisson 1999	X	X	X	X	X		X	X	X
Brandt 2001	X	X	X		***		X		
Bunyaratavej 2001			X		***		X		X
Caracuel 2001									X
Dickson 2001[2]					X		X		X
Seikagaku UK 2001									X
Seikagaku France 2001									X
Tamir 2001	X	X			X		X		
Hizmetli 2002									X
Karlsson 2002	X		X		X		X	X	X
Millner 2002									X
Petrella 2002	X		X	X	X		X		X
Raynauld 2002									X
Bayramoglu 2003									X
Jubb 2003	X		X		X		X	X	X
Kahan 2003									X
Pham 2003[3]	X								

Trial	Lo 2003	Wang 2004	Arrich 2005	Modowal 2005	Bellamy 2006[1]	Strand 2006	Bannuru 2011	Colen 2012	Rutjes 2012
Telik 2003									X
Tsai 2003					X		X		X
Altman 2004							X		X
Day 2004			X		X	X	X	X	X
Pham 2004[3, 4]					X		X		X
Wu 2004									X
Cubukcu 2005					X		X		
Huang 2005									X
Neustadt 2005							X		X
Sezgin 2005					X		X		X
Rolf 2005							X		
Kotevoglu 2006					X		X		X
Petrella 2006									X
Atay 2008									X
Blanco 2008									X
Heybeli 2008									X
Lundsgaard 2008								X	X
Petrella 2008							X	X	X
Altman 2009							X		X
Baltzer 2009							X	X	X
Baraf 2009							X		X
Diracoglu 2009									X
Petrella 2009									X
Chevalier 2010[5]							X	X	X
Jorgensen 2010								X	X
Kosuwon 2010									X
Kul-Panza 2010								X	X
Huang 2011									X
Altman 2011									
Navarro-Sarabia 2011									X
Petrella 2011									
Strand 2012a, Strand 2012b									

[1] The studies included in the Bellamy (2006) review were the ones used for supplemental analyses by Samson et al.

[2] Published first as abstract and later in full.

[3] Published first as abstract and later in full.

[4] Included in analysis by Colen et al. (2012) of Artz versus placebo but omitted for unreported reason from general HA versus placebo analysis.

[5] Included in analysis by Colen et al. (2012) of Synvisc versus placebo but omitted for unreported reason from general HA versus placebo analysis.