**Hyaluronic Acid/ Viscosupplementation**

**Order of Scheduled Presentations**

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Representing</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dr. Ghislaine Robert, M.D</td>
<td>Fidia Pharma USA Inc</td>
<td>No slides</td>
</tr>
<tr>
<td>2</td>
<td>Vinod Dasa MD</td>
<td>Department of Orthopaedic Surgery Louisiana State University Health Sciences Center</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Michael W Schucker MS, PAS, PA-C</td>
<td>Rockwood Clinic Bone &amp; Joint Center</td>
<td>No slides.</td>
</tr>
<tr>
<td>4</td>
<td>Jon E Block, PhD</td>
<td>The Jon Block Group</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Samir K Bhattacharyya, PhD</td>
<td>Mitek Sports Medicine/ DePuy Synthes</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Greg Devereux, Executive Director</td>
<td>WA Federation of State Employees</td>
<td>Letter.</td>
</tr>
</tbody>
</table>
Disclosure

Any unmarked topic will be considered a "Yes"

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Salary or payments such as consulting fees or honoraria in excess of $10,000.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>2. Equity interests such as stocks, stock options or other ownership interests.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>3. Status or position as an officer, board member, trustee, owner.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>4. Loan or intellectual property rights.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>5. Research funding.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>6. Any other relationship, including travel arrangements.</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

____________________________________________________________________________________

____________________________________________________________________________________

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Representation: if representing a person or organization, include the name and</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>funding sources (e.g. member dues, governmental/taxes, commercial products or services,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>grants from industry or government).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes to #7, provide name and funding Sources:

____________________________________________________________________________________

____________________________________________________________________________________

____________________________________________________________________________________

____________________________________________________________________________________

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X ___________________________  10/23/2013  Christlaine ROBERT

Signature          Date          Print Name

For questions contact:  Christine Masters
                        Health Technology Assessment
                        PO Box 42712
                        Olympia, WA 98504-2712
                        360-725-5126
### Disclosure

Any unmarked topic will be considered a "Yes"

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Salary or payments such as consulting fees or honoraria in excess of $10,000.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>2. Equity interests such as stocks, stock options or other ownership interests.</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>3. Status or position as an officer, board member, trustee, owner.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>4. Loan or intellectual property rights.</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>5. Research funding.</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>6. Any other relationship, including travel arrangements.</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

**BIOVENTUS**

If yes to #7, provide name and funding Sources:

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

**V. DASA**

Date: 10/3/13

For questions contact: Christine Masters  
Health Technology Assessment  
PO Box 42712  
Olympia, WA 98504-2712  
360-725-5128
Vinod Dasa MD

Associate Professor
LSU Dept of Orthopedic Surgery
New Orleans, LA

The challenge

APAP/Ibuprofen

reflux/ulcers, warfarin, clopidogrel, renal disease...

Intra-articular Steroids

Arthroplasty
Managing knee OA

- **Surgery**
  - COX-2's
  - High Dose NSAIDs + Gastroprotectant\(^1\)
  - IA Steroids\(^1\)
- **Moderate OA**
- **Severe OA**
  - Hyaluronic Acid
  - Simple analgesics, low dose NSAIDs\(^2\)
  - Exercise, Physical Therapy, Weight Loss, Orthotics, Nutraceuticals\(^3\)

Medication

- **NSAIDs**
  - Aspirin
  - Ibuprofen
  - Naproxen
  - GI and CVS effects
- **Narcotics**

**NSAID Facts**

- Causes hypertension
- Only 1 in 5 who have a serious problem from NSAIDs have warning symptoms
- Non-selective NSAIDs account for at least 16,500 deaths and 103,000 hospitalizations annually in the U.S.
- Four times more Americans die from NSAIDs annually than from cervical cancer
- Approximately the same number of Americans die from NSAID toxicity as die from AIDS each year
- Clinically important UGI events occur in 3-4.5% of regular NSAID takers
- In North America, the economic consequences of NSAID use results in $0.66 to $1.25 spent on UGI toxicities for each dollar spent on NSAIDs

---

**Systemic Considerations of NSAIDs**

---


---

Steroid injections

- Mod/severe OA
- Crystalline form (triamcinolone) provides slower absorption and longer effect than soluble forms (betamethasone)
- 3-4 injections/year
- Rare, self limited steroid synovitis and/or post steroid flare
Steroid Cocktail Components Used By Louisiana Orthopaedic Surgeons

Most Common Corticosteroid/Anesthetic Combinations

**22 Other combinations with frequency of 2 or less**
Steroid injections

- Pain relief within 24-48 hrs
- Lasts up to 6 weeks (maybe longer)

DM → ↑ Blood glucose (returns to normal in 24 hrs)

Corticosteroids: Chondrotoxicity

Lidocaine Potentiates the Chondrotoxicity of Methylprednisolone

Venkat Seshadri, M.D., Christian H. Cyte, Ph.D., and Constance R. Chu, M.D.


In Vivo Cytotoxic Effects of Benzonatine Chloride in Corticosteroid Injection Suspension

Daniel Gross, Matthew Cyte, Douglas Ge, Ziayang Yao, and Felix H. Sweeney


Lidocaine Exhibits Dose- and Time-Dependent Cytotoxic Effects on Bovine Articular Chondrocytes In Vivo

Jacek C. Krasz and Constance R. Chu


DOI: 10.1177/0363546507303470

LSUHSC Dept of Orthopedics©
Steroids: Ligament/tendon

Effects of local injection of corticosteroids on the healing of ligaments. A follow-up report

M.E. Wiggins, PD Fowks, MG Etheliff and WR Walsh

The Effects of Dexamethasone on Human Patellar Tendon Stem Cells: Implications for Dexamethasone Treatment of Tendon Injury

Jieming Zhang, Camille Kovacs, James H.C. Wang
JOURNAL OF ORTHOPAEDIC RESEARCH JANUARY 2013

Effect of Intra-Articular Corticosteroids on Ligament Properties
A Biomechanical and Histological Study in Rabbit Knees

Pace B. Nevis, M.D.1, 2 Edward S. Gook, Ph.D.1, 2
Neda S. Naseranian, Ph.D.1, 2 and Robert M. Cofield, M.D.1

Steroids:

Ligament/tendon

Intraarticular Injections

Mild/mod OA, young patient

Kenalog / marcaine / lidocaine = future problems?

Chondrolysis of the Glenohumeral Joint After Infusion of Bupivacaine Through an Intra-articular Pain Pump Catheter: A Report of 19 Cases

Mark R. Eddin, M.D., F.R.C.S.C.; and Mark J. Eddin, M.D., F.R.C.S.C.


Google search for "chondrolysis"
Disclosure

Any unmarked topic will be considered a "Yes"

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Salary or payments such as consulting fees or honoraria in excess of $10,000.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Equity interests such as stocks, stock options or other ownership interests.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Status or position as an officer, board member, trustee, owner.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Loan or intellectual property rights.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Research funding.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Any other relationship, including travel arrangements.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Ferring Pharmaceuticals (Euflexxa)

* Please see page 3 attached

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Representation: If representing a person or organization, include the name and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>funding sources (e.g. member dues, governmental/taxes, commercial products or services,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>grants from industry or government).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes to #7, provide name and funding Sources:

___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

Michael Schucian

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-726-5126
Dear HTCC Workgroup Committee,

I understand that the HTCC Workgroup is a public service workgroup established to safeguard the public interest by identifying medical tests and treatments where evidence shows they are safe, effective, and cost-effective. Balance, independence, objectivity and scientific rigor are a basis for public trust and crucial to the credibility and integrity of decisions. Attached is the Conflict of Interest that I have been required to sign prior to my verbal testimony. I personally would like to expand on my attestation when concerning this form, because I believe that I am in a unique situation with regards to the consultation, honoraria fees that I receive from the company (Ferring Pharmaceuticals) disclosed on my participant conflict disclosure. I do, as stated on the form receive consulting fees, and honoraria in excess of $10,000.00 from Ferring Pharmaceuticals (Euflexxa), but I think the committee should understand that I actually make less monetarily performing these services than I would as a physician assistant in my current orthopedic practice. The services that I perform for Ferring Pharmaceuticals do not compensate me in any way for time away from home/family, inconvenience of traveling, lost income due to reduced clinic hours/days, and having to use vacation time to make myself available for programs requiring significant travel time. As I have told the people of Ferring, I consult and do these programs because I have seen personally how hyaluronate does benefit a significant number of patients, is a non-surgical option for treating osteoarthritis of the knee, and for some, changes their life for the better. With this being said in all honesty I believe that I pose no potential conflict of interest on the subject of hyaluronate, all I sincerely want is the best possible treatments, modalities, and outcomes for all patient populations across the board.

Respectfully submitted,

Michael W. Schucker, MS PAS, PA-C
Rockwood Clinic Bone and Joint Center
Spokane, Washington
Disclosure

Any unmarked topic will be considered a "Yes"

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Salary or payments such as consulting fees or honoraria in excess of $10,000.</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2. Equity interests such as stocks, stock options or other ownership interests.</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3. Status or position as an officer, board member, trustee, owner.</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>4. Loan or intellectual property rights.</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>5. Research funding.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Any other relationship, including travel arrangements.</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

_____________________________________________________________

_____________________________________________________________

#6: Travel arrangements only (air, hotel)

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Representation: if representing a person or organization, include the name and</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>funding sources (e.g. member dues, governmental/taxes, commercial products or services</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or services, grants from industry or government).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes to #7, provide name and funding Sources:

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X Jon Block

Signature           Date 10/25/13           Jon Block

Print Name

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126
US-Approved Intra-Articular Hyaluronic Acid Injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized, Saline-Controlled Trials

Larry E. Miller and Jon E. Block

 Clin Med Insights Arthritis Musculoskelet Disord. 2013 Sep 1;6:57-63.

Presented by Jon E. Block Ph.D.
Founder & President of the Jon Block Group

Conducted and Reported Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
**Inclusion Criteria:**

- Injection of a US-approved HA product
- Randomized, sham-control study design
- Primary diagnosis of knee OA
- Identical treatment and follow-up conditions between IAHA and sham-control groups
- And at least one extractable efficacy or safety outcome

**Exclusion Criteria:**

- Concomitant interventional therapies were uniformly administered
- The study was published in a non-English language journal
- Or if data were available only from:
  - Abstracts
  - Conference proceedings
  - Websites
  - Or personal communication
PRISMA Flow Diagram

Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IAHA</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>2,673</td>
<td>2,193</td>
</tr>
<tr>
<td>Age, yr, mean (min–max)</td>
<td>65 (53–72)</td>
<td>62 (53–73)</td>
</tr>
<tr>
<td>Female gender, %, median (min–max)</td>
<td>64 (27–92)</td>
<td>65 (22–100)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (min–max)</td>
<td>28 (25–32)</td>
<td>29 (25–33)</td>
</tr>
<tr>
<td>Symptom duration, yr, mean (min–max)</td>
<td>4.5 (1.0–9.1)</td>
<td>4.3 (0.8–8.5)</td>
</tr>
<tr>
<td>Kellgren-Lawrence grade, median (min–max)</td>
<td>2.5 (1.9–3.0)</td>
<td>2.5 (1.8–3.5)</td>
</tr>
</tbody>
</table>
Standardized Mean Difference for Pre-to-Post Efficacy Changes with IAHA Injection

<table>
<thead>
<tr>
<th>Pain</th>
<th>SMD</th>
<th>95% CI</th>
<th>P-value</th>
<th>Standardized Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 4 to 13 weeks</td>
<td>1.37</td>
<td>1.12 to 1.61</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>• 14 to 26 weeks</td>
<td>1.14</td>
<td>0.89 to 1.39</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Function

<table>
<thead>
<tr>
<th>Pain</th>
<th>SMD</th>
<th>95% CI</th>
<th>P-value</th>
<th>Standardized Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 4 to 13 weeks</td>
<td>1.16</td>
<td>0.99 to 1.34</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>• 14 to 26 weeks</td>
<td>1.07</td>
<td>0.84 to 1.30</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Standardized Mean Difference for IAHA Injection vs. Saline Controls

<table>
<thead>
<tr>
<th>Pain</th>
<th>SMD</th>
<th>95% CI</th>
<th>P-value</th>
<th>Standardized Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 4 to 13 weeks</td>
<td>0.43</td>
<td>0.26 to 0.60</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>• 14 to 26 weeks</td>
<td>0.38</td>
<td>0.21 to 0.55</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Function

<table>
<thead>
<tr>
<th>Pain</th>
<th>SMD</th>
<th>95% CI</th>
<th>P-value</th>
<th>Standardized Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 4 to 13 weeks</td>
<td>0.34</td>
<td>0.16 to 0.51</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>• 14 to 26 weeks</td>
<td>0.32</td>
<td>0.18 to 0.45</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Risk Difference in Safety Outcomes for IAHA Injection vs. Saline Controls

<table>
<thead>
<tr>
<th>SAE</th>
<th>RD (%)</th>
<th>95% CI (%)</th>
<th>P-value</th>
<th>Risk Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Any</td>
<td>0.7</td>
<td>-0.2 to 1.5</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>• Treatment-related</td>
<td>0</td>
<td>-0.4 to 0.4</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>• Withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Any</td>
<td>0</td>
<td>-1.6 to 1.6</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>• AE-related</td>
<td>0.2</td>
<td>-0.4 to 0.8</td>
<td>0.46</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Variable</th>
<th>US Approved?</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SMD</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 4 to 13 weeks</td>
<td>0.42</td>
<td>0.31</td>
</tr>
<tr>
<td>• 14 to 26 weeks</td>
<td>0.38</td>
<td>0.26</td>
</tr>
<tr>
<td>Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 4 to 13 weeks</td>
<td>0.32</td>
<td>-0.02</td>
</tr>
<tr>
<td>• 14 to 26 weeks</td>
<td>0.32</td>
<td>0.10</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• SAE</td>
<td>0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>• Treatment-related SAE</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>• Withdrawal</td>
<td>0.0</td>
<td>0.3</td>
</tr>
<tr>
<td>• Withdrawal due to AE</td>
<td>0.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Subgroup Analysis of Study- and Patient-related Factors on Saline-corrected Knee Pain

<table>
<thead>
<tr>
<th>Factor</th>
<th>SMD</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 100 (n=14)</td>
<td>0.17</td>
<td>0.01 to 0.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt; 100 (n=20)</td>
<td>0.67</td>
<td>0.47 to 0.86</td>
<td></td>
</tr>
<tr>
<td>Jadad score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 (n=30)</td>
<td>0.34</td>
<td>0.20 to 0.48</td>
<td>0.03</td>
</tr>
<tr>
<td>&lt; 3 (n=4)</td>
<td>0.87</td>
<td>0.42 to 1.33</td>
<td></td>
</tr>
</tbody>
</table>

No other factors including age, body mass index, female gender proportion, symptom duration, Kellgren-Lawrence grade, or industry funding were statistically significant.

Subgroup Analysis of Study- and Patient-related Factors on Saline-corrected Knee Function

<table>
<thead>
<tr>
<th>Factor</th>
<th>SMD</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender proportion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 67% (n=9)</td>
<td>0.63</td>
<td>0.36 to 0.89</td>
<td>0.01</td>
</tr>
<tr>
<td>&lt; 67% (n=15)</td>
<td>0.25</td>
<td>0.10 to 0.39</td>
<td></td>
</tr>
<tr>
<td>Total sample size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 100 (n=13)</td>
<td>0.22</td>
<td>0.08 to 0.35</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt; 100 (n=11)</td>
<td>0.69</td>
<td>0.44 to 0.93</td>
<td></td>
</tr>
<tr>
<td>Jadad score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 (n=21)</td>
<td>0.28</td>
<td>0.15 to 0.40</td>
<td>0.002</td>
</tr>
<tr>
<td>&lt; 3 (n=3)</td>
<td>1.05</td>
<td>0.57 to 1.52</td>
<td></td>
</tr>
</tbody>
</table>

No other factors including age, body mass index, symptom duration, Kellgren-Lawrence grade, or industry funding were statistically significant.
Standardized Mean Difference for Pre-to-Post Efficacy Changes with IAHA Injection

<table>
<thead>
<tr>
<th>Pain</th>
<th>SMD</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 4 to 13 weeks</td>
<td>1.37</td>
<td>1.12 to 1.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• 14 to 26 weeks</td>
<td>1.14</td>
<td>0.89 to 1.39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Function</th>
<th>SMD</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 4 to 13 weeks</td>
<td>1.16</td>
<td>0.99 to 1.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• 14 to 26 weeks</td>
<td>1.07</td>
<td>0.84 to 1.30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Viscosupplementation on Knee Pain at 4 to 13 Weeks vs. Pre-Treatment
The accepted MCID is 2.0 cm or 30%.

Disclosure
Any unmarked topic will be considered a “Yes”

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Salary or payments such as consulting fees or honoraria in excess of $10,000.</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2. Equity interests such as stocks, stock options or other ownership interests.</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>3. Status or position as an officer, board member, trustee, owner.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Loan or intellectual property rights.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Research funding.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Any other relationship, including travel arrangements.</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

DePuy Synthes Mitek Sports Medicine, A Johnson & Johnson Company.

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

If yes to #7, provide name and funding Sources:

DePuy Synthes Mitek Sports Medicine, A Johnson & Johnson Company.

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

[Signature] 10/23/13 [Print Name]

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126
Do Hyaluronic Acid Injections Postpone Total Knee Replacement?

November 2013

Introduction and Objective

- More than 27 million adults in the US have knee osteoarthritis (OA), a painful and life-altering disease
- Viscosupplementation with hyaluronic acid (HA) injections helps restore synovial fluid properties in the knee, leading to less pain and improved clinical outcomes
- Total knee replacement (TKR) usually is reserved as the final treatment option
- The present study examined the association of the use of HA injections in delaying TKR in patients with knee OA
Database

Retrospective analysis of administrative data using the Truven MarketScan Commercial and Medicare Supplemental Database

• Contains healthcare experience of several million individuals (annually).
• Contains healthcare information from multiple payors
• These individuals' healthcare is provided under a variety of fee-for-service (FFS), fully capitated, and partially capitated health plans, including preferred provider organizations, point-of-service plans, indemnity plans, and health maintenance organizations.

Methods

• Patients
  — Continuously enrolled from 1/1/2007 through 12/31/2011
  — Diagnosis of Knee OA and Total Knee Replacement
  — Patients under 18 excluded
  — Patients excluded if HA was administered after their TKR

Time Line

- OA Diagnosis
- Pain / Anti-inflammatory mgmt
- 1st Spc Visit
- HA Injections
- TKR Procedure
- Time to TKR
Propensity Score Matched (PSM) populations were used

Of the 4,178 patients who received HA, 3,647 were successfully matched using the propensity scoring model factors*.


Association between HA Use and Time to TKR

Patients who received HA injections waited **233 days longer** from their first specialist visit to get to their TKR than patients who did not receive HA.
Repeat Use of HA and Time to TKR

For each additional episode of treatment, patients waited on average 203 days longer to get their TKR; a very consistent “dose response”

Discussion

- This observational, descriptive analysis of an administrative database provides data that suggest that patients receiving HA injections are able to postpone their TKR procedures from initial specialists visit by up to 2.6 years
- Robust patient population
- Propensity Matched Scored population limiting bias
- Although the analysis attempted to control for disease severity by propensity score matching, there could be remaining differences between the HA and non-HA populations not recorded in the database which could affect the interpretation of the results
November 7, 2013

Dorothy Frost Teeter, Director
Washington State Health Care Authority
626 8th Avenue SE
P.O. Box 45502
Olympia, WA 98504-5502

Director Teeter:

It has been brought to the attention of the Washington Federation of State Employees (WFSE) that the Health Technology Clinical Committee will be reviewing viscosupplementation at the upcoming November 15th meeting.

As you well know, the PEBB recently expanded UMP eligibility criteria for bariatric surgery to bring the plan’s coverage up to national standards and match what the other state plans offer. If viscosupplementation is removed as a covered benefit from the UMP, it is a loss of benefits to the bulk of our members, and creates a new disparity not only between the state-offered plans, but with other major insurance plans. Based on an informal review of benefit plans offered in Washington State, we found that all plans cover viscosupplementation with conditions. Should viscosupplementation coverage be eliminated for UMP, it would make the UMP an outlier.

Clearly, the WFSE is not a clinical expert, but we are very concerned that the state is the only insurer in Washington that feels there is new creditable evidence to change time-tested coverage policies for this technology. There is no new evidence we’re aware of that changes the efficacy or safety of this technology. It appears that the most significant new evidence is the change in the American Academy of Orthopaedic Surgeons Treatment Guidelines wherein viscosupplementation is no longer recognized as an effective treatment for osteoarthritis of the knee. While this recommendation is based on best practices, “expert opinion,” is not a highly-rated evidence source. Additionally, it could be argued that such a position by the Orthopaedic Surgeons is not impartial and unbiased.

The WFSE believes that it would be unfair and inconsistent for its members receiving care on a fee-for-service basis not to have appropriate access to viscosupplementation. The Federation believes that treatments should be consistently covered by both the fee-for-service and managed care health plans.
Respectfully,

Greg Devereux
Executive Director
WA Federation of State Employees

CC: Josh Morse (josh.morse@hca.wa.gov)
    Jason McGill (jason.mcgill@gov.wa.gov)
Hyaluronic Acid Injections for Knee Osteoarthritis, Re-Review

Robert D. Mootz, DC
Associate Medical Director
Department of Labor & Industries
November 15, 2013

OA of the Knee
- Affects up to 12% of older adults.
- Involves damage to articular cartilage, subchondral bone changes and may be painful.
- Usual care: PT, OT, assistive devices, NSAIDS, analgesics.
- Refractory Care: Steroids, aspiration

Issues
- NSAIDs are effective for OA however prolonged use may have serious GI effects. Steroid injections may worsen joint long term.

Intra Articular HA Injection
- AKA, viscosupplementation
- Thought to assist lubrication and improve cartilage repair

FDA Approval
- As a device, not a drug.
HA Injections for Knee OA

Agency Concerns

**2010**
- **Safety (Low)**
  - Adverse events increase with number of treatment courses, generally safe
- **Efficacy (Medium)**
  - Unknown mechanism, unstudied duration; of sub-clinical average result; additive not alternative
- **Cost (High)**
  - Usage and costs escalating rapidly

**2013**
- **Safety (Medium)**
  - Adverse event concerns persist
- **Efficacy (Medium)**
  - New studies available
- **Cost (Medium)**
  - Recent agency experience may attenuate some concerns

---

**2010 Decision - Covered With Conditions**

For treatment of pain associated with osteoarthritis (OA) of the knee when all of the following conditions are met:

- In patients who have not had an adequate response to non-pharmacological conservative treatment and simple analgesics;
- Is limited to two courses per year with at least four months between courses;
- Documented evidence of clinical benefit from the prior course of treatment is required for subsequent treatment courses.

Non-covered for other indications
HA Injections for Knee OA

**Safety Issues**

- Localized adverse effects appear to be more common than with comparators (e.g., placebo, saline).
- Serious adverse events such as pseudosepsis are rare but usually can be resolved.

**Effectiveness Issues**

- Statistically measurable improvements in pain and function reported in placebo trials. Clinical significance is questionable.
- Larger, better designed trials show smaller effects that are clinically insignificant.
- Benefit may be greater in less severe cases and individuals under age 65.
- Evidence suggests there is no effect on quality of life.
- Viscosupplementation (VS) may provide longer lasting benefit than steroids.
- There is inadequate evidence comparing VS to glucosamine/chondroitin or conservative measures such as exercise.
**Cost Issues**

- Agency experience suggests a rapid initial growth that has leveled off.
- There may be tradeoffs:
  - Some products may cost less per course, but may have increased risk for side effects when multiple doses are required.
- Published studies are of variable methodology and mixed conclusions.

---

**Codes and CMS Hyaluronic Injectables Pricing**

<table>
<thead>
<tr>
<th>HCPCS</th>
<th>Description</th>
<th>Price Basis</th>
<th>Medicare Price</th>
<th>Dosing/Injection Counts</th>
<th>Per Dose*</th>
<th>Treatment Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7321</td>
<td>Hyalgan/Supartz inj per dose</td>
<td>per dose</td>
<td>85.133</td>
<td>2 ml, 5 doses</td>
<td>85.133</td>
<td>$425.65</td>
</tr>
<tr>
<td>J7323</td>
<td>Euflexxa inj/dose</td>
<td>per dose</td>
<td>152.880</td>
<td>2 ml, 3 doses</td>
<td>152.880</td>
<td>$458.64</td>
</tr>
<tr>
<td>J7324</td>
<td>Orthovisc inj per dose</td>
<td>per dose</td>
<td>172.197</td>
<td>2 ml, 3 doses</td>
<td>172.197</td>
<td>$516.60</td>
</tr>
<tr>
<td>J7325</td>
<td>Synvisc 1 MG (8mg/mL)</td>
<td>per dose</td>
<td>12.570</td>
<td>2 ml, 3 doses</td>
<td>201.12</td>
<td>$603.36</td>
</tr>
<tr>
<td></td>
<td>Synvisc-One 1 MG (8mg/mL)</td>
<td>per dose</td>
<td>12.570</td>
<td>6 ml/dose, 1 dose</td>
<td>603.36</td>
<td>$603.36</td>
</tr>
<tr>
<td>J7326</td>
<td>Gel-One per dose</td>
<td>per dose</td>
<td>620.104</td>
<td>3 ml, 1 dose</td>
<td>620.10</td>
<td>$620.10</td>
</tr>
</tbody>
</table>
# PEBB Utilization

## Agency/Year

<table>
<thead>
<tr>
<th>Agency/Year</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>7-Yr Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEBB Avg Annual Members</td>
<td>160K</td>
<td>172K</td>
<td>205K</td>
<td>211K</td>
<td>213K</td>
<td>213K</td>
<td>213K</td>
<td>213K</td>
</tr>
<tr>
<td>All PEBB HA Patients</td>
<td>977</td>
<td>916</td>
<td>1183</td>
<td>1186</td>
<td>1327</td>
<td>1481</td>
<td>1517</td>
<td></td>
</tr>
<tr>
<td>PEBB Paid/Knee OA HA</td>
<td>$250K</td>
<td>$353K</td>
<td>$598K</td>
<td>$628K</td>
<td>$643K</td>
<td>$620K</td>
<td>$669K</td>
<td>$3.8M</td>
</tr>
<tr>
<td>Avg Paid /Procedure</td>
<td>$139</td>
<td>$131</td>
<td>$152</td>
<td>$152</td>
<td>$169</td>
<td>$161</td>
<td>$174</td>
<td></td>
</tr>
<tr>
<td>Avg Paid, Primary</td>
<td>$257</td>
<td>$270</td>
<td>$275</td>
<td>$309</td>
<td>$277</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEBB Primary % of Inj.</td>
<td>45.6%</td>
<td>49.7%</td>
<td>45.8%</td>
<td>45.6%</td>
<td>30.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee OA HA Patients</td>
<td>790</td>
<td>674</td>
<td>946</td>
<td>978</td>
<td>1063</td>
<td>1226</td>
<td>1290</td>
<td></td>
</tr>
<tr>
<td>Knee OA HA Injections</td>
<td>1797</td>
<td>2695</td>
<td>3932</td>
<td>4937</td>
<td>4594</td>
<td>4359</td>
<td>4372</td>
<td>26,686</td>
</tr>
<tr>
<td>Average Inj per patient</td>
<td>2.3</td>
<td>4</td>
<td>4.2</td>
<td>5</td>
<td>4.3</td>
<td>3.6</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Average Inj courses/pt</td>
<td>1.6</td>
<td>1.6</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEBB Comparator Counts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee OA Diagnosis Pts</td>
<td>3929</td>
<td>5174</td>
<td>5602</td>
<td>5906</td>
<td>6179</td>
<td>6472</td>
<td>6472</td>
<td></td>
</tr>
<tr>
<td>Knee Arthroplasty Pts</td>
<td>543</td>
<td>674</td>
<td>772</td>
<td>837</td>
<td>834</td>
<td>885</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# Medicare Utilization

## Agency/Year

<table>
<thead>
<tr>
<th>Agency/Year</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>7-Yr Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicaid Avg Annual Pts</td>
<td>379K</td>
<td>393K</td>
<td>417K</td>
<td>424K</td>
<td>435K</td>
<td>478K</td>
<td>478K</td>
<td></td>
</tr>
<tr>
<td>All Medicaid HA Patients</td>
<td>196</td>
<td>320</td>
<td>511</td>
<td>860</td>
<td>1081</td>
<td>1265</td>
<td>1265</td>
<td></td>
</tr>
<tr>
<td>Medicaid Paid/Knee OA HA</td>
<td>$97K</td>
<td>$149K</td>
<td>$216K</td>
<td>$278K</td>
<td>$284K</td>
<td>$398K</td>
<td>$378K</td>
<td>$1.8M</td>
</tr>
<tr>
<td>Avg Paid /Procedure</td>
<td>$196</td>
<td>$173</td>
<td>$151</td>
<td>$165</td>
<td>$93</td>
<td>$104</td>
<td>$100</td>
<td></td>
</tr>
<tr>
<td>Avg Paid, Primary</td>
<td>$188</td>
<td>$205</td>
<td>$240</td>
<td>$254</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Mcare % of Inj.</td>
<td>51.0%</td>
<td>30.7%</td>
<td>32.3%</td>
<td>28.2%</td>
<td>33.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee OA HA Patients</td>
<td>167</td>
<td>275</td>
<td>437</td>
<td>690</td>
<td>941</td>
<td>1104</td>
<td>1124</td>
<td></td>
</tr>
<tr>
<td>Knee OA HA Injections</td>
<td>494</td>
<td>860</td>
<td>1426</td>
<td>1682</td>
<td>3042</td>
<td>3843</td>
<td>3782</td>
<td>15,129</td>
</tr>
<tr>
<td>Average Inj per patient</td>
<td>3</td>
<td>3.1</td>
<td>3.3</td>
<td>2.4</td>
<td>3.2</td>
<td>3.5</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Average Inj courses/pt</td>
<td>1.2</td>
<td>1.1</td>
<td>1.2</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicaid Comparator Counts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee OA Diagnosis Pts</td>
<td>9714</td>
<td>10770</td>
<td>11447</td>
<td>10866</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee Arthroplasty Pts</td>
<td>564</td>
<td>616</td>
<td>646</td>
<td>529</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Robert Mootz, DC

November 15, 2013

WA - Health Technology Clinical Committee

11

HA Injections for Knee OA

L & I Utilization

<table>
<thead>
<tr>
<th>Agency/Year</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>7-Yr Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>L&amp;I Avg Annual Patients</td>
<td>163K</td>
<td>156K</td>
<td>147K</td>
<td>126K</td>
<td>123K</td>
<td>121K</td>
<td>122K</td>
<td></td>
</tr>
<tr>
<td>All L&amp;I HA Patients</td>
<td>214</td>
<td>509</td>
<td>479</td>
<td>504</td>
<td>508</td>
<td>488</td>
<td>432</td>
<td></td>
</tr>
<tr>
<td>L&amp;I Paid/Knee OA HA</td>
<td>$133K</td>
<td>$340K</td>
<td>$377K</td>
<td>$302K</td>
<td>$308K</td>
<td>$307K</td>
<td>$270K</td>
<td>$2.04M</td>
</tr>
<tr>
<td>Knee OA HA Patients</td>
<td>154</td>
<td>364</td>
<td>438</td>
<td>351</td>
<td>352</td>
<td>321</td>
<td>262</td>
<td></td>
</tr>
<tr>
<td>Knee OA HA Injections</td>
<td>395</td>
<td>1136</td>
<td>1303</td>
<td>1131</td>
<td>992</td>
<td>954</td>
<td>868</td>
<td>6,779</td>
</tr>
<tr>
<td>Average Inj per patient</td>
<td>2.6</td>
<td>3.1</td>
<td>3</td>
<td>3.2</td>
<td>2.8</td>
<td>3</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Average Inj courses/pt</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L&amp;I Comparator Counts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee OA Diagnosis Pts</td>
<td>7888</td>
<td>8387</td>
<td>8578</td>
<td>8028</td>
<td>7375</td>
<td>7168</td>
<td>7209</td>
<td></td>
</tr>
<tr>
<td>Knee Arthroplasty Pts</td>
<td>242</td>
<td>281</td>
<td>328</td>
<td>362</td>
<td>355</td>
<td>366</td>
<td>314</td>
<td></td>
</tr>
</tbody>
</table>

PEBB Utilization Example

HA Injections for Knee OA: Other Agencies Similar

PEBB Primary Avg Injection Course Allowed $ by Product, 2009-2012

<table>
<thead>
<tr>
<th>Injection Course</th>
<th>Euflexxa</th>
<th>Hyalgan</th>
<th>Orthovisc</th>
<th>Synvisc One</th>
<th>Synvisc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price</td>
<td>$834</td>
<td>$1,177</td>
<td>$926</td>
<td>$751</td>
<td>$932</td>
</tr>
<tr>
<td>Injectable Material</td>
<td>$166</td>
<td>$126</td>
<td>$203</td>
<td>$630</td>
<td>$201</td>
</tr>
<tr>
<td>Professional Fee</td>
<td>$111</td>
<td>$109</td>
<td>$106</td>
<td>$121</td>
<td>$110</td>
</tr>
<tr>
<td>Inj Count/Course</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>% Total Allowed</td>
<td>12.4%</td>
<td>7.8%</td>
<td>8.4%</td>
<td>12.3%</td>
<td>7.1%</td>
</tr>
</tbody>
</table>
**Coverage Decisions**

- NICE 2008 recommended against
  - Emphasized small effect size and cost
- Oregon Health Evidence Review Committee 2012
  - Non-coverage due to insignificant clinical effects

**Guidelines less positive since 2010**

- AAOS (2013) did not recommend HA (strong)
  - 2010 Did not recommend for or against
  - 2013 Based on original studies; Considered MCID = 0.39
- ACR (2012) made no recommendations for HA
  - 2000 recommendation similar to HTCC (recommend for inadequate response to other treatment)
• Based on reasonable level of MCID, evidence does not show superiority to placebo/sham; type of product; cost; or number of injections.
• Additional evidence since 2010 demonstrates lack of efficacy.
• Persistent evidence suggesting adverse events are a concern.
• Products requiring multiple injections per course may slightly increase risk for adverse events.
• Professional societies have tightened guidelines or recommended against use since 2010.
• Other well done evidence-based coverage reviews have made non-coverage decisions based on this evidence.

Consider making non-coverage determination

• Meaningful clinical effect on pain still not demonstrated; little evidence on other patient outcomes.
• Harms occur, usually minor, but include serious adverse events (pseudosepsis).

If HTCC finds evidence suggestive of net health benefit, continue coverage conditions including:
• Age
• FDA Indications
• Require evidence of conservative management
• Limit number of treatment courses
• Leave product type to agency discretion
Questions?

More Information:
http://www.hca.wa.gov/hta/Pages/hyaluronic_visco.aspx

HA Injections for Knee OA

Supplemental Information

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).
### Related Medical Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20610</td>
<td>Arthrocentesis, aspiration and/or injection, major joint or bursa, evaluation and management</td>
</tr>
<tr>
<td>J7320</td>
<td>Hylan G-F 20, 16 mg for intra-articular injection [i.e., Synvisc]</td>
</tr>
<tr>
<td>J7317</td>
<td>Sodium hyaluronate, per 20 to 25 mg dose for intra-articular injection</td>
</tr>
<tr>
<td></td>
<td>[i.e., Hyalgan or Supartz]</td>
</tr>
<tr>
<td>Q4083</td>
<td>Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose</td>
</tr>
<tr>
<td>Q4084</td>
<td>Hyaluronan or derivative, Synvisc, for intra-articular inj, per dose</td>
</tr>
<tr>
<td>Q4085</td>
<td>Hyaluronan or derivative, Euflexxa, for intra-articular inj, per dose</td>
</tr>
<tr>
<td>Q4086</td>
<td>Hyaluronan or derivative, Orthovisc, for intra-articular inj, per dose</td>
</tr>
<tr>
<td>J7321</td>
<td>Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose</td>
</tr>
<tr>
<td>J7322</td>
<td>Hyaluronan or derivative, Synvisc, for intra-articular inj, per dose</td>
</tr>
<tr>
<td>J7323</td>
<td>Hyaluronan or derivative, Euflexxa, for intra-articular inj, per dose</td>
</tr>
<tr>
<td>J7324</td>
<td>Hyaluronan or derivative, Orthovisc, for intra-articular inj, per dose</td>
</tr>
<tr>
<td>J7325</td>
<td>Synvisc and Synvisc-1 (single injection tx)</td>
</tr>
<tr>
<td>J7326</td>
<td>Gel-One Cross-linked Hyaluronate, Zimmer</td>
</tr>
</tbody>
</table>
Hyaluronic Acid/ Viscosupplementation

Clinical Expert

Howard Alan Chansky, MD
Professor & Vice-Chair, Orthopaedics and Sports Medicine, University of Washington
Chief, Section of Orthopaedics, VA Puget Sound Health Care System
Chief, Orthopaedics and Sports Medicine, University of Washington Medical Center
Disclosure
Any unmarked topic will be considered a "Yes"

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Salary or payments such as consulting fees or honoraria in excess of $10,000.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Equity interests such as stocks, stock options or other ownership interests.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Status or position as an officer, board member, trustee, owner.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Loan or intellectual property rights.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Research funding.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Any other relationship, including travel arrangements.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Representation: if representing a person or organization, include the name and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>funding sources (e.g. member dues, governmental/taxes, commercial products or services,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>grants from industry or government).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes to #7, provide name and funding Sources:

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X [Signature] 11/24/13 Howard Chan

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5125
CURRICULUM VITAE

Howard Alan Chansky, MD

Professor & Vice-Chair, Orthopaedics and Sports Medicine
University of Washington

Chief, Section of Orthopaedics, VA Puget Sound Health Care System
Chief, Orthopaedics and Sports Medicine, University of Washington Medical Center

1660 South Columbian Way S-112-ORT
Seattle, Washington 98108
(206) 764-2215 – Office
(206) 764-2529 – Fax
chansky@u.washington.edu

PERSONAL DATA
Birth: May 10, 1960; Boston, MA
Citizenship: U.S.A.

EDUCATION
May 1982 B.S. Degree (Electrical Engineering)
Cornell University, Ithaca, NY

May 1987 M.D. Degree
University of Pennsylvania School of Medicine,
Philadelphia, PA

POSTGRADUATE TRAINING
June 1987 - June 1988 Internship—Department of General Surgery
The Hospital of The University of Pennsylvania
Philadelphia, PA

June 1988 - June 1992 Residency—Department of Orthopaedic Surgery
The Hospital of The University of Pennsylvania
Philadelphia, PA

Department of Orthopedics
University of Washington, Seattle, WA

FACULTY POSITIONS
1988 – 1992 Assistant Instructor, Department of Orthopaedic Surgery
The Hospital of The University of Pennsylvania,
Philadelphia, PA

Aug. 1992 - Feb. 1996 Acting Instructor, Department of Orthopaedics
University of Washington Medical Center and the Children’s
Hospital & Medical Center, Seattle, WA

Aug. 1993 - Feb. 1996 Acting Instructor, Department of Orthopaedics
Attending Physician and Research Fellow
Howard A. Chansky, MD

VA Puget Sound Health Care System, Seattle, WA

Feb. 1996 – Jun. 2002  Assistant Professor, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine, Seattle, WA

January 2001 – Present  Associate Medical Staff, Seattle Cancer Care Alliance, Seattle, WA

July 2002 – June 2005  Associate Professor, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine, Seattle, WA

June 2004 – Present  Vice Chair, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine, Seattle, WA

Sept 2004 – Aug 2005  Senator, Faculty Senate, University of Washington, Seattle, WA

July 2005 – Present  Professor, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine, Seattle, WA

**HOSPITAL POSITIONS**

Feb. 1993 – Present  Staff Orthopaedic Surgeon
VA Puget Sound Health Care System, Seattle, WA

Feb. 1993 - Present  Staff Orthopaedic Surgeon
University of Washington Medical Center, Seattle, WA

Feb. 1996 – Present  Staff Orthopaedic Surgeon
Harborview Medical Center, Seattle, WA

Feb. 1996 - Present  Courtesy Staff
Children’s Hospital & Medical Center, Seattle, WA

Mar. 1999 - Present  Chief, Section of Orthopaedics
VA Puget Sound Health Care System, Seattle, WA

Feb. 2010 – Present  Chief, Orthopaedics and Sports Medicine
University of Washington Medical Center

**HONORS**

1978 - 1982  Dean’s List, eight out of eight semesters at Cornell University

1981  Eta Kappa Nu Electrical Engineering Honor Society

1981  Tau Beta Pi Engineering Honor Society

1981  Vice President of Psi Upsilon Fraternity

1982  Senior Kodak Award for Academic Excellence (one of the top five graduates in the School of Electrical Engineering)
1982  B.S.E.E. with “Distinction” from Cornell University

1987  M.D. in the “Outstanding” Category from the University of Pennsylvania

1995  “New Investigator Recognition Award,” Orthopaedic Research Society

June 1996  “Academic Faculty Teaching Award,” University of Washington, Department of Orthopaedics & Sports Medicine

2004  Musculoskeletal Transplant Foundation / OREF Herndon Research Residency Awards: Splicing Factors Effect Chondrocyte Differentiation and Collagen Synthesis, Principal Investigator (Resident Principal Investigator: Eric Klineberg, M.D.)

June 2004  “Academic Faculty Teaching Award,” University of Washington, Department of Orthopaedics & Sports Medicine

2004  Accepted into membership by the American Orthopaedic Association

2006 – 2012  Checkbook.org Top Doctor

2011  UWMC Service Award

2011 - 2012  US News and World Report Top Doctor

**BOARD CERTIFICATION**
American Board of Orthopaedic Surgery
Part I (written)—Passed July 1992
Part II (oral)—Passed July 1995
Recertified—April 2004

**CURRENT LICENSE TO PRACTICE**
Medical License No. 29712 (active)

State of Pennsylvania  Pennsylvania Medical Physician and Surgeon, 1989
Medical License No. 43161E (inactive)

**PROFESSIONAL ORGANIZATIONS**
1995 - Present  Member, American Board of Orthopaedic Surgery

1995 - Present  Member, Orthopaedic Research Society

1995 - Present  Member, American Medical Association

1997 - Present  Member, American Academy of Orthopaedic Surgeons

2004 - Present  Member, American Orthopaedic Association
TEACHING RESPONSIBILITIES

A. RESPONSIBILITY FOR COURSES

1993 – Present
Orthopaedic Pathology Review Course
Children's Hospital & Regional Medical Center

1995 – Present
Supervisor, Orthopaedic Residency Rotation at the Puget Sound
Veterans Administration Medical Center, Seattle, WA

1997 – Present
Career Counselor, Medical Student Career Counseling
University of Washington School of Medicine, Seattle, WA

1998 – Present
Preceptor for MEDEX Physician Assistant Program
University of Washington School of Medicine, Seattle, WA

Instructor, Problem Based Learning, Multidisciplinary PBL
Component, University of Washington School of Medicine,
Seattle, WA

January 2000 – Present
Director, Orthopaedic Resident Workshop (Ortho “Boot Camp”)
Department of Orthopaedics, University of Washington, Seattle,
WA

Instructor, Problem Based Learning, Multidisciplinary PBL
Component, University of Washington School of Medicine,
Seattle, WA

Instructor, Problem Based Learning, Multidisciplinary PBL
Component, University of Washington School of Medicine,
Seattle, WA

May 2004
Career Counselor, Residency Selection Forum, University of
Washington School of Medicine

B. SPONSORSHIPS

1998 – 2001
Faculty Sponsor for Resident Research, Resident: Matt Camuso,
MD. Project title: “Supraphysiologic Testosterone
Administration in Elderly Men Undergoing Total Joint
Replacement and Fixation of Hip Fracture”, University of
Washington School of Medicine, Seattle, WA

March 1999 – March 2000
Sponsor for Medical Student Research Training Program.
Medical Student: David Woods. Project title: “Supraphysiologic
Testosterone Administration in Elderly Men Undergoing
Operation Fixation of Hip Fracture.” Award: $2,000, University
of Washington School of Medicine, Seattle, WA

January 2000 – 2002
Faculty Sponsor for Resident Research, Resident: Tim Rapp,
MD, Project 1: “Clonality of Chondroid Tumors.” Project 2:
“Oncogenic Fusion Protein TLS/CHOP Interferes with RNA
Splicing,” University of Washington School of Medicine,
Seattle, WA
July 2000 – 2001  Faculty Sponsor for Medical Student Research: Student: Jeremiah Clinton, Project: Cloning and Sequencing of the TLS-Associated Splicing Factors TASR-1 and TASR-2, University of Washington School of Medicine, Seattle, WA

April 2001 – 2002  Faculty Sponsor for Medical Student Research, ISMS and MSRT, Student: David Odell, Project: Alternative Splicing and Fusion Proteins in Ewing’s sarcoma, University of Washington School of Medicine, Seattle, WA

2003 – 2005  Faculty Sponsor for Medical Student Research. Student: Waqqar Khan-Farooqi, Project: RNA interference to inhibit EWS/FLI-1 Ewing’s sarcoma fusion protein, University of Washington School of Medicine, Seattle, WA

2003 – 2006  Faculty Sponsor for Medical Student Research. Student: Burt Yaszay, Project: DNA microarray analysis of Ewing’s sarcoma cell lines treated with short-interfering RNAs, University of Washington School of Medicine, Seattle, WA

2003 – 2006  Faculty Sponsor for Medical Student Research. Student: Eric Klineberg, Project: Splicing Factors Effect Chondrocyte Differentiation and Collagen Synthesis, University of Washington School of Medicine, Seattle, WA

2004 – 2005  Faculty Sponsor for Medical Student Research. Student: Allison MacLennan, Project: The role of DKKI in the genesis of Ewing’s sarcoma, University of Washington School of Medicine, Seattle, WA

2004 – 2005  Faculty Sponsor for Medical Student Research. Student: Evan Ellis, Project: Biomechanical analysis of patella tracking with subvastus versus standard approach in total knee arthroplasty, University of Washington School of Medicine, Seattle, WA

2006 – 2007  Faculty Sponsor for Medical Student Research. Student: Jason Wilcox, Project: Silencing of EWS/FLI1 expression by lentivirus-mediated RNAi, University of Washington School of Medicine, Seattle, WA

2008 – 2009  Faculty Sponsor for Medical Student Research. Student: Dustin Sepich, Project: Hip fracture outcomes in the Seattle Veterans Health Administration, University of Washington School of Medicine, Seattle, WA

C. PRESENTATIONS AND LECTURES

December 1992  The Surgical Treatment of Fibrous Dysplasia, Department of Orthopaedics Grand Rounds, Brown University

June 1993 - present  Musculoskeletal Pathology Review Course, Children’s Hospital & Medical Center, Seattle, WA

Howard A. Chansky, MD  May 7, 2012
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993 - present</td>
<td>Orthopaedic Resident Workshop, Orthopaedic Tumors and Infections</td>
</tr>
<tr>
<td>August 1993- present</td>
<td>Resident Lecture Series, University of Washington Department of Orthopaedics: Musculoskeletal Oncology (monthly)</td>
</tr>
<tr>
<td>October 1993</td>
<td>American Foot and Ankle Society Review Course: Tumors of the Foot and Ankle, Seattle, WA</td>
</tr>
<tr>
<td>April 1995</td>
<td>Grand Rounds, University of Washington Department of Orthopaedics: Biological and Clinical Aspects of Cartilage Transplantation</td>
</tr>
<tr>
<td>September 1995</td>
<td>Resident Lecture Series, University of Washington Department of Orthopaedics: Molecular Biology for Orthopaedic Surgeons</td>
</tr>
<tr>
<td>June 1996</td>
<td>Grand Rounds, University of Washington Department of Orthopaedics: The Science and Treatment of Osteomyelitis</td>
</tr>
<tr>
<td>February 1997</td>
<td>Grand Rounds, University of Washington Department of Orthopaedics: Skeletal Metastases: Diagnosis and Treatment</td>
</tr>
<tr>
<td>March 1997</td>
<td>Grand Rounds, University of Washington, VA Puget Sound Health Care System, Seattle Division, Department of Medicine: Infectious Arthritis, The Orthopaedic Perspective</td>
</tr>
<tr>
<td>July 1997</td>
<td>National Kidney Cancer Association Annual Convention: Modern Multidisciplinary Treatment of Metastatic Bone Disease, SeaTac, WA</td>
</tr>
<tr>
<td>August 2000</td>
<td>Multidisciplinary Oncology Conference, University of Washington, Department of Radiation Oncology: Multidisciplinary Prophylaxis and Treatment of Metastatic Bone Disease</td>
</tr>
<tr>
<td>November 2000</td>
<td>Multidisciplinary Oncology Conference, University of Washington, VA Puget Sound Health Care System: Metastatic Bone Disease--The Orthopaedic Perspective</td>
</tr>
<tr>
<td>February 2001</td>
<td>Grand Rounds, University of Washington Department of Orthopaedics and Sports Medicine, Assisted Scott Hacker MD in preparation of presentation on biology of cartilage injury and reconstruction</td>
</tr>
<tr>
<td>April 2001</td>
<td>Pacific Crest School: What is the life of a doctor really like?</td>
</tr>
<tr>
<td>April 2002</td>
<td>Sarcoma Meeting, Osaka University, Osaka, Japan,</td>
</tr>
<tr>
<td>June 2004</td>
<td>Grand Rounds, University of Washington Department of Rheumatology: Orthopaedic Controversies and the Limits of Current Technology</td>
</tr>
<tr>
<td>Date</td>
<td>Event</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>September 2004</td>
<td>Lower Extremity Assessment of Adults Workshop, 27th Annual National Conference: Advanced Practice in Primary and Acute Care, University of Washington School of Nursing, Washington State Convention &amp; Trade Center, Seattle, WA,</td>
</tr>
<tr>
<td>September 2004</td>
<td>RNA Interference Workshop: Target Validation and Potential Therapeutic Applications For Childhood Cancer. Cancer Therapy Evaluation Program National Cancer Institute and NIH Office of Rare Diseases and Children’s Oncology Group, Arlington, Virginia</td>
</tr>
<tr>
<td>January 2005</td>
<td>Grand Rounds, University of Washington Department of Rheumatology: Ewing's Sarcoma--Sarcoma Fusion Proteins and RNA Interference</td>
</tr>
<tr>
<td>September 2006</td>
<td>Arkansas Cancer Research Center’s Forum, University of Arkansas for Medical Sciences: The Role of Cellular Senescence and pRB in the Biology of Ewing's Sarcoma</td>
</tr>
<tr>
<td>October 2006</td>
<td>Margo Johnson Pathology Review Course, Department of Orthopaedics &amp; Sports Medicine, University of Washington: The Role of Cellular Senescence and pRB in the Biology of Ewing's Sarcoma</td>
</tr>
<tr>
<td>September 2009</td>
<td>Chief of Medicine Conference, VA Puget Sound Health Care System: Septic Arthritis: the Surgical Perspective</td>
</tr>
<tr>
<td>October 2009</td>
<td>Margo Johnson Pathology Review Course, Department of Orthopaedics &amp; Sports Medicine, University of Washington: Paget’s Disease: Orthopedic Implications</td>
</tr>
<tr>
<td>October 2010</td>
<td>Margo Johnson Pathology Review Course, Department of Orthopaedics &amp; Sports Medicine, University of Washington: Paget’s Disease: Orthopedic Implications</td>
</tr>
<tr>
<td>October 2010</td>
<td>Visiting Professor, Dartmouth Hitchcock Medical Center Senior Residents’ Day. Molecular biology and animal models of Ewing's sarcoma</td>
</tr>
<tr>
<td>September 2011</td>
<td>Harkins Resident Education Symposium, University of Washington: Surgical management of extremity sarcoma</td>
</tr>
<tr>
<td>October 2011</td>
<td>Margo Johnson Pathology Review Course, Department of Orthopaedics &amp; Sports Medicine, University of Washington: Paget’s Disease: Orthopedic Implications</td>
</tr>
</tbody>
</table>
D. INVITED KNOWLEDGEBASE ENTRIES


EDITORIAL RESPONSIBILITIES

1996 - present  Ad hoc reviewer, Journal of Orthopaedic Research

2001 - present  Ad hoc reviewer, International Journal of Cancer

2001 - present  Section Medical Editor, Orthopedic Oncology, e-Medicine Online, www.eMedicine.com

2004 – present  Ad hoc reviewer, Cellular and Molecular Life Sciences

2004 - present  Ad hoc reviewer, Clinical Orthopaedics & Related Research

2005 – present  Ad hoc reviewer, University of Pennsylvania Orthopaedic Journal

2005 – present  Ad hoc reviewer, European Journal of Human Genetics

SPECIAL LOCAL RESPONSIBILITIES

1993 - 2005  Surgical Quality Insurance Committee, VA Puget Sound Health Care System, Seattle, WA

1993 - 2004  Infection Control Committee, VA Puget Sound Health Care System, Seattle, WA

1993 - Present  Chair, Same Day Surgery Clinical Pathway Committee, VA Puget Sound Health Care System, Seattle, WA


1997 - 2010  Medical Director, Same Day Services, VA Puget Sound Health Care System, Seattle, WA

Dec. 1998 – March 1999  Member, Search Committee for Assistant Professor of Medicine, University of Washington
1999 - 2008  Member, Departmental Budget Council Steering Committee, Department of Orthopaedics & Sports Medicine, University of Washington

1999 - Present  Member, Residency Review Committee, Department of Orthopaedics & Sports Medicine, University of Washington

Nov. 17 - 19, 1999  Participant, Northwest Network Clinical Retreat, Coeur d’Alene, ID, sponsored by The Department of Veterans Affairs, VA Learning University

June 2000 – June 2001  Member, Search Committee for Chief of Surgery/Vice-Chairman Dept. of Surgery, VAMC/University of Washington School of Medicine

2003  Member, Search Committee for Orthopaedic Spine Surgeon, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine

2004  Member, Search Committee for Orthopaedic Oncologist, Department of Orthopaedics & Sports Medicine, University of Washington School of Medicine

2004  Member, Search Committee for General Oncologic Surgeon, VA Puget Sound Health Care System, Seattle Division

2004  Member, Search Committee for General Surgeon, VA Puget Sound Health Care System, Seattle Division

2004 – 2006  Member, VA/UW Executive Development Program, VA Puget Sound Health Care System, VISN 20

2004 – 2006  Senator, Faculty Senate, University of Washington

2004 – Present  Board Member, Board of Directors, Cancer Research and Biostatistics (CRAB), Seattle, Washington

2007  Chair, Search Committee for Chief of Radiology & Diagnostic Services, VA Puget Sound Health Care System

2008  Field Advisory Committee for Orthopaedics, Veterans Administration Healthcare System

2009 - 2011  Member, Search Committee for Chair, Department of Orthopaedics and Sports Medicine, University of Washington School of Medicine

2010  Chair, Search Committee for UWMC Oncology Faculty member, Department of Orthopaedics and Sports Medicine, University of Washington School of Medicine
2010 – 2011 Chair, Search Committee for Harborview Trauma Faculty member, Department of Orthopaedics and Sports Medicine, University of Washington School of Medicine

2010 – Present Member, VISN 20 Surgical Strategic Planning Workgroup, Veterans Health Administration

June 29 – 30, 2010 Inaugural UW Medicine Patients First Leadership Development Institute Conference, Seattle

November 2 – 3, 2010 UW Medicine Patients First Leadership Development Institute Conference, Seattle

February 2, 2011 UW Medicine Patients First Leadership Development Institute Conference, Seattle

May 10, 2011 UW Medicine Patients First Leadership Development Institute Conference, Seattle

September 27, 2011 UW Medicine Patients First Leadership Development Institute Conference, Seattle

October, 2011 – present Member, Search Committee for Chief of Anesthesiology, VA Puget Sound Health Care System

RESEARCH FUNDING

A. PREVIOUSLY FUNDED PROJECTS

Zimmer Incorporated: Molecular studies of chondrosarcoma cell lines and EXT genes, Principal Investigator, $120,000. 1998-2001.

Biopure Incorporated: A multicenter, randomized, single-blind red blood cell-controlled, parallel group study to evaluate the effect on allogeneic red blood cell use and the safety of room temperature stable hemoglobin-based oxygen carrier-201 (HBOC-201) when administered therapeutically and perioperatively in orthopaedic surgery patients who have not received erythropoietin nor undergone autologous blood donation. Site Co-Investigator at VAPSHCS, $78,000. 1999-2000.

Orthopaedic Research and Education Foundation: The Role of Sarcoma Fusion Proteins in the Genesis of Ewing's Sarcoma, Principal Investigator, $100,000. 2002-2004.


B. ACTIVELY FUNDED PROJECTS


National Institutes of Health: TLS and TLS Leukemia Fusion Protein, Co-Investigator, $680,000. 2002-2006.


National Institutes of Health: Chondrogenesis and histone modification enzymes, Co-investigator, $1,225,000. 2004-2009.

BIBLIOGRAPHY

A. MANUSCRIPTS IN REFEREED JOURNALS


30) Yang L, Ma X, Lyone A, Zou J, Blackburn ML, Pan J, Yang D, Matsushita H, Mei b, Zielinska-Kwiatkowska A, **Chansky HA**. Proper expression of helix-loop-helix protein Id2 is important to chondrogenic differentiation of ATDC5 cells. *Biochem J* 2009 May 1; 419(3):635-43.

31) Yang L, Hu HM, Zielinska-Kwiatkowska A, **Chansky HA**. FOXO1 is a direct target of EWS-FLI1 oncogenic fusion protein in Ewing’s sarcoma cells. *Biochem Biophys Res Commun* 2010 Nov 5, 402(1):129-34.

32) Yang L, Ma XY, Blackburn ML, Matsushita HM, **Chansky HA**. Inhibitor of DNA binding protein 2 regulates chondrocyte differentiation. In revision, *Matrix Biology*.

B. **BOOK CHAPTERS**


C. OTHER PUBLICATIONS


D. **ABSTRACTS & PRESENTATIONS**


20) Howlett AT, **Chansky HA**, Conrad EU, et al: Treatment of aneurysmal bone cysts with curettage, cryotherapy, and bone grafting. Accepted for poster presentation at the


43) Yang, L, Clinton, J, Zielinska-Kwiatkowska, A, Blackburn, M, Matsushita, H, Mei, B, Chansky, HA: Screening for genes involved in chondrocyte differentiation through
random mutagenesis introduced by retroviral insertion. Orthopaedic Research Society, Chicago, IL, March 2006.

44) Hu H, Munro K, Zielinska-Kwiatkowska A, Yang L, Chansky HA: FKHR is upregulated and cyclin D1 is downregulated after RNAi-mediated knockdown of EWS/FLI-1 in Ewing's sarcoma cell lines. Orthopaedic Research Society, Chicago, IL, March 2006.


55) Yang L, Zielinska-Kwiatkowska A; Chansky HA. In vivo effects of Type II EWS-Fli1 expression in mesenchymal cells. Orthopaedic Research Society, Long Beach, CA, January 13, 2011.
Hyaluronic Acid/Viscosupplementation (Re-review)

Teresa L. Rogstad, MPH,
Project Leader, Hayes, Inc.
November 2013

Abbreviations

- HA, hyaluronic acid
- MA, meta-analysis
- IACS, intraarticular corticosteroids
- ITT, intention-to-treat
- NSAIDS, nonsteroidal anti-inflammatory drugs
- OA, osteoarthritis
- OR, odds ratio
- Pt, patient
- RR, relative risk
- RCT, randomized controlled (or comparator) trial
- SMD, standardized mean difference (also referred to as effect size)
- SR, systematic review
- WMD, weighted mean difference
- WOMAC, Western Ontario McMasters University Index
Shorthand references

- **2009 Bannuru review, HA vs IACS** (Bannuru et al., 2009)
- **2010 report**, report presented to WA HCA, May 2010
- **2011 Bannuru review, MA 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 MA** (Colen et al., 2012)
- **Reichenbach review, MA of hylan vs HA** (Reichenbach et al., 2007)
- **Rutjes review, 2012 MA** (Rutjes et al., 2012)
- **Samson review, 2007 HTA prepared for AHRQ** (Samson et al., 2007)
- **Update report**, current report for WA HCA

Background

- **Knee OA**, most common form of OA
  - 6% > 30 yrs
  - 9.5%–12.1% > 60 yrs
- **Treatment**
  - Nonpharmacological therapy, e.g., physical therapy
  - Acetaminophen
  - NSAIDs (downside: gastrointestinal, cardiovascular events)
  - IACS (downside: short–lived benefits, damage with long–term use)
HA/Viscosupplementation

- Replaces depleted natural HA
  - Viscous lubricant, elastic shock absorber
- FDA approved
  - Euflexxa (Bio–HA) (Ferring)
  - Gel–One (Zimmer Inc./Seikagaku Corporation)
  - Hyalgan (Sanofi–Aventis/Fidia)
  - Orthovisc (Depuy Mitek Inc./Anika Therapeutics)
  - Supartz (Arzt, Artzal) (Bioventus/Seikagaku)
  - Synvisc and Synvisc–One (Genzyme)
- Cross–linked hyaluronan chains: Highest molecular weight
  - Synvisc (Hylan G–F 20, hylan)
  - Gel–One (approved since 2010 report)
- Non–cross–linked HA

Policy context

- 2010 conclusion:
  - Lower mean pain scores and improved mean function a few weeks after treatment, peaking at 3 mos.
  - Magnitude of benefit of HA alone may be too small to be clinically important.
- 3 new SRs with MA (2011–2012)
  - Safety concerns raised by 1 SR
- Updated guidelines, more negative
  - American Association of Orthopaedic Surgeons (AAOS)
  - American College of Rheumatology (ACR)
- No CMS National Coverage Determination
**PICO**

**Populations:** Adults with OA of the knee  
**Intervention:** Viscosupplementation (HA 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**

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 time frame**
  - From December 2009 forward
  - Last search July 5, 2013
- **Eligible studies**
  - SRs
  - RCTs (controlled or comparator)
  - For KQ #2 (safety) and KQ #3 (differential effectiveness): Observational studies
  - For KQ #4 (cost): Any cost study or economic evaluation
- **Quality assessment**
  - Hayes methodology (similar to GRADE)

### Evidence selection (red=new evidence)

<table>
<thead>
<tr>
<th>KQ</th>
<th>SRs with MA (6 Total)</th>
<th>RCTs (4 New)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1a</td>
<td>5 SRs: Samson 2007 (Bellamy 2006), Bannuru 2009 (HA vs IACS), Bannuru 2011 (efficacy over time), Colen 2012, Rutjes 2012</td>
<td>3 RCTs Allman 2011; Navarro-Sarabia 2011; Strand 2012a, Strand 2012b</td>
<td>---</td>
</tr>
<tr>
<td>#1b</td>
<td>2 SRs, comparator RCTs: Reichenbach 2007, Colen 2012, 1 SR indirect comparison: Rutjes 2012</td>
<td>1 RCT Petrella 2011</td>
<td>---</td>
</tr>
<tr>
<td>#2</td>
<td>2 SRs: Samson 2007 (Bellamy 2006), Rutjes 2012</td>
<td>22 RCTs w/ sample sizes ≥200; overlap w/ SRs</td>
<td>4 case series: 3 in Samson review; Foti 2011, 1 narrative review: Goldberg and Coutts</td>
</tr>
<tr>
<td>#4</td>
<td>4 economic evaluations: Torrance et al., 2002; Kahan et al., 2003; Yen et al., 2004; NICE, 2008</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
An explanation, Samson review

- 2007 AHRQ technology assessment
- Covered 6 MAs
- Largest and most comprehensive: Bellamy 2006
  - Cochrane Review
  - Pooled estimates highlighted in update report
- Others:
  - Lo 2003
  - Wang 2004
  - Arrich 2005
  - Modowal 2005
  - Strand 2006

Findings, Key Question #1a: preview

<table>
<thead>
<tr>
<th>Outcome # Studies</th>
<th>Direction of Findings (Quality of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain * 4 good SRs w/ MA + 1 RCT = 81 RCTs total, &gt; 10,000 pts</td>
<td>(moderate)</td>
</tr>
<tr>
<td>Physical function* 3 good SRs w/ MA)</td>
<td>(moderate)</td>
</tr>
<tr>
<td>Quality of life* 6 fair–good RCTs, 2147 pts</td>
<td>(moderate)</td>
</tr>
<tr>
<td>Repeat course* 3 RCTs w/ high dropout)</td>
<td>(low)</td>
</tr>
</tbody>
</table>

*Generally placebo-controlled trials (saline injection)
Clinical relevance of pain and function improvement – *stay tuned.*

Findings, Key Question #1a: preview (cont.)

<table>
<thead>
<tr>
<th>Outcome # Studies</th>
<th>Direction of Findings (Quality of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder rates 11 placebo–controlled RCTs w/ deficiencies</td>
<td>(low)</td>
</tr>
<tr>
<td>Responder rates 2 good pragmatic RCTs</td>
<td>(moderate, generalizability?)</td>
</tr>
<tr>
<td>Versus NSAIDs 4 RCTs reviewed by Bellamy 2006</td>
<td>(study quality not available)</td>
</tr>
<tr>
<td>Versus IACS 1 fair–good SR, study quality poor</td>
<td>HA longer lasting (low)</td>
</tr>
<tr>
<td>Versus glucosamine and/or chondroitin</td>
<td>? (no evidence)</td>
</tr>
</tbody>
</table>
Typical trial participants

- **Age** 53–71 yrs
- **Sex** distribution varied widely
- **Body mass index** 29–33 kg/m²
- **OA duration** 6–9 yrs
- **Severity** Kellgren–Lawrence grade 2–3 (0–4 scale)
- **Baseline pain** 42–60 on 100–mm scales or equivalent
- **NSAIDs** previously tried
- **No IACS** within previous 3 mos
- **Concomitant pain medication** allowed (~67% of larger studies disallowed NSAIDs; washout period)
- **Not reported**: History of trauma; compliance prior to trial; use of IACS previously or during study

Findings, Key Question #1a: pain at ~3 mos*

*Peak effect according to 3 SRs with MA.

- Weight-bearing pain, VAS (**Bellamy 2006**)
  - **WMD –11.0** (CI, –17.8 to –8.2); I²=82% (21 RCTs, 2090 pts)
  - VAS preferred (**Colen 2012**)
    - **WMD –10.20** (CI, –15.97 to –4.42); I²=92% (18 RCTs, 2801 pts)
  - Weight-bearing pain, WOMAC (**Bellamy 2006**)
    - **SMD –1.0** (CI, –1.6 to –0.5); I²=88% (7 RCTs, 639 pts)
  - WOMAC preferred (**Rutjes 2012**)
    - All trials: **SMD –0.37** (CI, –0.46 to –0.28); P<0.001; τ²=0.09, P<0.001 for heterogeneity (68 RCTs, 9617 pts)
    - n>100/grp + adequate assessor blinding: **SMD –0.11** (CI, –0.18 to –0.04); τ²=0.01 (18 RCTs, 5094 pts)

*Moderate quality*: Large # fair–good RCTs, good MAs, consistent direction/significance of pooled estimates but inconsistency across studies.
Findings, Key Question #1a: physical function at ~3 mos*

*No clear pattern for peak function effects (Bannuru 2011)

- Weight-bearing pain, WOMAC (Bellamy 2006)
  - SMD -0.9 (CI, -1.3 to -0.4); I²=84%
- WOMAC preferred (Rutjes 2012)
  - All trials: SMD -0.33 (CI, -0.43 to -0.22); P<0.001; τ²=0.10, P<0.001 for heterogeneity
  - n=100/grp+adequate assessor blinding: SMD -0.09 (CI, -0.17 to -0.00); τ²=0.01 (15 RCTs, 4296 pts)

Moderate quality: Same considerations as for pain

Clinical relevance: mean within-group or individual improvement from baseline

<table>
<thead>
<tr>
<th>Source</th>
<th>Term Used</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samson review</td>
<td>Positive response,</td>
<td>20– to 40–point improvement, WOMAC pain (100-point scale)</td>
</tr>
<tr>
<td>Colen review</td>
<td>MCID, pain</td>
<td>10– to 30–point improvement, 100-point scale</td>
</tr>
<tr>
<td>4 RCTs</td>
<td>Clinical response,</td>
<td>≥20–point improvement, 100-point scale</td>
</tr>
<tr>
<td>OMERACT–OARSI</td>
<td>Clinical response,</td>
<td>≥20% or ≥10 mm (100–mm VAS). 2 subscales: (a) WOMAC pain, (b) WOMAC physical function, or (c) patient global assessment</td>
</tr>
<tr>
<td></td>
<td>Strict clinical response</td>
<td>Pain or physical function: ≥50% and ≥20 mm on 100-mm VAS</td>
</tr>
<tr>
<td>IMMPACT (Dworkin 2008)</td>
<td>MCID, pain</td>
<td>10% to 20% or 1 cm (10–cm VAS)/10 mm (100–mm VAS)</td>
</tr>
<tr>
<td></td>
<td>Moderate (clinically important) improvement</td>
<td>30% or 2.0–2.7 cm (10–cm VAS)/20–27 mm (100–mm VAS)</td>
</tr>
<tr>
<td></td>
<td>Substantial improvement</td>
<td>50%</td>
</tr>
</tbody>
</table>

OMERACT=Outcome Measures in Rheumatology Clinical Trials; MCID=minimal clinically important difference; OARSI=Osteoarthritis Research Society International; IMMPACT=the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.
Clinical relevance: *between-group* trial effect

<table>
<thead>
<tr>
<th>Source</th>
<th>Term Used</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMPACT (Dworkin 2009)</td>
<td>Clinically important group difference</td>
<td>Always less than clinically important within-group (individual) improvement (adjustment for placebo effect). No value specified. Responder rates—better approach to analysis in trials.</td>
</tr>
<tr>
<td>Rutjes review</td>
<td>MCID, pain</td>
<td>Effect size (SMD), 0.37 (based on research suggesting ~1 cm on 10-cm VAS as minimal to moderate clinical improvement)</td>
</tr>
</tbody>
</table>

Clinical relevance, KQ #1a findings: pain

- **WMDs**: **11.0** (Bellamy 2006), **10.20** (Colen 2012) on 100-mm scales
  - Clinical response within groups or in individuals = 10–30
  - Between-group trial differences might be smaller, but no recognized threshold.
  - Bellamy conclusion: “HA is effective”
  - Colen conclusion: “Clinical relevance is debatable”
- **SMD**: **0.37** (Rutjes 2012)
  - Prespecified MCID for trial effect: **0.37** (equivalent to ~1-point difference on 10-cm VAS).
  - Conclusion emphasized clinically *irrelevant* effect (0.11) in large trials with adequate assessor blinding
Clinical relevance, KQ #1a findings: physical function at 3 mos

- SMDs:
  - 0.9 (Bellamy 2006, 7 RCTs)
  - 0.33 (Rutjes 2012, 48 RCTs)
- No definitions of clinically relevant trial-based effect on physical function
- Rutjes et al. called the effect “moderate”
  - But emphasized the clinically irrelevant effect (0.09) in large trials with adequate assessor blinding.

Findings, Key Question #1a: responder rates (vs placebo)

- 11 double-blind RCTs (4029 pts)
- Response (variable f/u intervals)
  - HA arms: 30%–81%
  - Placebo arms: 27%–68%
- Results favored HA, 9 RCTs (f/u 2 mos to 34 wks)
  - Absolute difference: 3–16 percentage points
  - NNT 7–16, depending on f/u
- Results favored placebo, 2 RCTs (f/u 3 mos)
  - Absolute difference: −2 to −3 percentage points

*Low quality*: Lack of or unclear statistical significance, some studies. Some inconsistency in direction of findings.
Findings, Key Question #1a: responder rates (add-on to usual care)

- 2 pragmatic RCTs (761 pts)
  - **Response**
    - HA arms: Pain 69%-88%; composite 31%-65%
    - Placebo arms: Pain 40%-68%; composite 14%-40%
  - **Absolute rate differences**
    - 15–27 percentage points favoring HA
    - NNT values: 4–6
  - All differences statistically significant
  - **Moderate quality.** Good RCTs (except neither pt nor assessor blinding), consistent
  - Industry funding in 1 study; unclear in other

Findings, Key Question #1a: other

- **Quality of life (low quality)**
  - 6 fair–good RCTs (2147 pts)
  - 4 studies: No effect (no group difference)
  - 2 studies: Improvement in HA arms, no data for placebo arms
- **Repeat course of injection (low)**
  - 3 RCTs w/ high dropout rate between courses
  - Efficacy, 2nd course ≈ 1st
- **Versus NSAIDs (no quality rating)**
  - 4 RCTs in Bellamy review
  - HA=NSAIDs (pain)
- **Versus IACS (low)**
  - Bannuru 2009 review; pain relief (7 RCTs, 606 pts)
  - IACS superior to HA up to 1 mo, then reverses
  - At 17–26 wks: SMD –0.39 (CI, 0.18–0.59); I²=0 (favors HA)
Findings, Key Question #1a: recap

<table>
<thead>
<tr>
<th>Outcome # Studies</th>
<th>Direction of Findings (Quality of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain * 4 good SRs w/ MA + 1 RCT=81 RCTs total, &gt;10,000 pts</td>
<td>(moderate)</td>
</tr>
<tr>
<td>Physical function* 3 good SRs w/ MA</td>
<td>(moderate)</td>
</tr>
<tr>
<td>Quality of life* 6 fair-good RCTs, 2147 pts</td>
<td>(moderate)</td>
</tr>
<tr>
<td>Repeat course* 3 RCTs w/ high dropout</td>
<td>(low)</td>
</tr>
</tbody>
</table>

*Generally placebo-controlled trials (saline injection)

Findings, Key Question #1a: preview (cont.)

<table>
<thead>
<tr>
<th>Outcome # Studies</th>
<th>Direction of Findings (Quality of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder rates 11 placebo–controlled RCTs w/ deficiencies</td>
<td>(low)</td>
</tr>
<tr>
<td>Responder rates 2 good pragmatic RCTs</td>
<td>(moderate, generalizability?)</td>
</tr>
<tr>
<td>Versus NSAIDs 4 RCTs reviewed by Bellamy 2006</td>
<td>(study quality not available)</td>
</tr>
<tr>
<td>Versus IACS 1 fair–good SR, study quality poor</td>
<td>HA longer lasting (low)</td>
</tr>
<tr>
<td>Versus glucosamine and/or chondroitin</td>
<td>(no evidence)</td>
</tr>
</tbody>
</table>
Take-home message, clinical relevance

- Main pooled estimates = or slightly > SR authors’ definitions of MCID.

- Rutjes 2012: In 18 larger RCTs with adequate assessor blinding, pooled estimates < MCID.

Findings, KQ #1b: hylan (Synvisc) vs non-cross-linked HA

- Small but NS pain effect favoring hylan
  - Reichenbach 2007: SMD -0.27 (CI, -0.55 to 0.01); $I^2=88\%$ (13 comparator RCTs, 2085 pts). No effect w/o 2 outliers; MCID defined as -0.30.
  - Colen 2012: SMD -0.07 (CI, -0.24 to 0.10); $I^2=72\%$ (12 comparator RCTs). Inconsistency across trials.
  - Rutjes 2012, subset (indirect) analysis: SMD -0.53 vs -0.29 ($P=0.099$) (75 noncomparator RCTs, 9722 pts)

- Increased risk of adverse events
  - Reichenbach 2007: RR=1.91 (CI, 1.04–3.49) (6 RCTs w/ consistent findings favoring non-cross-linked HA)

Low quality: Poor studies, inconsistency/imprecision
Findings, KQ #1b: efficacy by molecular weight

- Reichenbach 2007 (SR)
  - Metaregression, no association.
- Petrella 2011 (RCT):
  - High + low slightly superior to high or low alone (P<0.001).
  - NS difference favoring low molecular weight compared with high and low weight.

_Low quality:_ Poor study quality, metaregression is indirect substitute for comparator trials.

Findings, Key Question #2: preview

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk, HA vs Control</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient local adverse reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious (systemic) events, <em>but</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk difference &lt;0.09%</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Causal relationship unclear for most events</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-term safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat course</td>
<td>?</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Late events (&gt;1 yr)</td>
<td>?</td>
<td>No data</td>
</tr>
</tbody>
</table>

Copyright © 2013 Winifred S. Hayes, Inc.
Findings, KQ #2: any adverse event

- **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)

- **Rutjes 2012**
  - All trials (25 RCTs, 5204 pts): RR = 1.04 (CI, 0.99–1.09); no heterogeneity
  - n=100/group + 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.

---

Findings, KQ #2: any adverse event (cont.)

- **Case series rates (f/u ≤2 wks after last injection)**
  - Hylan (Synvisc)
    - 5.3%–8.3% of persons (2 series, 4589 pts, mix of first-time and repeat courses of treatment)
    - 2.1%–2.7% of injections (2 series, 5468 injections, mix of first-time and repeat courses of treatment)
  - Non–cross–linked HA
    - 0.8% of pts (1 series, 1266 pts; some hip OA included)
Findings, KQ #2: local adverse event

- Rutjes review
  - Any: RR=1.34 (CI, 1.13–1.60); no heterogeneity
  - Flares: RR=1.51 (significant)
  - Effusions: RR=1.15 (NS)

- Goldberg review and case report
  - 29 cases pseudosepsis
  - All but 1 following hylan injection, and typically after ≥ 2 injections within a course of treatment

Findings, KQ #2: serious adverse event

- Rutjes review
  - All trials w/ data: RR=1.41 (CI, 1.02–1.97); no heterogeneity (14 RCTs, 3667 pts)
    - 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+adequate assessor blinding: RR=1.55 (CI, 1.07–2.24); no heterogeneity (11 RCTs)
Findings, KQ #2: serious adverse event (cont.)

- Individual RCT results
  - 22 RCTs w/ sample size $\geq 200$ (overlap w/ 14 RCTs in Rutjes review)
  - No serious adverse events attributed to treatment

- Case series (follow-up $\leq 2$ weeks)
  - 3 series described in Samson review
    - All involving hylan
    - 1 event (large effusion w/ synovitis)
  - 1 series (Foti 2011)
    - Hyalgan
    - 0.08% of pts (pain or swelling at injection site, other)

Findings, KQ #2: other comparisons

- Versus NSAIDs (Bellamy 2006)
  - More local reactions but fewer systemic adverse events with HA.

- Versus 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); gastrointestinal events, 3.5% vs 11.9%; none serious.

- Incidence during 2nd course
  - $\approx$ incidence during 1st (2 RCTs; Euflexxa, Altman 2011; Gel–One; Strand 2012b).
  - Much higher per-person or per-injection during repeat course (2 case series, hylan).
Findings, Key Question #2: recap

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk, HA vs Control</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient local adverse reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious (systemic) events, but**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk difference &lt;0.09%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causal relationship unclear for most events</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td><strong>Long-term safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat course</td>
<td>?</td>
<td>Mixed findings</td>
</tr>
<tr>
<td>Late events (&gt;1 yr)</td>
<td>?</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insufficient evidence</td>
</tr>
</tbody>
</table>

Findings, KQ #3

- **Greater benefit:** Age ≤ 65 years, less severe OA (low quality)
  - 1 SR/MA (Wang 2004) (20 RCTs)
  - Magnitude of difference unknown
  - Outdated (substantial # missing RCTs)

- **Insufficient evidence**
  - Race/ethnicity
  - Gender
  - Primary versus secondary OA
  - Disease duration
  - Weight (body mass index)
  - Prior treatments
## Findings, KQ #4

<table>
<thead>
<tr>
<th>Country</th>
<th>Perspective</th>
<th>Time Frame</th>
<th>Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Societal</td>
<td>1-yr</td>
<td>Usual care alone (hylan)</td>
<td>CAD 10,000/QALY, 1999 costs (USD 11,273/QALY, 2013 dollars) CAD 2505/QALY per patient improved, 1999 costs (USD 2824/QALY, 2013 dollars)</td>
</tr>
<tr>
<td>France</td>
<td>Societal</td>
<td>9 mos</td>
<td>Usual care alone? (hylan)</td>
<td>HA more effective than usual care alone Comparable costs (unclear funding)</td>
</tr>
</tbody>
</table>

## Findings, KQ #4 (cont.)

<table>
<thead>
<tr>
<th>Country</th>
<th>Perspective</th>
<th>Time Frame</th>
<th>Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>National Health Service (NHS)</td>
<td>26 wks</td>
<td>Placebo (reference unstated)</td>
<td>1 trial: cost–effectiveness ratio exceeded NHS threshold Other trial: placebo both more effective and less expensive No comparison of adverse effects Products not available in the United States</td>
</tr>
</tbody>
</table>
Findings, KQ #4: limitations

- Small # of studies
- May not apply to the U.S.
- More meaningful studies used hylan (Synvisc), >10 years old
- No data specific to single-injection treatments
- No data for HA vs IACS
- 3 studies: societal perspective (including productivity losses), not payer perspective

Practice guidelines

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Relevant Recommendations</th>
<th>Quality/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Rheumatology (ACR), 2012</td>
<td>No evidence-based recommendation possible.</td>
<td>Good (5 of possible 7) Search ended December 2010.</td>
</tr>
<tr>
<td>NICE, 2008</td>
<td>Not recommended for OA.</td>
<td>Good (2010 rating, no numerical score)</td>
</tr>
<tr>
<td>OARSI (2007-2010)</td>
<td>May be useful in pts w/ OA of knee (level of evidence la, strength of recommendation 64% on 100-point VAS).</td>
<td>Good (6 of possible 7) Possible corporate influence and somewhat outdated.</td>
</tr>
</tbody>
</table>
### Selected payer policies

<table>
<thead>
<tr>
<th>Payer</th>
<th>Policy</th>
</tr>
</thead>
</table>
| Aetna     | Medically necessary for OA of knee when:  
• Physical therapy and pharmacological treatment → no functional improvement after ≥ 3 months.  
• Inadequate relief from IACS.  
Additional series medically necessary after ≥ 3 months since last series if:  
• Documented reduction in analgesics or anti-inflammatory medication during 3 mos following previous series.  
• Documented improvement in pain and function. |
| CMS       | No National Coverage Determination                                                                                                    |
| Regence   | No coverage policy, but medication policy requires prior authorization and limits coverage to 2 courses per year.                       |
| Group Health | Same as Regence.                                                                                                       |
| OR HERC   | Should not be covered for pain associated with OA of knee (HERC = Health Evidence Review Commission).                            |

### Final summary: main findings

- **Efficacy**: Improved pain and function, peaking by 3 months.  
  - Magnitude of placebo-adjusted benefit may be too small to be clinically important for many, if not most, patients.  
- **Effectiveness in practice**: Some evidence of clinically meaningful benefit when added to usual care.  
- **Longer lasting than IACS** (low quality), but no information on patients’ past experience with IACS.  
- Efficacy by molecular weight uncertain; hylan may be less safe.  
- Increased risk of **local reactions**, but generally transient and not severe.  
- **Reduced risk of gastrointestinal events**.  
- Efficacy may be greater in **pts ≤ 65 yrs of age and with less severe OA**.  
- **Cost–effectiveness** has not been studied in U.S. setting.
Gaps in the evidence

- Responder rates and economic evaluation in current, U.S. real-world practice.
- Efficacy/safety of different dosing regimens and repeat treatments.
- Comparison with glucosamine and/or chondroitin.
- Causal relationship between viscosupplementation and systemic adverse events.
- Long-term safety data.
- Differential effectiveness and safety by patient characteristics and previous treatment history.

Miller and Block, 2013 (not included in report)

- Published September 2013 in *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*.
- Funded by HA Viscosupplementation Coalition (Bioventus, DePuy Synthes Mitek, Ferring, Fidia, Zimmer).
- SR with MA, 29 RCTs using FDA-approved products.
- Pooled estimates of between-group differences.
  - Pain at 4–13 wks: SMD **0.43** (CI, 0.26–0.60; *P*<0.001)
  - Pain at 14–26 wks: SMD 0.38 (CI, 0.21–0.55; *P*<0.001)
  - Function at 4–13 wks: SMD **0.34** (CI, 0.16–0.51; *P*<0.001)
  - Function at 14–26 wks: SMD 0.32 (CI, 0.18–0.45; *P*<0.001)
  - High heterogeneity: *I²*=74%–92%; *P*<0.001
  - Evidence of publication bias for pain but not function
- Rutjes review: SMD **0.37** for pain and SMD **0.33** for function.
- No definition of clinical relevance/response, sensitivity analyses, or comparison with estimates derived from trials of non-FDA products.
HTCC Coverage and Reimbursement Determination
Analytic Tool

HTA’s goal is to achieve better health care outcomes for enrollees and beneficiaries of state programs by paying for proven health technologies that work.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:
1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

**Principle One: Determinations are Evidence based**

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective\(^1\) as expressed by the following standards\(^2\):
- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

**Principle Two: Determinations result in health benefit**

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms\(^3\):
- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely

\(^1\) Based on Legislative mandate: See RCW 70.14.100(2).

\(^2\) The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

\(^3\) The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm
to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.

- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

### Using Evidence as the Basis for a Coverage Decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. **Availability of Evidence:**

   Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. **Sufficiency of the Evidence:**

   Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence\(^4\) using characteristics such as:

   - Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
   - The amount of evidence (sparse to many number of evidence or events or individuals studied);
   - Consistency of evidence (results vary or largely similar);
   - Recency (timeliness of information);
   - Directness of evidence (link between technology and outcome);
   - Relevance of evidence (applicability to agency program and clients);
   - Bias (likelihood of conflict of interest or lack of safeguards).

   Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

<table>
<thead>
<tr>
<th>Not Confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very certain of evidentiary support. Further information is unlikely to change confidence</td>
</tr>
</tbody>
</table>

---

\(^4\) Based on GRADE recommendation: [http://www.gradeworkinggroup.org/FAQ/index.htm](http://www.gradeworkinggroup.org/FAQ/index.htm)
3. **Factors for Consideration - Importance**

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology’s safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

**Medicare Coverage and Guidelines**

[from page 83 of evidence report]

**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.

[from page 74 of evidence report]

**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 regarding 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).
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.
HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document: What are the key factors and health outcomes and what evidence is there?

<table>
<thead>
<tr>
<th>Safety Outcomes</th>
<th>Safety Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient local adverse reaction</td>
<td></td>
</tr>
<tr>
<td>Systemic events</td>
<td></td>
</tr>
<tr>
<td>Pain or swelling @ injection site</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy – Effectiveness Outcomes</th>
<th>Efficacy / Effectiveness Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>Physical Function</td>
<td></td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
</tr>
<tr>
<td>Repeat course</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Special Population / Considerations Outcomes</th>
<th>Special Population Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>OA severity</td>
<td></td>
</tr>
</tbody>
</table>
Disease duration  
BMI  
Prior treatments

<table>
<thead>
<tr>
<th>Cost</th>
<th>Cost Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct cost, product/procedure</td>
<td></td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td></td>
</tr>
</tbody>
</table>

### Clinical Committee Evidence Votes

#### First Voting Question
The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

**Is there sufficient evidence under some or all situations that the technology is:**

<table>
<thead>
<tr>
<th></th>
<th>Unproven (no)</th>
<th>Equivalent (yes)</th>
<th>Less (yes)</th>
<th>More (yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost-effective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Discussion
Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
• Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
• Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote
Based on the evidence about the technologies’ safety, efficacy, and cost-effectiveness, it is

______ Not Covered _______ Covered Unconditionally _______ Covered Under Certain Conditions

Discussion Item
Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon?

Clinical Committee Findings and Decisions

Next Step: Cover or No Cover
If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions
If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   • Refer to evidence identification document and discussion.
   • Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   • Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   • What are the known conditions/criteria and evidence state
   • What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.
**Efficacy Considerations:**
- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests’ accuracy
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices

**Safety**
- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening.
- Other morbidity concerns
- Short term or direct complication versus long term complications
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

**Cost Impact**
- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

**Overall**
- What is the evidence about alternatives and comparisons to the alternatives
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?