

# Signal Detection Report: Glucosamine Therapy for Treating Osteoarthritis

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## Signal Detection Report date

July, 2017

## Key Findings

- Expert opinion: One expert stated that the original review's recommendations were no longer valid and was aware of new evidence that would strengthen the findings of the original review. A second expert did not know if the original review's recommendations were still valid.
- Literature evidence: No signal was identified

**Summary Decision:** the review the does require updating at this time

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## **Introduction**

Previous research evaluating a cohort of published systematic reviews demonstrated that 7% of reviews were out of date by the time of publication, while as many as 23% went out of date within two years of being completed.[1] The utility of systematic review-based evidence depends on their remaining up-to-date. As such, the Cochrane Complementary Medicine Field and the Knowledge Synthesis group at the Ottawa Hospital Research Institute (OHRI) have determined a set of existing reviews of interest for which signal detection work using the Ottawa Method's qualitative/quantitative signal detection approach has been performed. [1]

The Ottawa method involves identification of qualitative and quantitative signals/triggers indicating the need of updating of a systematic review. [1]. The Ottawa method has been used to assess the need for updating systematic reviews in the past. [1; 2] A graphical overview of our approach and application of the Ottawa signal detection method is provided in Appendix A, Figure 1 of this report. This work assessed potential triggers signifying the need for updating of six past Cochrane Complementary Medicine reviews. The conclusion as to whether or not each of the reviews is in need of updating was made based on the identification of qualitative and quantitative signals.

## **Methods**

We contacted content experts to provide input on whether conclusions from the review were still valid, and if they were aware of any new evidence that could potentially signal the need for a review update. This process included the authors from the original review, and also reached out to the lead authors on the included studies of the review. If we did not find sufficient number of experts we then reached out to those who had responded and asked whether they could suggest possible content experts.

Summaries and conclusions were collected for each key question (or possibly key endpoint) within each review; this summary was shared with consulting experts when seeking their input regarding the findings, as well as when establishing the presence of updating triggers. See Appendix B for the survey sent to content experts.

Experts were asked their perspectives on the following features of each review: a) whether the conclusion is still valid in their own opinion (to be answered as yes/no/don't know); b) whether he/she is aware of new evidence published since the publication date of the review being assessed (with details if yes); and c) any additional information or perspectives to be shared. If an expert indicated an opinion that one or more conclusions of the review was out of date and/or provided specific evidence they felt was critical to the decision regarding updating, we verified it by assessing the evidence brought forward by the expert(s).

Experts were given 10 business days to respond. Two reminders were sent, and a conflict of interest disclosure statement was also sent to all experts that participated. The survey was kept open until a minimum of two clinical experts responded.

One reviewer screened the evidence provided by the content experts, and determined whether the studies met the inclusion criteria of the original review. Data was extracted by one reviewer. The identification of qualitative signals was carried out using the Ottawa method qualitative signals. The definition and categories of qualitative signals are presented in Appendix C.

An information specialist provided modified PRESS [8] evaluations of the original review's search strategy, commenting on databases, search dates and terminology. This information is provided in Appendix D in order to inform any future updating for the original review.

### **Expert Opinion**

Of the 17 experts contacted, two responded to our questions on glucosamine for the management of osteoarthritis. We did not hear back from about half of the experts, and although the other half agreed to participate, there was lack of follow through on the survey.

One expert thought that the original review's conclusions were no longer valid, and wrote that he "believe[d] there is now enough high quality evidence (trials and meta-analyses) to state that non-Rotta glucosamine is non-superior to placebo." The expert provided new evidence he believed would strengthen the findings of the original review. The other expert answered "don't know" to all the survey questions.

### **Flow of New Evidence Suggested**

Four references were put forth by the content experts. All of these publications met the original review's inclusion criteria, and were assessed for qualitative signals.

## **Signal Detection Results:**

### **Findings of the original review**

Overall Conclusion of the Review: "Pooled results from studies using a non-Rotta preparation or adequate allocation concealment failed to show benefit in pain and WOMAC function while those studies evaluating the Rotta preparation showed that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic OA. Therefore, the results in favor of glucosamine are mixed, and further research is still needed to clarify the true efficacy of glucosamine in OA." [3]

Further Details: "The previous review from 2005, with 20 studies and 2570 participants, showed that glucosamine sulphate taken orally in amounts of 1500 mg/day produced a 28% (per cent change from baseline) benefit in pain and an increase in function of 21% (per cent change in Lequesne Index from baseline) in osteoarthritis, without side effects. If only the best designed studies are included, the benefit in pain and WOMAC function is no longer present; as shown in this update which includes 25 studies and 4963 patients. Inclusion of five new studies reduces the overall benefit on pain to 22% and

function to 11% in the Lequesne Index. Pooled results from studies using a non-Rotta preparation or adequate allocation concealment failed to show benefit in pain and WOMAC function, while those studies evaluating the Rotta preparation showed that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic OA. WOMAC outcomes of pain and function showed a superiority of glucosamine over placebo for only the Rotta preparation of glucosamine. Some studies suggest the Rotta preparation of glucosamine sulfate may slow radiological progression of OA of the knee over a three year period. The ability of glucosamine to improve symptoms and delay radiological progression of OA affecting other joint sites also needs further research. Glucosamine was as safe as placebo in terms of the number of participants reporting adverse reactions (relative risk ratio 0.99; 95% CI 0.91 to 1.07).”[3]

### **New findings:**

Fransen et al., 2015 reported findings from a double-blind, randomized, placebo-controlled trial of patients with chronic and frequent knee pain. 605 participants were randomized to glucosamine sulfate (n=152), chondroitin sulfate (n=151), both glucosamine and chondroitin (n=151), and placebo (n=151). Participants were treated and followed for two years. The authors reported that “after adjusting for factors associated with structural disease progression... allocation to the dietary supplement combination (glucosamine–chondroitin) resulted in a statistically significant ( $p=0.046$ ) reduction of 2-year [joint space narrowing] compared to placebo: mean difference 0.10 mm (95% CI 0.002 mm to 0.20 mm); no significant structural effect for the single treatment allocations was detected. All four allocation groups demonstrated reduced knee pain over the first year, but no significant between-group differences ( $p=0.93$ ) were detected.” The study has found no significant difference between groups for WOMAC pain and WOMAC function. The authors conclude that “while all allocation groups demonstrated reduced knee pain over the study period, none of the treatment allocation groups demonstrated significant symptomatic benefit above placebo.”[4]

Kwoh et al., 2014 described findings from a randomized, double-blind, placebo-controlled trial of participants with chronic and frequent knee pain, and osteoarthritis diagnosed using the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) score. 201 participants were randomized to 24 weeks of treatment with glucosamine hydrochloride as a beverage (n=98) or a placebo beverage (n=103). The authors reported that “the adjusted odds ratio (OR) for the likelihood of decreased cartilage damage over 24 weeks in any [Whole-Organ MRI Score] WOMMS-scored sub-region of the knee in the glucosamine treatment group compared to the control group was 0.938 (95% confidence interval [95% CI] 0.528, 1.666). Compared to subjects treated with glucosamine, control subjects showed more improvement in BMLs (adjusted OR 0.537, 95% CI 0.291, 0.990) but no difference in worsening BMLs (adjusted OR 0.691, 95% CI 0.410, 1.166) over 24 weeks. There was no indication that treatment with glucosamine decreased the excretion of urinary CTX-II ( $\beta = -0.10$ , 95% CI -0.21, 0.002).” The study didn’t find any significant difference between the treatment group and controls for WOMAC pain and function subscales or total WOMAC. The authors concluded that “the results of this short-term study provide no evidence of structural benefits (i.e., improvements in MRI morphologic features or urinary CTX-II excretion) from glucosamine supplementation in individuals with chronic knee pain.”[5]

Petersen et al., 2011 reported findings from a double-blind randomized controlled trial of participants with bilateral tibiofemoral osteoarthritis of the knee based on the American College of Rheumatology clinical and radiographic classification criteria. 36 participants were randomized to 12 weeks of strength training in combination with the NSAID ibuprofen (n=12), glucosamine sulfate (n=12), or placebo (n=12). The authors reported that “No differences between groups were observed in gains in muscle [cross sectional area] CSA. Training combined with ibuprofen increased maximal isometric strength by an additional 0.22Nm/kg (95% confidence interval [CI], .01–.42; p= .04), maximal eccentric muscle strength by .38Nm/kg (95% CI, .05–.70; p = .02), and eccentric muscle work by .27J/kg (95% CI, .01–.53; p = .04) in comparison with placebo. Training combined with glucosamine increased maximal concentric muscle work by an additional .24J/kg versus placebo (95% CI, .06 –.42; p = .01). Glucosamine reduced pain by 0.79 VAS points vs placebo after training (95% CI, .24 –1.33; *P*<.01).” The authors concluded that “in patients with knee OA, NSAID or glucosamine administration during a 12-week strength-training program did not improve muscle mass gain, but improved maximal muscle strength gain in comparison with treatment with placebo. However, we do not find that the benefits are large enough to justify taking NSAIDs or glucosamine.”[6]

Sawitzke et al., 2010 described a double-blind, placebo-controlled study of patients with knee osteoarthritis (as confirmed by radiographic criteria.) 662 participants were randomized to 24 months of treatment with glucosamine hydrochloride (n=134,) chondroitin sulfate (n=126,) both glucosamine and chondroitin (n=129,) Celecoxib (n=142) or placebo (n=131.) The authors reported that “compared with placebo, the odds of achieving a 20% reduction in WOMAC pain were celecoxib: 1.21, glucosamine: 1.16, combination glucosamine/CS: 0.83 and CS alone: 0.69, and were not statistically significant.” No statistically significant difference was found for WOMAC function or WOMAC pain between the groups. The authors concluded that “over 2 years, no treatment achieved a clinically important difference in WOMAC pain or function as compared with placebo. However, glucosamine and celecoxib showed beneficial but not significant trends.”[7]

**Adverse effects:** There were no safety alerts for glucosamine found from the key sources identified in the methods section. Three of the studies suggested by the experts identified mild adverse effects with no significant differences between study groups [4, 5, 7], and no patients reported side effects in the other study.[6]

Withdrawal: Fransen et al, 2015 reported no major differences between allocation groups for withdrawal [4]. Kwoh et al., 2014 reported that only 4 subjects in the control group and 3 in the glucosamine group dropped out.[5]

### **Quantitative Signal: No signal was identified**

Pooling of new evidence did not change the overall pooled estimates of the original review. For instance, adding new data [4, 5] to the overall meta-analysis comparing glucosamine and placebo for pain demonstrated a very slight change in the magnitude of the original results [new pooled SMD -0.40, 95% CI -0.61, -0.18, *p*<0.00001 (Figure 2) versus original SMD -0.47, 95% CI -0.72, -0.23, *p* = 0.00017]. We also pooled data for the study using Glucosamine Hydrochloride [5] for the non-Rotta sub-analysis

on pain, and results did not change [new pooled SMD -0.05, 95% CI -0.18, 0.08 (Figure 3) versus original SMD -0.05, 95% CI -0.15, 0.05]. Similarly, results for the outcome WOMAC function were consistent with the original review's findings [new pooled SMD -0.06, 95% CI -0.14, 0.02 (Figure 4) versus original SMD -0.08, 95% CI -0.17, 0.00]

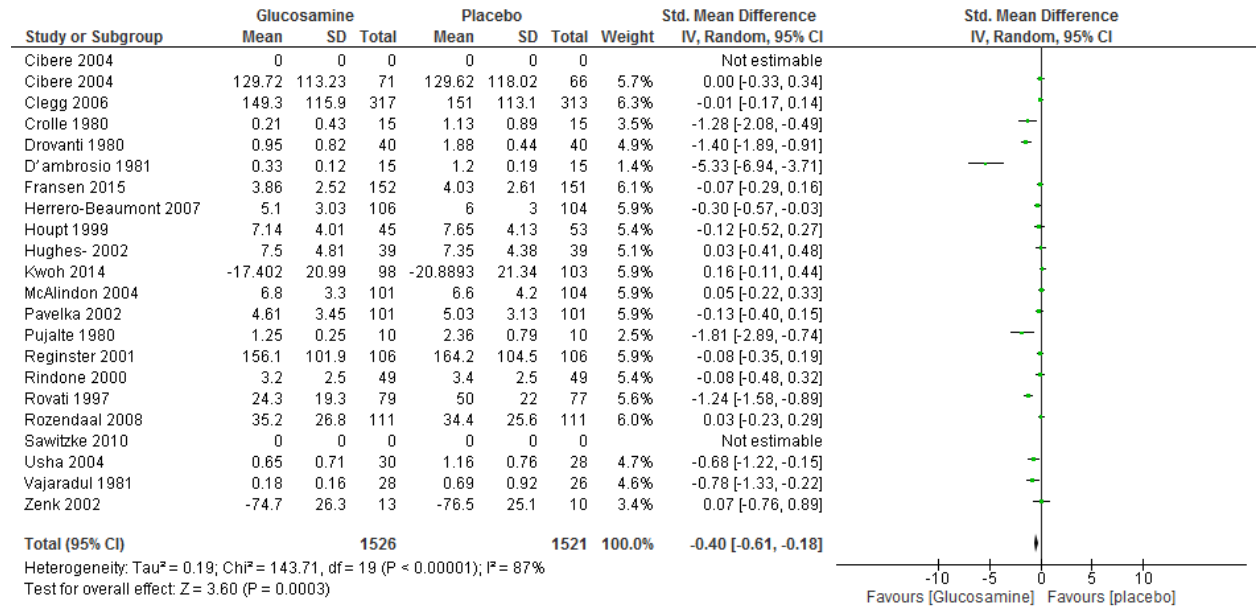


Figure 2: Pain - Overall for Glucosamine versus placebo

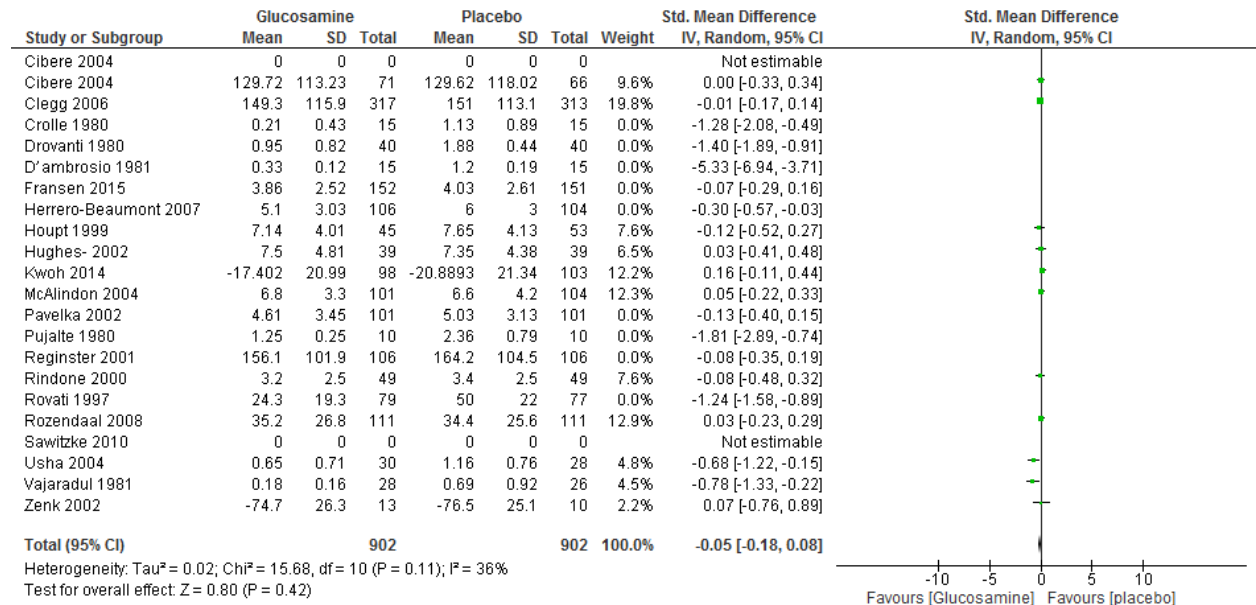


Figure 3: Pain – Non-Rotta preparation for Glucosamine versus placebo

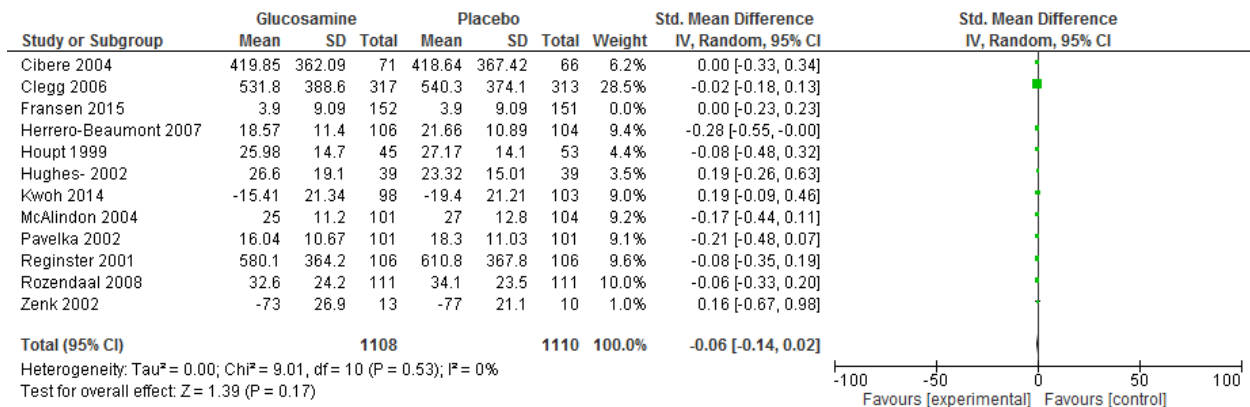


Figure 4: Womac Function for Glucosamine versus placebo

**Qualitative Signal: No signal was identified**

New evidence was mainly consistent with the original review’s findings. The sample size in the new studies ranged from 36-662, and pain was measured by different methods, including diaries, visual analog scale (VAS) and WOMAC. All four studies reported data on the pain outcome. Of these, one study[6] reported significantly reduced pain with glucosamine compared with placebo (consistent to the original review finding for glucosamine sulfate), and three studies[4,5, 7] didn’t find a statistically significant difference between the groups. This is similar to the original review findings of no significant difference between the treatment and placebo for WOMAC pain. One study [4] also reported no statistically significant results for maximum knee pain between the groups. For WOMAC function, three studies [4,5,7] reported similar results to the original review findings of no statistically significant difference between glucosamine and placebo.

Only one study[4] assessed changes in joint space, and found no significant effect for glucosamine compared with placebo at the 2 year follow-up (MD -0.03, 95% CI -0.13 to 0.07). There were also no significant difference in joint space narrowing between the four treatment groups (F test p=0.106.) One study[5] assessed joint structure, and found no benefit for treatment with glucosamine compared with placebo for cartilage damage and bone marrow lesion scores.

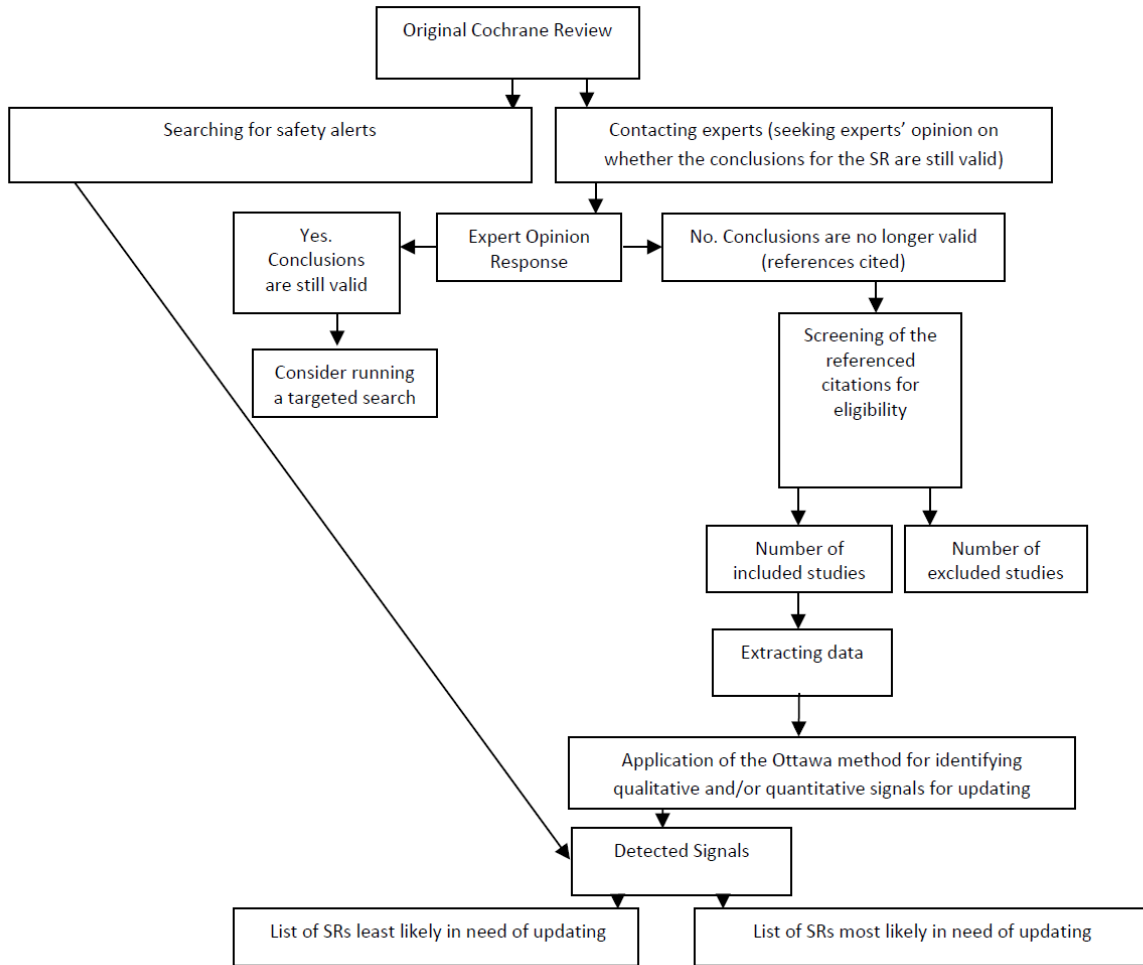
**Conclusion:** No signal was identified. As such, the original review does not require updating at this time.

**References:**

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**Appendix A: Overview of the Modified Ottawa Method**



**Figure 1:** The process of signal detection methods for Cochrane reviews

**Appendix B: Expert Opinion Survey**

Conclusions from systematic review	Is the conclusion(s) in this review still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in this review? (Yes/No/Don't know) If yes, please provide references	Comments
<p><b>Review Objective:</b> To assess the effectiveness and toxicity of glucosamine in the pharmacological management of primary or secondary osteoarthritis (OA) in adults. Both symptomatic effectiveness and structural effectiveness (that is, delay in radiological progression of OA) were evaluated.</p>			
<p><b>Overall Conclusion of the Review:</b> Pooled results from studies using a non-Rotta preparation or adequate allocation concealment failed to show benefit in pain and WOMAC function while those studies evaluating the Rotta preparation showed that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic OA. Therefore, the results in favor of glucosamine are mixed, and further research is still needed to clarify the true efficacy of glucosamine in OA.</p> <p><u>Further Details:</u> The previous review from 2005, with 20 studies and 2570 participants, showed that glucosamine sulphate taken orally in amounts of 1500 mg/day produced a 28% (per cent change from baseline) benefit in pain and an increase in function of 21% (per cent change in Lequesne Index from baseline) in osteoarthritis, without side effects. If only the best designed studies are included, the benefit in pain and WOMAC function is no longer present; as shown in this update which includes 25 studies and 4963 patients. Inclusion of five new studies reduces the overall benefit on pain to 22% and function to 11% in the Lequesne Index. Pooled results</p>			

<p>from studies using a non-Rotta preparation or adequate allocation concealment failed to show benefit in pain and WOMAC function, while those studies evaluating the Rotta preparation showed that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic OA. WOMAC outcomes of pain and function showed a superiority of glucosamine over placebo for only the Rotta preparation of glucosamine. Some studies suggest the Rotta preparation of glucosamine sulfate may slow radiological progression of OA of the knee over a three year period. The ability of glucosamine to improve symptoms and delay radiological progression of OA affecting other joint sites also needs further research. Glucosamine was as safe as placebo in terms of the number of participants reporting adverse reactions (relative risk ratio 0.99; 95% CI 0.91 to 1.07).</p>			
<p><b>Comparing GS or GH versus placebo</b></p> <p>Results from 18 RCTs were pooled for the outcome variable of reduction in pain, where pain was measured by a number of different methods (Cibere 2004; Clegg 2006; Crolle 1980; D'ambrosio 1981; Drovanti 1980; Herrero-Beaumont 2007; Houpt 1999; Hughes 2002; McAlindon 2004; Pavelka 2002; Pujalte 1980; Reginster 2001; Rindone 2000; Rovati 1997; Rozendaal 2008; Usha 2004; Vajaradul 1981; Zenk 2002). The summary standardized mean difference (SMD) (random-effects model) was -0.47 (95% CI - 0.72 to -0.23). A negative SMD in this case meant that glucosamine was significantly superior to placebo in terms of its ability to reduce levels of pain. The relative per cent change from baseline was 22% (using McAlindon 2004 in the calculation as the most representative study).</p>			

<p><b>Comparing GS to placebo for the Lequesne Index scores</b></p> <p>results from five RCTs were pooled (Herrero-Beaumont 2007; Noack 1994; Pavelka 2002; Reichelt 1994, Rovati 1997). The summary SMD (random-effects model) was -0.47 (95% CI -0.82 to -0.12). A negative SMD in this case meant that glucosamine was significantly superior to placebo in terms of its ability to improve Lequesne Index scores. The relative per cent change from baseline was 11% (using Herrero-Beaumont 2007 in the calculation as the most representative study).</p>			
<p><b>Comparing GS to placebo for Lequesne Index scores in which the outcome was dichotomous (per cent responders based on change in Lequesne Index)</b></p> <p>Relative risk ratios (RR) were pooled across two RCTs (Noack 1994; Reichelt 1994). The summary RR (fixed-effect model) for likelihood of being a responder was 1.52 (95% CI 1.20 to 1.91).</p>			
<p><b>Comparing GS or GH to placebo for WOMAC pain subscale scores</b></p> <p>The summary SMD (fixed-effect model) for 10 RCTs (Cibere 2004; Clegg 2006; Herrero-Beaumont 2007; Houpt 1999; Hughes 2002; McAlindon 2004; Pavelka 2002; Reginster 2001; Rozendaal 2008; Zenk 2002) was -0.06 (95% CI -0.14 to 0.03). In this outcome there was no statistical difference between glucosamine and placebo</p>			
<p><b>Comparing GS or GH to placebo for WOMAC stiffness subscale scores</b></p> <p>The summary SMD (fixed-effect model) for seven RCTs</p>			

<p>(Cibere 2004; Clegg 2006; Houpt 1999; Hughes 2002; Pavelka 2002; Rozendaal 2008; Zenk 2002) was -0.02 (95% CI - 0.13 to 0.08). In this outcome there was no statistical difference between glucosamine and placebo.</p>			
<p><b>Comparing GS or GH to placebo for WOMAC function subscale scores</b></p> <p>The summary SMD (fixed-effect model) for 10 RCTs (Cibere 2004; Clegg 2006; Herrero-Beaumont 2007; Houpt 1999; Hughes 2002; McAlindon 2004; Pavelka 2002; Reginster 2001; Rozendaal 2008; Zenk 2002) was - 0.08 (95% CI -0.17 to 0.00). In this outcome there was no statistical difference between glucosamine and placebo.</p>			
<p><b>Comparing GS or GH to placebo for WOMAC total scores</b></p> <p>The summary SMD (fixed-effect model) for six RCTs (Cibere 2004; Herrero-Beaumont 2007; Houpt 1999; Pavelka 2002; Reginster 2001; Zenk 2002) was -0.18 (95% CI -0.31 to - 0.05). In this outcome there was a statistical difference favoring glucosamine over placebo.</p>			
<p><b>Comparing GS to placebo for changes in minimum joint space width for the knee or hip</b></p> <p>The summary mean difference (MD) (fixed-effect model) for two RCTs (Pavelka 2002; Reginster 2001) measuring minimum joint space width at the knee was 0.32 (95% CI 0.05 to 0.58). This was statistically significant in favour of glucosamine and showed that glucosamine slowed the natural radiological progression of OA. Rozendaal 2008 measured minimum joint space width changes in the hip and found inconsistent results in the four sites they measured; however, none of the</p>			

95% CI achieved a minimal clinically important change of 0.25 mm.			
<p><b>Comparing GS to placebo for patient global assessment</b></p> <p>Clegg 2006 measured the patient assessment of disease status score on a 0 to 100 scale and found a non-statistically significant result (mean difference 1.10, 95% CI -2.77 to 4.97). Houpt 1999 asked patients to respond to whether they felt better than at the start of the trial and also found a non-statistically significant result (RR 1.21, 95% CI 0.80 to 1.82).</p>			
<p><b>Comparing GS to placebo for physician global assessment</b></p> <p>Clegg 2006 measured the physician assessment of disease status score on a 0 to 100 scale and found a non-statistically significant result (mean difference 0.80, 95% CI -2.78 to 4.38). This corresponds to a relative per cent change from baseline of -1.5% (95% CI -5.4%, 8.5%). The outcome measured in Drovanti 1980 and Pujalte 1980 was a physician rating of a good or excellent response of their patients. The pooled RR was 2.26 (95% CI 1.49 to 3.43) in favour of glucosamine.</p>			
<p><b>Comparing GS to an NSAID (piroxicam, ibuprofen, celecoxib) for the outcome variable of pain, where pain was measured by a number of different methods</b></p> <p>The summary pooled SMD (random-effects model) for four RCTs was -0.27 (95% CI -0.65 to 0.11) (Clegg 2006; Qiu 1998; Rovati 1997; Vaz 1982). In this outcome there was no statistical difference between glucosamine and NSAIDs</p>			
<p><b>Comparing GS to an NSAID (piroxicam, ibuprofen) for the outcome variable of change in the Lequesne Index</b></p>			

<p><b>scores</b></p> <p>The summary SMD (random-effects model) for two pooled studies was -0.36 (95% CI -1.07 to 0.35) (Muller-FassBender 94; Rovati 1997). In this outcome there was no statistical difference between glucosamine and placebo.</p>			
<p>One RCT (Mehta 2007) compared <b>GS to a polyherbal supplement</b> (reparagen) and, as such, this unique comparator was not included in the meta-analyses described above. In this study, a 20% reduction in WOMAC pain was found in 84% of glucosamine participants and 94% of participants taking the polyherbal supplement at eight weeks. The difference between the two groups was not statistically significant.</p>			
<p><b><u>Sensitivity analysis: Adequate allocation concealment</u></b></p> <p><b>Comparing GS or GH versus placebo in studies with adequate allocation concealment:</b></p> <p>Results from 11 RCTs were pooled for the outcome variable of reduction in pain, where pain was measured by a number of different methods (Cibere 2004; Clegg 2006; Herrero-Beaumont 2007; Houpt 1999; Hughes 2002; McAlindon 2004; Pavelka 2002; Reginster 2001; Rovati 1997; Rozendaal 2008; Zenk 2002). The summary SMD (random-effects model) was -0.16 (95% CI -0.36 to 0.04). In this outcome there was no statistical difference between glucosamine and placebo. This corresponds to a decrease in the treatment group of 0.70 points (95% CI 1.5 points lower to 0.17 points higher) on a 0 to 20 WOMAC scale (using McAlindon 2004 for the calculation). The relative per cent change from baseline was -7% (95% CI -17%, 1.8%).</p>			

<p><b>Comparing GS to placebo in studies with adequate allocation concealment for the Lequesne Index scores</b></p> <p>Results from four RCTs were pooled (Herrero-Beaumont 2007; Noack 1994; Rovati 1997; Pavelka 2002). The summary SMD (random-effects model) was - 0.54 (95% CI -0.96 to -0.12). A negative SMD in this case meant that glucosamine was significantly superior to placebo in terms of its ability to improve Lequesne index scores.</p>			
<p><b>Comparing GS to placebo in studies with adequate allocation concealment for Lequesne Index scores in which the outcome was dichotomous (per cent responders based on change in Lequesne index)</b></p> <p>The summary RR (fixed-effect model) from one RCT (Noack 1994) for likelihood of being a responder was 1.43 (95% CI 1.08 to 1.91).</p>			
<p><b>Comparing GS or GH to placebo in studies with adequate allocation concealment for WOMAC pain subscale scores</b></p> <p>The summary SMD (fixed-effect model) for 10 RCTs (Cibere 2004; Clegg 2006; Herrero-Beaumont 2007; Houpt 1999; Hughes 2002; McAlindon 2004; Pavelka 2002; Reginster 2001; Rozendaal 2008; Zenk 2002) was - 0.06 (95% CI -0.14 to 0.03). In this outcome there was no statistical difference between glucosamine and placebo. This corresponds to a decrease in the treatment group of 0.25 points (95% CI 0.59 points lower to 0.13 points higher) on a 0 to 20 WOMAC scale (using McAlindon 2004 for the calculation).</p>			
<p><b>Comparing GS or GH to placebo in studies with adequate allocation concealment for WOMAC stiffness subscale scores</b></p>			

<p>The summary SMD (fixed-effect model) for seven RCTs (Cibere 2004; Clegg 2006; Houpt 1999; Hughes 2002; Pavelka 2002; Rozendaal 2008; Zenk 2002) was -0.02 (95% CI -0.13 to 0.08). In this outcome there was no statistical difference between glucosamine and placebo.</p>			
<p><b>Comparing GS or GH to placebo in studies with adequate allocation concealment for WOMAC function subscale scores</b></p> <p>The summary SMD (fixed-effect model) for 10 RCTs (Cibere 2004; Clegg 2006; Herrero-Beaumont 2007; Houpt 1999; Hughes 2002; McAlindon 2004; Pavelka 2002; Reginster 2001; Rozendaal 2008; Zenk 2002) was -0.08 (95% CI -0.17 to 0.00). In this outcome there was no statistical difference between glucosamine and placebo. This corresponds to a decrease in the treatment group of 1.02 points (95% CI 2.04 points lower to 0 points higher) on a 0 to 68 WOMAC scale. The relative per cent change from baseline was -3% (95% CI -6%, 0%).</p>			
<p><b>Comparing GS or GH to placebo in studies with adequate allocation concealment for WOMAC total scores</b></p> <p>The summary SMD (fixed-effect model) for six RCTs (Cibere 2004; Herrero-Beaumont 2007; Houpt 1999; Pavelka 2002; Reginster 2001; Zenk 2002) was -0.18 (95% CI -0.31 to -0.05). In this outcome, there was a statistically significant difference which favored glucosamine over placebo.</p>			
<p><b>Comparing GS to placebo for changes in minimum joint space width for the knee or hip</b></p>			

<p>The summary mean difference (MD) (fixed-effect model) for two RCTs (Pavelka 2002; Reginster 2001) measuring the minimum joint space width at the knee was 0.32 (95% CI 0.05 to 0.58). This was statistically significant in favour of glucosamine and showed that glucosamine slowed the natural radiological progression of OA. Rozendaal 2008 measured minimum joint space width changes in the hip and found inconsistent results in the four sites they measured; however, none of the 95% CIs achieved a minimal clinically important change of 0.25 mm. The main outcomes for this comparison are summarized in the Summary of findings table 1.</p>			
<p><b><u>Subgroup analysis: Rotta preparation</u></b></p> <p><b>Comparing GS to placebo in studies using the Rotta preparation for pain</b></p> <p>Results from eight RCTs were pooled (Crolle 1980; D'ambrosio 1981; Drovanti 1980; Herrero-Beaumont 2007; Pavelka 2002; Pujalte 1980; Reginster 2001; Rovati 1997) for the outcome variable of reduction in pain. The summary SMD (random-effects model) was -1.11 (95% CI -1.66 to -0.57). A negative SMD in this case meant that glucosamine was significantly superior to placebo in terms of its ability to reduce pain. The relative per cent change from baseline was -42.2% (95% CI -63.0%, -21.6%) (using Herrero-Beaumont 2007 in the calculation as the most representative study).</p>			
<p><b>Comparing GS to placebo in studies using the Rotta preparation for the Lequesne Index scores</b></p> <p>Results from five RCTs were pooled (Herrero-Beaumont 2007; Noack 1994; Pavelka 2002; Reichelt 1994; Rovati 1997). The summary SMD (random-effects model) was -</p>			

<p>0.47 (95% CI -0.82 to -0.12). A negative SMD in this case meant that glucosamine was significantly superior to placebo in terms of its ability to improve Lequesne Index scores.</p>			
<p><b>Comparing GS to placebo in studies using the Rotta preparation for Lequesne Index scores in which the outcome was dichotomous (per cent responders based on change in Lequesne Index)</b></p> <p>The summary RR (fixed-effect model) from two RCTs (Noack 1994; Reichelt 1994) for likelihood of being a responder was 1.52 (95% CI 1.20 to 1.91).</p>			
<p><b>Comparing GS to placebo in studies using the Rotta preparation for WOMAC pain subscale scores</b></p> <p>Results from three RCTs were pooled (Herrero-Beaumont 2007; Pavelka 2002; Reginster 2001). The summary SMD (fixed-effect model) was -0.17 (95% CI -0.32 to -0.01). In this outcome glucosamine was significantly superior to placebo in terms of its ability to improve WOMAC pain scores.</p>			
<p><b>Comparing GS to placebo in studies using the Rotta preparation for WOMAC stiffness subscale scores</b></p> <p>The result from one RCT (Pavelka 2002) was -0.22 (95% CI -0.50 to 0.06). In this outcome there was no statistical difference between glucosamine and placebo.</p>			
<p><b>Comparing GS to placebo in studies using the Rotta preparation for WOMAC function subscale scores</b></p> <p>Results from three RCTs were pooled (Herrero-Beaumont 2007; Pavelka 2002; Reginster 2001). The summary SMD (fixed-effect model) was -0.19 (95% CI -0.35 to -0.03). In this outcome glucosamine was</p>			

<p>significantly superior to placebo in terms of its ability to improve WOMAC function scores. The relative per cent change from baseline was -7.6% (95% CI -14.0%, -1.2%) (using Herrero-Beaumont 2007 in the calculation as the most representative study).</p>			
<p><b>Comparing GS to placebo using the Rotta preparation for WOMAC total scores</b></p> <p>The summary SMD (fixed-effect model) for three RCTs (Herrero-Beaumont 2007; Pavelka 2002; Reginster Glucosamine therapy for treating osteoarthritis (Review) 12 Copyright © 2009 The Cochrane Collaboration. Published by John Wiley &amp; Sons, Ltd. 2001) was -0.25 (95% CI -0.40 to -0.09). A negative SMD in this case meant that glucosamine was statistically significantly superior to placebo. The main outcomes for this comparison are summarized in the Summary of findings table 2</p>			
<p><b><u>Subgroup analysis: Non-Rotta preparation</u></b></p> <p><b>Comparing GS to placebo in studies using a non-Rotta preparation for pain</b></p> <p>Results from 10 RCTs were pooled (Cibere 2004; Clegg 2006; Houpt 1999; Hughes 2002; McAlindon 2004; Rindone 2000; Rozendaal 2008; Usha 2004; Vajaradul 1981; Zenk 2002) for the outcome variable of reduction in pain. The summary SMD (fixed-effect model) was -0.05 (95% CI -0.15 to 0.05). In this outcome there was no statistical difference between glucosamine and placebo.</p>			
<p><b>Comparing GS to placebo in studies using a non-Rotta preparation for WOMAC pain subscale scores</b></p>			

<p>Results from seven RCTs were pooled (Cibere 2004; Clegg 2006; Hughes 2002; Houpt 1999; McAlindon 2004; Rozendaal 2008; Zenk 2002). The summary SMD (fixed-effect model) was -0.01 (95% CI -0.11 to 0.10). In this outcome there was no statistical difference between glucosamine and placebo</p>			
<p><b>Comparing GS to placebo in studies using a non-Rotta preparation for WOMAC stiffness subscale scores:</b></p> <p>Results from six RCTs were pooled (Cibere 2004; Clegg 2006; Houpt 1999; Hughes 2002; Rozendaal 2008; Zenk 2002). The summary SMD (fixedeffect model) was 0.01 (95% CI -0.10 to 0.13). In this outcome there was no statistical difference between glucosamine and placebo.</p>			
<p><b>Comparing GS to placebo in studies using a non-Rotta preparation for WOMAC function subscale scores:</b></p> <p>Results from six RCTs were pooled (Cibere 2004; Clegg 2006; Houpt 1999; Hughes 2002; Rozendaal 2008; Zenk 2002). The summary SMD (fixed-effect model) was -0.01 (95% CI -0.13 to 0.10). In this outcome there was no statistical difference between glucosamine and placebo.</p>			
<p><b>Comparing GS or GH to placebo using the non-Rotta preparation for WOMAC total scores</b></p> <p>The summary SMD (fixed-effect model) for three RCTs (Cibere 2004; Houpt 1999; Zenk 2002) was -0.02 (95% CI -0.27 to 0.22). In this outcome there was no statistical difference between glucosamine and placebo</p>			
<p><b><u>Toxicity of glucosamine in OA</u></b></p> <p><b>Overall:</b> the safety profile of glucosamine in the 25 RCTs was excellent. For example, out of the 1883 participants randomized to glucosamine treatment in the RCTs, only</p>			

<p>62 (3.3%) were withdrawn because of toxicity. The total number of participants reporting an adverse reaction was 436 (30%) based on 21 RCTs (n = 1451). In the 1482 participants randomized to a placebo group, 70 (4.7%) were withdrawn because of toxicity and 418 (39%) reported an adverse reaction (n = 1061). Therefore, glucosamine was as safe as placebo.</p>			
<p><b>Comparing GS or GH to placebo for number of participants reporting adverse reactions</b></p> <p>The summary RR (fixed-effect model) for 13 RCTs was 0.99 (95% CI 0.91 to 1.07).</p>			
<p><b>Comparing GS or GH to placebo for number of withdrawals due to toxicity</b></p> <p>The summary RR (fixed-effect model) for 12 RCTs was 0.76 (95% CI 0.55 to 1.05).</p>			
<p><b>Comparing GS to NSAIDs for number of participants reporting adverse reactions</b></p> <p>The summary RR (fixed-effect model) for four RCTs was 0.29 (95% CI 0.19 to 0.44). Therefore, GS was significantly less likely than NSAIDs to produce adverse reactions.</p>			
<p><b>Comparing GS to NSAIDs for number of withdrawals due to toxicity</b></p> <p>The summary RR (random-effects model) for four RCTs was 0.16 (95% CI 0.02 to 1.46). Therefore, glucosamine was significantly less likely than NSAIDs to result in withdrawal due to toxicity</p>			
<p>Abbreviations: GH = GS = NSAIDs = Non-steroidal anti-inflammatory drugs, OA = osteoarthritis; RCT = Randomized controlled trial, WOMAC = Western Ontario and McMaster Universities Arthritis Index</p>			



## **Appendix C: The Ottawa Method Qualitative Signals\***

### **Potentially invalidating change in evidence**

This refers to a situation in which it is expected that clinicians do not act upon the results of the original systematic review (SR) and the agency/organization that supported the original production of the SR would retract the SR until it is updated. Criteria for potentially invalidating change in evidence are presented below.

This category of signals (A1-A3) specifies findings from a pivotal trial\*\*, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

### **Major change in evidence**

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of “opposing findings” – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

\* Please, see Shojania et al. 2007 for further definitions and details

\*\*A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

## **Appendix D: Modified PRESS Review for Original Review's Search Strategy**

The original search was executed in November 1999, updated in January 2005, and updated again in January 2008, when additional databases were added. The precise dates of the searches are not provided with the exception of Embase (the documentation lists the search as being performed in the 1980 to week 2, January 2008 database version). Although the manuscript indicates that the full strategies are available in an appendix, only the MEDLINE strategy is provided. The strategy is a textual representation of the search statements and set numbers and does not show the strategy exactly as run in each database, complete with full database name and version, date run, and number of hits per line.

One shortcoming of the strategy is the use of the human population limit, rather than the recommended method of removing animal-only records. Applying the human limit removes all in-process and other unindexed records (often the newest records in the database but including also publisher-supplied records). This situation may have been alleviated in the 2008 update through inclusion of the MEDLINE in-process and daily update databases but the problem would have persisted in the other databases (e.g., Embase, AMED). Without the full strategies, it is impossible to confirm what approach was taken.

The strategy is well constructed from a PICO standpoint, with no language or date limits, but there is an extensive range of free-text vocabulary that could have been employed. Some of this vocabulary might have emerged subsequent to the original 1999 search but should still have been reviewed and potentially incorporated in any of the updates. There are alternate spellings for osteoarthritis (osteoarthritis/osteoarthrosis) and additional vocabulary (coxarthrosis). Some broader vocabulary might also have been useful in this search (e.g., arthrosis, degenerative arthritis/arthrosis, inflammatory arthritis/arthrosis). Glucosamine has a large list of synonyms, including but not limited to acetylglucosamide, chitosamine, dona, glucosamide, glucose amine, hespercorbin, and xicil.

In conclusion, the strategy has limitations with regard to vocabulary, search limits and documentation, and potentially relevant citations may have been missed.